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Autonomic Disorders

Article 1: Physiology and Pathophysiology of the Autonomic Nervous System

Eduardo E. Benarroch, MD, FAAN. Continuum (Minneap Minn). February 2020; 26 (1 Autonomic Disorders):12–24.

ABSTRACT

PURPOSE OF THE REVIEW:

This article reviews the anatomic, functional, and neurochemical organization of the sympathetic and parasympathetic outputs; the effects on target organs; the central mechanisms controlling autonomic function; and the pathophysiologic basis for core symptoms of autonomic failure.

RECENT FINDINGS:

Functional neuroimaging studies have elucidated the areas involved in central control of autonomic function in humans. Optogenetic and other novel approaches in animal experiments have provided new insights into the role of these areas in autonomic control across behavioral states, including stress and the sleep-wake cycle.

SUMMARY:

Control of the function of the sympathetic, parasympathetic, and enteric nervous system functions depends on complex interactions at all levels of the neuraxis. Peripheral sympathetic outputs are critical for maintenance of blood pressure, thermoregulation, and response to stress. Parasympathetic reflexes control lacrimation, salivation, pupil response to light, beat-to-beat control of the heart rate, gastrointestinal motility, micturition, and erectile function. The insular cortex, anterior and midcingulate cortex, and amygdala generate autonomic responses to behaviorally relevant stimuli. Several nuclei of the hypothalamus generate coordinated patterns of autonomic responses to internal or social stressors. Several brainstem nuclei participate in integrated control of autonomic function in relationship to respiration and the sleep-wake cycle. Disorders affecting the central or peripheral autonomic pathways, or both, manifest with autonomic failure (including orthostatic hypotension, anhidrosis, gastrointestinal dysmotility, and neurogenic bladder or erectile dysfunction) or autonomic hyperactivity, primary hypertension, tachycardia, and hyperhidrosis.

KEY POINTS

- **The sympathetic nervous system mediates patterns of responses critical for maintenance of blood pressure, local regulation of blood flow, thermoregulation, and response to exercise and stress.**

- Autonomic dysreflexia results from interruption of supraspinal pathways coordinating the activity of preganglionic sympathetic neurons.
- Norepinephrine elicits vascular and visceral smooth muscle contraction via α_1 receptors, presynaptic inhibition of neurotransmitter release via α_2 receptors, cardiac stimulation via β_1 receptors, and vasodilation and smooth muscle relaxation via β_2 and β_3 receptors.
- The parasympathetic nervous system is critical for lacrimation, salivation, pupil reaction to light, beat-to-beat control of the heart rate, gastrointestinal motility and secretion, micturition, and erectile function.
- Parasympathetic neurons releasing acetylcholine activate smooth muscle contraction, exocrine gland secretion, and vasodilation via M_3 receptors and inhibit cardiac function via M_2 receptors; neurons releasing nitric oxide and vasoactive intestinal polypeptide elicit vasodilation and smooth muscle relaxation.
- The insula is the primary viscerosensory cortex and contributes to conscious bodily sensation.
- The anterior midcingulate cortex and the anterior insular cortex are part of the so-called salience network and are activated during tasks associated with increased sympathetic activity.
- The central nucleus of the amygdala triggers autonomic, endocrine, and motor response to emotionally salient stimuli.
- The hypothalamus initiates specific patterns of autonomic responses to internal or external stressors via projection from the paraventricular and dorsomedial nuclei and orexin/hypocretin neurons.
- The periaqueductal gray coordinates autonomic, somatomotor, and pain modulatory responses to stress.
- The parabrachial nucleus is involved in arousal, respiratory control, and modulation of cardiovascular and gastrointestinal reflexes.
- The nucleus of the solitary tract is the first relay station for medullary cardiovascular, respiratory, and gastrointestinal reflexes.
- Sympathoexcitatory neurons of the rostral ventrolateral medulla, including the C1 group, mediate the baroreflex and responses to hypoxia and other internal stressors.
- Neurons of the rostral ventromedial medulla and nucleus raphe pallidus mediate sympathoexcitatory responses to external stressors and exposure to cold.
- Arterial blood pressure is primarily regulated by the sympathetic noradrenergic input to skeletal muscle and mesenteric blood vessels, mediated by α_1 receptors and driven by premotor neurons in the rostral ventrolateral medulla.
- The baroreceptor reflex is the principal mechanism for short-term, moment-to-moment control of blood pressure, buffering acute fluctuations in response to orthostatic changes or stress.
- Baroreflex-triggered sympathetic vasoconstriction mediated by α_1 receptors and skeletal muscle and splanchnic vessels is critical to prevent orthostatic hypotension, which may be a manifestation of disorders affecting every step of the efferent baroreflex sympathoexcitatory pathway.
- Baroreflex afferent failure manifests with fluctuating hypertension and hypotension.
- Impaired heart rate response to deep breathing is a reliable index of cardiovagal failure.
- The sympathetic output to the sweat glands and skin blood vessels is critical for thermoregulation.
- Peripheral autonomic denervation results in exaggerated responsiveness of target organs to cholinergic or adrenergic agonists (denervation supersensitivity).

Article 2: Autonomic History, Examination, and Laboratory Evaluation

William P. Cheshire Jr, MD, FAAN. Continuum (Minneap Minn). February 2020; 26 (1 Autonomic Disorders):25–43.

ABSTRACT

PURPOSE OF REVIEW:

Autonomic disorders offer a fascinating view of the complexity of the nervous system. Their impact on human health ranges from benign to severe. Deciphering autonomic symptoms and signs draws on the cognitive skills and personal interest in the plight of patients that first attracted many physicians to the field of neurology. This article provides tools to sharpen those skills.

RECENT FINDINGS:

Autonomic neuroscience and accumulated clinical knowledge have led to the categorization of autonomic disorders into specific syndromes that can be identified on the basis of clinical phenotypes and physiologic responses to standardized stimuli in the autonomic laboratory. A key development has been the ability to distinguish neurogenic orthostatic hypotension from other causes of hypotension. Quantification of sudomotor responses has proven valuable in the diagnosis of thermoregulatory disorders and small fiber neuropathies such as those related to diabetes mellitus. Increasing attention has focused on autonomic failure as a defining feature of neurodegenerative α-synucleinopathies, especially multiple system atrophy. As awareness of autonomic disorders has increased, the once obscure term *dysautonomia* has entered into common parlance.

SUMMARY:

With appropriate knowledge and experience, neurologists can diagnose autonomic dysfunction accurately and with confidence. The opportunity to play an important role in caring for patients with autonomic disorders is worth the effort.

KEY POINTS

- Autonomic disorders are common and diverse in character and can present with sustained or episodic hypofunction or hyperfunction of sympathetic or parasympathetic systems.
- A thoughtful autonomic history is the most important component of the evaluation of the patient with autonomic symptoms. The art of the history consists in taking a jumble of clues and formulating a coherent set of questions and conclusions.
- Key aspects of the autonomic history are timing of onset, temporal course, associated illness or context, modifying factors, and use of medications and dietary supplements.
- The impact of autonomic symptoms on daily functioning and quality of life is important. Standing activities may be limited, and tolerance of heat or cold may be impaired. Social and job-related function may also be impaired.
- Dysautonomias are syndromic and cluster into recognizable patterns of presentation that help to organize the history and examination.
- Sympathetic noradrenergic failure causes neurogenic orthostatic hypotension, which is often worse in the morning, in hot environments, after exercise, or after meals.
- Sympathetic noradrenergic hyperactivity causes hypertension, tachycardia, palpitations, pupillary dilatation, and piloerection.
- Sympathetic adrenergic failure occurs in adrenal failure and presents with fatigue. Sympathetic adrenergic hyperactivity causes palpitations, dilated pupils, facial pallor, palmar sweating, and decreased intestinal motility.
- Sympathetic cholinergic failure causes hypohidrosis or anhidrosis. When severe or widespread, patients may be at risk for heat-related illness, including heatstroke. Anticholinergic medications or carbonic anhydrase inhibitors can contribute to anhidrosis.
- Sympathetic cholinergic hyperactivity causes increased sweating. Opioids, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors may contribute to sweating. Consider serotonin syndrome in the patient who has increased the dose of a serotonergic agent.

- Orthostatic hypotension is a sustained reduction in systolic blood pressure of >20 mm Hg within 3 minutes of standing, with or without symptoms. Orthostatic hypotension cannot be diagnosed by symptoms alone but requires measurement of blood pressure.
- Postural tachycardia syndrome is a sustained increase in heart rate during standing or head-up tilt ≥30 beats/min above baseline, or, for patients younger than 20 years of age, ≥40 beats/min above baseline. The tachycardia must not be in response to orthostatic hypotension.
- About one-third of orthostatic hypotension is neurogenic, as recognized by impaired blood pressure responses to the Valsalva maneuver and by deficient reflex tachycardia. Blood pressure drops in neurogenic orthostatic hypotension can also be more profound than orthostatic hypotension that does not have a neurogenic basis.
- Harlequin syndrome consists of strikingly unilateral facial flushing provoked by heat stress. The opposite side of the face, which remains pale, is abnormal and lacks sympathetic vasomotor innervation.
- Physicians who perform autonomic testing should be knowledgeable about the autonomic nervous system and its disorders.
- The quantitative sudomotor axon reflex test evaluates distal postganglionic sudomotor neurons innervating eccrine glands. This test is a sensitive method for detecting small fiber peripheral neuropathies, but the results can be confounded by medications that inhibit sweating. Such medications should be withheld in advance of testing when it is safe to do so.
- A sensitive test of cardiovagal function is the variation in heart rate with sinusoidal deep breathing, which assesses respiratory sinus arrhythmia. Another method is the Valsalva ratio, which is the maximum heart rate divided by the minimum heart rate in response to straining.
- The Valsalva maneuver consists of four phases. Phases I and III are mechanical and occur at the beginning and end of straining. Baroreflex-sympathoneural (noradrenergic cardiovascular) function is assessed by how quickly and completely the blood pressure recovers during phases II and IV and overshoots in phase IV in response to the drop in blood pressure early in phase II that occurs in response to straining.
- Not all tilt-table tests are the same, but the duration and conditions of the test are adjusted to the goals of the test. A duration of 5 minutes is sufficient to establish neurogenic orthostatic hypotension. Longer durations of tilt are needed when assessing orthostatic intolerance and syncope.
- Personal health devices that display autonomic data such as heart rate and blood pressure are increasingly available to patients. Such data have become part of the autonomic evaluation. The numbers can be useful, but they can also be misinterpreted.
- Dysautonomia is not a specific diagnosis but rather a broad category. No one universal treatment exists for "dysautonomia." Treatment decisions must be directed to the patient's specific diagnosis and condition.

Article 3: Autoimmune Autonomic Disorders

Steven Vernino, MD, PhD, FAAS, FAAN. Continuum (Minneap Minn). February 2020; 26 (1 Autonomic Disorders):44–57.

ABSTRACT

PURPOSE OF REVIEW:

Autonomic disorders sometimes occur in the context of systemic autoimmune disease or as a direct consequence of autoimmunity against the nervous system. This article provides an overview of autonomic disorders with potential autoimmune etiology.

RECENT FINDINGS:

Recent evidence highlights a close association between the autonomic nervous system and inflammation. The autonomic nervous system regulates immune function, and autonomic manifestations may occur in a number of systemic autoimmune diseases. In a few instances, autoimmunity directly influences autonomic function. Autoimmune autonomic ganglionopathy is the prototypic antibody-mediated autonomic disorder. Over time, a better understanding of the clinical spectrum of autoimmune autonomic ganglionopathy, the significance of ganglionic nicotinic acetylcholine receptor antibodies, other immune-mediated autonomic neuropathies, and autonomic manifestations of other systemic or neurologic autoimmune disorders has emerged.

SUMMARY:

Autoimmune autonomic disorders may be challenging, but correct identification of these conditions is important. In some cases, potential exists for effective immunomodulatory treatment.

KEY POINTS

- The autonomic nervous system regulates inflammation through a cholinergic anti-inflammatory reflex.
- Some cases of autoimmune autonomic failure are associated with antibodies against the ganglionic nicotinic acetylcholine receptor.
- Synaptic transmission in all autonomic ganglia requires acetylcholine and the ganglionic nicotinic acetylcholine receptor.
- Autoimmune autonomic ganglionopathy is an antibody-mediated disorder caused by antibodies to the ganglionic nicotinic acetylcholine receptor.
- Features of autoimmune autonomic ganglionopathy include prominent cholinergic failure, orthostatic hypotension, and abnormal pupillary light responses.
- Paresthesia (but not pain) occurs in autoimmune autonomic ganglionopathy without objective evidence of sensory neuropathy.
- Low levels of ganglionic nicotinic acetylcholine receptor (<0.2 nmol/L) antibody are nonspecific and should not be considered diagnostic of an autoimmune autonomic disorder.
- Immunotherapy may be beneficial for autoimmune autonomic ganglionopathy.
- Intermediate levels of ganglionic nicotinic acetylcholine receptor antibodies may be associated with chronic cases of autoimmune autonomic ganglionopathy or with limited forms of autonomic failure such as isolated gastrointestinal dysmotility.
- Chronic idiopathic anhidrosis is suspected to be an autoimmune disorder but is not associated with ganglionic nicotinic acetylcholine receptor antibodies.
- Acute autonomic and sensory neuropathy differs from autoimmune autonomic ganglionopathy in clinical features and response to treatment and is not associated with ganglionic nicotinic acetylcholine receptor antibodies.
- The clinical features of acute immune-mediated sensory and autonomic neuropathy are varied but often include neuropathic pain, orthostatic hypotension, and gastrointestinal dysmotility.
- Paraneoplastic autonomic neuropathy is most commonly associated with small cell lung carcinoma and anti-Hu antibodies.
- Severe gastrointestinal dysmotility with gastroparesis is the most common presentation of paraneoplastic autonomic/enteric neuropathy.
- Other clinical syndromes such as limbic encephalitis may coexist with paraneoplastic autonomic neuropathy.
- Patients with Lambert-Eaton myasthenic syndrome commonly report dry mouth, constipation, and sexual dysfunction.
- Various autonomic disturbances can be seen in patients with Guillain-Barré syndrome independent of the severity of muscle weakness.

- Autonomic hyperactivity (hypertension, tachycardia, hypersalivation) can be seen in disorders associated with voltage-gated potassium channel complex antibodies (leucine-rich glioma inactivated protein 1 [LGI1] and contactin-associated proteinlike 2 [CASPR2]).
- Central autonomic dysfunction may be seen in patients with *N*-methyl-D-aspartate (NMDA) receptor antibody encephalitis.
- Encephalitis associated with severe gastrointestinal dysmotility has been associated with dipeptidyl-peptidase–like protein 6 (DPPX) antibodies.
- Autonomic dysfunction may be seen in patients with Sjögren syndrome.
- Autonomic symptoms in Sjögren syndrome are mostly cholinergic. In addition to sicca symptoms, orthostatic intolerance with tachycardia and gastrointestinal symptoms are seen.
- Various degrees of autonomic dysfunction have been reported in systemic lupus erythematosus, rheumatoid arthritis, and scleroderma and may represent effects of deconditioning and chronic systemic inflammation rather than autonomic neuropathy.
- An autoimmune basis for postural tachycardia syndrome has been proposed but not yet proven.
- Various autoantibodies have been found in patients with postural tachycardia syndrome.

Article 4: Autonomic Peripheral Neuropathy

Roy Freeman, MBChB. Continuum (Minneap Minn). February 2020; 26 (1 Autonomic Disorders):58–71.

ABSTRACT

PURPOSE OF REVIEW:

This article provides a summary of the autonomic neuropathies, including neuropathies associated with diabetes mellitus, neuropathies due to amyloid deposition, immune-mediated autonomic neuropathies (including those associated with a paraneoplastic syndrome), inherited autonomic neuropathies, and toxic autonomic neuropathies. The presenting features, diagnostic investigations, and natural history of these neuropathies are discussed.

RECENT FINDINGS:

Recent findings in autonomic peripheral neuropathy include data on the epidemiology and atypical presentations of diabetic autonomic neuropathy, treatment-induced neuropathy of diabetes mellitus, the presentation of immune-mediated neuropathies, and advances in hereditary neuropathy associated with amyloidosis and other hereditary neuropathies.

SUMMARY:

Knowledge and recognition of the clinical features of the autonomic neuropathies, combined with appropriate laboratory and electrophysiologic testing, will facilitate accurate diagnosis and management.

KEY POINTS

- A generalized autonomic neuropathy typically occurs in the setting of a generalized diabetic polyneuropathy but may occur in isolation.
- Treatment-induced neuropathy of diabetes mellitus should be considered when a patient with diabetes mellitus presents with the sudden onset of pain and autonomic dysfunction. This is a reversible diabetic peripheral neuropathy.

- Prominent autonomic features do not occur in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and when patients present with such features, alternative diagnoses should be considered. The peripheral neuropathy associated with hereditary amyloidosis is sometimes misdiagnosed as CIDP, particularly in nonendemic areas.
- The peripheral neuropathy associated with hereditary transthyretin amyloidosis has a heterogeneous presentation, even within families in endemic areas.
- When autonomic features occur in combination with peripheral nerve excitability and neuropsychiatric features such insomnia, agitation, hallucinations, and memory loss, antibodies to the voltage-gated potassium channel complex protein should be considered.
- Among the hereditary sensory and autonomic neuropathies (HSANs), autonomic manifestations are most prominent in HSAN III (also known as Riley-Day syndrome or familial dysautonomia). HSAN III is caused by homozygous mutations in the *ELP1* gene.
- Chemotherapeutic agents are the most common cause of a toxic autonomic neuropathy. Predisposing factors to a chemotherapy-induced peripheral neuropathy include genetic factors and an underlying clinical or subclinical peripheral neuropathy.

Article 5: Synucleinopathies

Elizabeth A. Coon, MD; Wolfgang Singer, MD. Continuum (Minneap Minn). February 2020; 26 (1 Autonomic Disorders):72–92.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the α-synucleinopathies pure autonomic failure, multiple system atrophy, dementia with Lewy bodies, and Parkinson disease with respect to autonomic failure.

RECENT FINDINGS:

The pattern and severity of autonomic involvement in the synucleinopathies is related to differences in cellular deposition and neuronal populations affected by α-synuclein aggregation, which influences the degree and manifestation of autonomic failure. Clinical and laboratory autonomic features distinguish the different synucleinopathies based on pattern and severity. These features also determine which patients are at risk for evolution from pure autonomic failure to the synucleinopathies with prominent motor involvement, such as multiple system atrophy, dementia with Lewy bodies, or Parkinson disease.

SUMMARY:

Autonomic failure is a key feature of the synucleinopathies, with varying type and degree of dysfunction from predominantly peripheral involvement in the Lewy body disorders to central involvement in multiple system atrophy.

KEY POINTS

- α-Synuclein aggregation in central and peripheral autonomic structures may lead to autonomic manifestations of orthostatic hypotension, urogenital dysfunction, gastrointestinal dysmotility, or thermoregulatory dysfunction.
- Rapid eye movement sleep behavior disorder is a unifying feature of the synucleinopathies and may precede autonomic or motor features in the various diseases.
- Pure autonomic failure is a sporadic, gradually progressive neurodegenerative disorder characterized by orthostatic hypotension with a tendency for syncope.

- Supine hypertension is found in approximately half of all patients with pure autonomic failure; it may be severe and often complicates treatment of orthostatic hypotension.
- The diagnosis of pure autonomic failure is based on detection of orthostatic hypotension, usually with clinical history or evaluation consistent with widespread autonomic failure.
- Evaluation in pure autonomic failure reveals peripheral involvement with decreased uptake on cardiac functional imaging and low levels of supine norepinephrine that have minimal to no increase upon standing.
- A subset of patients with pure autonomic failure phenoconvert to a synucleinopathy with motor or cognitive impairment, or both. Greater severity and earlier autonomic symptoms with central autonomic failure on autonomic testing predicts conversion to multiple system atrophy (MSA).
- MSA is characterized by autonomic failure with motor symptoms of predominant parkinsonism (MSA-P) or predominant cerebellar ataxia (MSA-C), although parkinsonism and ataxia often overlap later in disease.
- Autonomic dysfunction in MSA tends to occur early and be severe, with orthostatic hypotension that may have concomitant supine hypertension and genitourinary failure characterized by sexual dysfunction and urinary retention leading to incontinence.
- Autonomic function testing in MSA generally shows orthostatic hypotension with central autonomic dysfunction characterized by a large degree of anhidrosis on thermoregulatory sweat test with relatively preserved quantitative sudomotor axon reflex test volumes.
- Characteristic brain MRI findings in MSA include the putaminal rim sign, which is more commonly seen in MSA-P, and the hot cross bun sign, which is more commonly seen in MSA-C.
- Treatment for MSA involves a multidisciplinary team managing autonomic failure, motor features, sleep, and respiratory dysfunction.
- The neuropathologic hallmark of MSA is oligodendroglial cytoplasmic inclusions, which are frequently found in the substantia nigra, basal ganglia, brainstem, cerebellum, and spinal cord.
- The diagnosis of dementia with Lewy bodies (DLB) is based on the presence of dementia, often with early prominent deficits in attention, executive function, and visuoperceptual ability along with core clinical features that include fluctuating cognition, visual hallucinations, rapid eye movement sleep behavior disorder, and parkinsonism. Syncope and severe autonomic dysfunction are supportive clinical features.
- The degree of autonomic failure in DLB is less severe than MSA but more prominent than typically seen in Parkinson disease.
- Constipation, neurogenic bladder, and orthostasis are common nonmotor symptoms in Parkinson disease reflecting autonomic dysfunction.
- Orthostatic hypotension is found in 30% to 50% of all patients with Parkinson disease, and treatment with dopaminergic medications may contribute to blood pressure drop.
- Thermoregulatory dysfunction in Parkinson disease may manifest as heat or cold intolerance, intermittent hyperhidrosis episodes, and hypohidrosis.
- The Lewy body disorders typically have early and more extensive peripheral α-synuclein involvement, although central involvement of autonomic structures likely contributes to orthostatic hypotension in DLB.

Article 6: Postural Tachycardia Syndrome and Neurally Mediated Syncope

Jeremy K. Cutsforth-Gregory, MD. Continuum (Minneap Minn). February 2020; 26 (1 Autonomic Disorders):93–115.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the diagnosis and management of the most common disorders of orthostatic intolerance: postural tachycardia syndrome (POTS) and neurally mediated syncope.

RECENT FINDINGS:

POTS is a heterogeneous syndrome caused by several pathophysiologic mechanisms that may coexist (limited autonomic neuropathy, hyperadrenergic state, hypovolemia, venous pooling, joint hypermobility, deconditioning). Neurally mediated syncope occurs despite intact autonomic reflexes. Management of orthostatic intolerance aims to increase functional capacity, including standing time, performance of daily activities, and exercise tolerance. Nonpharmacologic strategies (fluid and salt loading, physical countermaneuvers, compression garments, exercise training) are fundamental for patients with POTS, occasionally complemented by medications to raise blood pressure or slow heart rate. Neurally mediated syncope is best managed by recognition and avoidance of triggers.

SUMMARY:

Significant negative effects on quality of life occur in patients with POTS and in patients with recurrent neurally mediated syncope, which can be mitigated through targeted evaluation and thoughtful management.

KEY POINTS

- The normal response to standing, via activation of the baroreflex, is a small fall in systolic blood pressure, a small rise in diastolic blood pressure, and a small rise in heart rate.
- Orthostatic intolerance is the inability to tolerate upright posture because of symptoms of cerebral hypoperfusion or sympathetic activation, or both, which are relieved with recumbency.
- Postural tachycardia syndrome (POTS) is the most prevalent form of orthostatic intolerance.
- POTS is defined as a symptomatic and sustained heart rate increment of 30 beats/min or more within 10 minutes of standing or head-up tilt in the absence of orthostatic hypotension; the standing heart rate is often 120 beats/min or higher. For individuals 12 to 19 years of age, the required increment is at least 40 beats/min.
- The main POTS mechanisms are impaired sympathetically mediated vasoconstriction in the lower limbs (neuropathic POTS), excessive cardiac sympathoexcitatory responses (hyperadrenergic POTS), volume dysregulation, joint hypermobility, and physical deconditioning.
- A postinfectious autoimmune process is likely in many patients with POTS, as evidenced by an antecedent illness of presumed viral etiology in approximately one-half and organ-specific autoantibodies in up to one-third.
- Hyperadrenergic POTS is characterized by episodes of tachycardia, sweating, and hypertension that can be triggered by upright posture, physical activity, and emotional stimuli, and episodes may even occur during sleep.
- Most patients with POTS have some degree of hypovolemia, with low plasma and total blood volumes resulting in reduced cardiac preload upon standing.
- A sizable minority of patients with POTS have hypermobile joints consistent with an underlying disorder of the connective tissue matrix, most commonly Ehlers-Danlos syndrome hypermobility type.
- Many patients with POTS have additional chronic conditions, including inappropriate sinus tachycardia, migraine and other headaches, visceral hypersensitivity, gastrointestinal dysmotility, chronic fatigue, insomnia, and fibromyalgia.
- The syndrome of inappropriate sinus tachycardia is defined as a sinus heart rate higher than 100 beats/min at rest, with a mean 24-hour heart rate higher than 90 beats/min, accompanied by bothersome palpitations.
- Patients with suspected POTS should undergo comprehensive cardiac and neurologic examinations, supine and standing heart rate and blood pressure measurement, and a 12-lead ECG.
- The primary objective of POTS management is to improve patients' functional capacity (ie, increase the time that they can stand, perform daily activities, and exercise).
- Physical counterpressure maneuvers for patients with POTS aim to counteract venous pooling and include crossing the legs, bending forward at the waist, rising on toes, slow marching in place, and squatting.

- Compression garments for patients with POTS should cover the abdomen and thighs.
- Patients with POTS should engage in a graduated exercise program that includes both endurance and resistance training.
- Medications should be considered for treatment of POTS only after nonpharmacologic strategies have been implemented.
- Beta-blockers are probably most beneficial for patients with hyperadrenergic POTS.
- Pyridostigmine reduces orthostatic tachycardia and improves chronic symptoms of POTS without aggravating supine hypertension.
- Syncope is a transient loss of consciousness and postural muscle tone due to global cerebral hypoperfusion, with relatively abrupt onset and spontaneous, complete, and relatively prompt recovery.
- Syncope can occur at any age, with the first peak usually occurring in the teen or young adult years and a second peak near 80 years of age. Syncope at younger age is usually the neurally mediated type.
- The typical episode of neurally mediated syncope can be divided into prodrome and unresponsive phases. The prodrome can be of variable duration, generally less than 1 minute, and is recognized or later recalled by only two-thirds of patients.
- When syncope occurs abruptly without any prodrome, the clinician should be suspicious for ventricular arrhythmia.
- Prolonged unresponsiveness in alleged syncope should raise concern for epilepsy, vertebrobasilar insufficiency, subarachnoid hemorrhage, traumatic brain injury, hypoglycemia, drug or medication intoxication, or psychogenic pseudosyncope.
- Convulsive syncope can be distinguished from an epileptic seizure by the number of myoclonic jerks: fewer than 10 in syncope, more than 20 in seizures.
- Neurally mediated syncope is associated with one or both of two hemodynamic patterns. The vasodepressor pattern is an abrupt fall in blood pressure that occurs beyond the time cutoff (3 minutes) for orthostatic hypotension; the cardioinhibitory pattern is a pronounced bradycardia of fewer than 40 beats/min or asystole of more than 3 seconds.
- Vasovagal syncope may be a protective reflex response to excessive sympathetic activity, to which the heart is particularly prone.
- Prodromal symptoms typically occur when mean blood pressure falls below 60 mm Hg. Unresponsiveness occurs below 50 mm Hg at heart level, corresponding to 30 mm Hg cerebral arterial pressure.
- In contrast to postexertional syncope, which is a benign reflex syncope, syncope during exertion points toward ventricular arrhythmias, atrioventricular block, hypertrophic obstructive cardiomyopathy, aortic stenosis, or subclavian steal syndrome.
- Patients with psychogenic pseudosyncope often deny any prodrome, report longer periods of apparent loss of consciousness (up to several minutes), and may be suggestible. A definite diagnosis of psychogenic pseudosyncope is made by recording normal blood pressure, heart rate, and EEG during an episode.
- Tilt-table test results must be interpreted with caution, as both false negatives and false positives are common.
- Neurally mediated syncope, especially vasovagal and the various situational syncopes, is most effectively managed by recognition and avoidance of triggers.

Article 7: Sweating Disorders

Elizabeth A. Coon, MD; William P. Cheshire Jr, MD, FAAN. Continuum (Minneap Minn). February 2020; 26 (1 Autonomic Disorders):116–137.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews disorders of sweating, including hyperhidrosis and anhidrosis due to central or peripheral autonomic nervous system causes.

RECENT FINDINGS:

Disorders of thermoregulation and sweating may manifest with hyperhidrosis or hypohidrosis/anhidrosis. Primary disorders of hyperhidrosis may significantly impact quality of life yet tend to be benign. Many sweating disorders present with compensatory hyperhidrosis due to areas of anhidrosis. Anhidrosis may occur due to either central or peripheral damage to the autonomic nervous system. The thermoregulatory control of sweating involves central pathways from the hypothalamus to the brainstem and then spinal cord as well as projections to peripheral structures, including the sympathetic chain ganglia, peripheral nerves, and eccrine sweat glands. Disruption at any point of this pathway may lead to impaired sweating. Characterization of sweating dysfunction helps localize different autonomic disorders to guide diagnosis and may allow for evaluation of treatment effect.

SUMMARY:

Sweating dysfunction manifests in myriad ways, including essential hyperhidrosis, complete anhidrosis with heat intolerance, and compensatory hyperhidrosis due to anhidrosis, and often indicates involvement of underlying central or peripheral autonomic dysfunction.

KEY POINTS

- Warm-sensitive neurons in the preoptic nucleus of the hypothalamus respond to subtle changes in core temperature to invoke a sympathetic nervous system response of generalized sweating, vasodilation, and hyperpnea triggering radiant and evaporative heat loss.
- Innervation of sweat glands is predominantly by unmyelinated C fibers to cholinergic M_3-type receptors.
- The highest density of sweat glands involved in thermoregulation is on the forehead, followed by the upper limbs and then the trunk and lower limbs, whereas acral (hands and feet) sweating is chiefly triggered by emotional stimuli.
- Hyperhidrosis is defined as excessive sweating beyond the need to maintain core temperature; it tends to be more socially limiting than medically worrisome.
- Medications frequently cause hyperhidrosis, with common offenders including selective serotonin reuptake inhibitors, opioids, and prostaglandin inhibitors.
- Shapiro syndrome is characterized by episodic hypothermia and hyperhidrosis with abnormalities of midline structures, such as agenesis of the corpus callosum.
- Paroxysmal sympathetic hyperactivity after acquired brain injury is characterized by paroxysmal sympathetic overreactivity leading to diaphoresis, fever, flushing, shivering, hypertension, tachypnea, tachycardia, and, occasionally, motor involvement.
- Primary focal hyperhidrosis frequently involves palms and soles and may significantly interfere with quality of life.
- Treatment options for primary focal hyperhidrosis include topical agents, systemic medications, iontophoresis, or endoscopic thoracic sympathotomy.
- Cold-induced sweating syndrome is a genetic disorder characterized by profuse truncal sweating when exposed to cold with paradoxical anhidrosis when exposed to heat.
- Autonomic dysreflexia may occur in patients with spinal cord injuries with lesions above T6 and is characterized by hypertension with concomitant bradycardia and facial flushing with profuse sweating above the level of the spinal cord lesion.
- Treatment for autonomic dysreflexia involves fast-acting antihypertensives with urgent identification of the trigger, such as bowel or bladder distension or skin irritation.
- Harlequin syndrome is characterized by hemifacial flushing and hyperhidrosis contralateral to sympathetic denervation and may include Horner syndrome when oculosympathetic fibers are involved.
- Patients with multiple system atrophy typically have a high degree of anhidrosis, which is predominantly due to a central/preganglionic lesion.

- Patients with Parkinson disease typically have mild distal anhidrosis that is peripheral in origin, whereas patients with dementia with Lewy bodies also show a peripheral pattern of sweat loss that is to a greater degree than in patients with Parkinson disease.
- Patients with autoimmune autonomic ganglionopathy may manifest a high degree of anhidrosis, which tends to increase distally; the degree of autonomic failure may correlate with the antibody titer.
- Familial dysautonomia is characterized by episodes of orthostatic hypotension or hypertension in addition to profuse sweating related to underlying neuropathy and central sudomotor pathway hyperexcitability.
- Diabetic autonomic neuropathy is the most common cause of autonomic neuropathy and may manifest as length-dependent sweat loss and focal areas of anhidrosis or lead to global anhidrosis when severe.
- Chronic idiopathic anhidrosis is characterized by heat intolerance and widespread anhidrosis in the absence of accompanying autonomic failure; the pattern of anhidrosis may be preganglionic or postganglionic.

Article 8: Autonomic Hyperactivity

Alejandro A. Rabinstein, MD, FAAN. Continuum (Minneap Minn). February 2020; 26 (1 Autonomic Disorders):138–153.

ABSTRACT

PURPOSE OF REVIEW:

Autonomic hyperactivity is a relatively common consequence of severe acute brain injury and can also be seen with spinal cord and peripheral nerve disorders. This article reviews basic pathophysiologic concepts regarding autonomic hyperactivity, its various forms of clinical presentation, and practical management considerations.

RECENT FINDINGS:

Paroxysmal sympathetic hyperactivity is most common after traumatic brain injury but can also occur after other forms of severe acute diffuse or multifocal brain injury. Formal criteria for the diagnosis and severity grading of paroxysmal sympathetic hyperactivity have now been proposed. A growing body of literature is beginning to elucidate the mechanisms underlying this disorder, but treatment remains based on observational data. Our mechanistic understanding of other distinct forms of autonomic hyperactivity, such as autonomic dysreflexia after traumatic spinal cord injury and dysautonomia after Guillain-Barré syndrome, remains rudimentary, yet clinical experience shows that their appropriate management can minimize the risk of serious complications.

SUMMARY:

Syndromes of autonomic hyperactivity can result from injury at all levels of the neuraxis. Much more research is needed to refine our understanding of these disorders and guide optimal management decisions.

KEY POINTS

- Recognition of autonomic hyperactivity is important because it can provoke dangerous complications.
- Injury at multiple levels of the neuraxis can cause autonomic hyperactivity.
- Damage causing disconnection of sympathetic centers from descending inhibitory pathways and maladaptive changes in the spinal cord can result in excessive sympathetic responses.
- Sympathetic signs predominate in most patients with central autonomic hyperactivity.
- Autonomic hyperactivity may cause exaggerated responses to various medications and therefore puts patients at risk of serious iatrogenic complications.
- Careful attention can reliably distinguish paroxysmal sympathetic hyperactivity caused by brain injury from adrenergic manifestations of sepsis, pulmonary embolism, or seizures.

- Paroxysmal sympathetic hyperactivity can be seen in up to one-third of patients with severe traumatic brain injury.
- Standardized criteria have been proposed for the diagnosis and severity assessment of paroxysmal sympathetic hyperactivity.
- Young age and coma are associated with higher risk of paroxysmal sympathetic hyperactivity.
- Deep brain lesions affecting connecting tracts, as seen with diffuse axonal injury, are commonly seen in patients with paroxysmal sympathetic hyperactivity.
- Management of paroxysmal sympathetic hyperactivity includes minimizing stimulation and using abortive (eg, morphine) and preventive (eg, gabapentin and propranolol) medications.
- Paroxysmal sympathetic hyperactivity can negatively affect the outcome of traumatic brain injury.
- Although primarily a complication of traumatic brain injury, paroxysmal sympathetic hyperactivity can occur after other forms of acute brain injury, most notably global anoxia-ischemia.
- Autonomic dysreflexia occurs after severe spinal cord injury at the cervical or upper thoracic (T5 and above) levels.
- Episodes of autonomic dysreflexia are often triggered by urinary retention, fecal impaction, or nursing care.
- Sudden hypertension is the most common and most serious manifestation of autonomic dysreflexia.
- Close attention to potential triggers is the key element in the management of autonomic dysreflexia.
- The clinical presentation of dysautonomia in Guillain-Barré syndrome is unpredictable and potentially life-threatening.
- Rapid fluctuations in blood pressure and heart rate, urinary retention, and adynamic ileus are the most prevalent expressions of dysautonomia in Guillain-Barré syndrome.
- Dysautonomic signs in patients with Guillain-Barré syndrome are best managed conservatively to prevent iatrogenic complications.

Article 9: Management of Orthostatic Hypotension

Jose-Alberto Palma, MD, PhD; Horacio Kaufmann, MD, FAAN. Continuum (Minneap Minn). February 2020; 26 (1 Autonomic Disorders):154–177.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the management of orthostatic hypotension with emphasis on neurogenic orthostatic hypotension.

RECENT FINDINGS:

Establishing whether the cause of orthostatic hypotension is a pathologic lesion in sympathetic neurons (ie, neurogenic orthostatic hypotension) or secondary to other medical causes (ie, non-neurogenic orthostatic hypotension) can be achieved by measuring blood pressure and heart rate at the bedside. Whereas fludrocortisone has been extensively used as first-line treatment in the past, it is associated with adverse events including renal and cardiac failure and increased risk of all-cause hospitalization. Distinguishing whether neurogenic orthostatic hypotension is caused by central or peripheral dysfunction has therapeutic implications. Patients with peripheral sympathetic denervation respond better to norepinephrine agonists/precursors such as droxidopa, whereas patients with central autonomic dysfunction respond better to norepinephrine reuptake inhibitors.

SUMMARY:

Management of orthostatic hypotension is aimed at improving quality of life and reducing symptoms rather than at normalizing blood pressure. Nonpharmacologic measures are the key to success. Pharmacologic options include volume expansion with fludrocortisone and sympathetic enhancement with midodrine, droxidopa, and norepinephrine reuptake inhibitors. Neurogenic supine hypertension complicates management of orthostatic hypotension and is primarily ameliorated by avoiding the supine position and sleeping with the head of the bed elevated.

KEY POINTS

- Diagnosing orthostatic hypotension requires blood pressure measurements. The presence of orthostatic intolerance is not sufficient or necessary to diagnose orthostatic hypotension.
- Orthostatic hypotension is very common in the elderly, usually due to drug effects, volume depletion, or cardiovascular deconditioning.
- Neurogenic orthostatic hypotension is a feature of neurologic disorders affecting sympathetic pathways, including diabetes mellitus, neurodegenerative synucleinopathies, and amyloid neuropathies.
- Exercise, meals (postprandial hypotension), prolonged bed rest (physical deconditioning), and hot and humid environments typically worsen symptoms of neurogenic orthostatic hypotension.
- Patients with cognitive impairment may not accurately identify symptoms of orthostatic hypotension, despite low blood pressure when standing.
- A heart rate increase of at least 0.5 beats/min for each 1 mm Hg fall in systolic blood pressure (ΔHR/ΔSBP ratio ≥0.5 beats per minute/mm Hg) is sensitive and specific to diagnose non-neurogenic orthostatic hypotension.
- Treatment of orthostatic hypotension should be geared to the patients' symptoms and their impact on daily function rather than a target blood pressure.
- The initial treatment of orthostatic hypotension focuses on nonpharmacologic measures first: removing offending medications, increasing salt and fluid intake, using compression garments, and instituting physical maneuvers and exercise.
- Drugs that reduce intravascular volume (eg, diuretics) or induce vasodilatation (eg, α-adrenergic blockers, nitrates, phosphodiesterase-5 inhibitors, tricyclic antidepressants, centrally acting α-adrenergic agonists) exacerbate orthostatic hypotension and worsen symptoms; thus, they should be reduced or discontinued.
- In patients with orthostatic hypotension, anemia should be investigated and treated.
- Because carbohydrate-rich meals trigger insulin, a potent vasodilator, patients with neurogenic orthostatic hypotension should reduce carbohydrate content, eat smaller and more frequent meals, and choose low glycemic index carbohydrates.
- Bolus water drinking produces a marked, albeit short-lived, increase in blood pressure in patients with neurogenic orthostatic hypotension.
- Waist-high compression stockings are effective to increase blood pressure in patients with neurogenic orthostatic hypotension, although compliance is very low. Elastic abdominal binders are a good alternative.
- Sleeping with the head of the bed raised 30 to 45 degrees reduces nocturnal hypertension, thus decreasing natriuresis, which, in turn, prevents volume depletion overnight and improves orthostatic tolerance the next morning.
- When medications for neurogenic orthostatic hypotension are used, patients should be taught to avoid the flat position, sleep with the head of the bed raised 30 to 45 degrees, and measure their own blood pressure.
- Determining the site of the autonomic lesion (central versus peripheral) in patients with neurogenic orthostatic hypotension has important therapeutic implications. Patients with central autonomic dysfunction (ie, decentralization) have a more pronounced pressor response to norepinephrine reuptake inhibitors, whereas patients with peripheral autonomic dysfunction (ie, denervation) have a more pronounced pressor response to norepinephrine enhancers and agonists.

- For patients who still remain symptomatic despite nonpharmacologic measures, stepwise pharmacologic treatment begins with low-dose fludrocortisone (0.1 mg/d), particularly in patients with volume depletion.
- Frequently used fludrocortisone dosages range from 0.05 mg/d to 0.2 mg/d. There is little benefit in increasing fludrocortisone to dosages higher than 0.2 mg/d. Common short-term side effects include hypokalemia; long-term side effects include left ventricular hypertrophy and renal failure.
- In patients with anemia of chronic disease and orthostatic hypotension, subcutaneous recombinant human erythropoietin increases blood pressure and improves orthostatic tolerance.
- When starting droxidopa, a careful titration is required to identify the best dose for each patient and prevent excessive supine hypertension.
- Treatment with norepinephrine reuptake inhibition is emerging as a potentially effective option for patients with neurogenic orthostatic hypotension, particularly those with autonomic dysfunction from damage to the central nervous system (eg, decentralization).
- Pyridostigmine alone has little effect to increase blood pressure. It appears to have synergistic effects when combined with midodrine or atomoxetine.
- Neurogenic supine hypertension is best treated with postural measures, ie, avoiding the flat position and sleeping with the head of the bed raised 30 to 45 degrees with the help of an electric bed or mattress. In patients with refractory supine hypertension and high risk of organ damage, short-acting antihypertensives at bedtime might be considered.

Article 10: Lower Urinary Tract and Bowel Dysfunction in Neurologic Disease

Jalesh N. Panicker, MD, DM, FRCP; Ryuji Sakakibara, MD, PhD, FAAN. Continuum (Minneap Minn). February 2020; 26 (1 Autonomic Disorders):178–199.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of the clinical presentation, investigations, and treatment options for lower urinary tract and bowel dysfunction in patients with neurologic diseases.

RECENT FINDINGS:

The site of the neurologic lesion influences the pattern of lower urinary tract dysfunction. Antimuscarinic agents are first-line management for urinary incontinence; however, the side effect profile should be considered when prescribing them. β_3-Receptor agonists are a promising alternative oral medication. Botulinum toxin injections into the detrusor have revolutionized the management of neurogenic detrusor overactivity.

Bowel dysfunction commonly presents as constipation and fecal incontinence. Gastrointestinal emergencies may arise, including intestinal pseudoobstruction, intussusception, volvulus, and stercoral ulcer (ulcer of the colon due to pressure and irritation resulting from severe, prolonged constipation). Bowel function tests in neurologic patients often show a combination of slow transit and anorectal dysfunction. Management for slow transit constipation includes bulking agents, softening agents, yogurt/probiotics, and prokinetic agents. Suppositories, botulinum toxin injections, and transanal irrigation are options for managing anorectal constipation.

SUMMARY:

Functions of the lower urinary tract and bowel are commonly affected in neurologic disease. Neurologists play an important role in assessing lower urinary tract and bowel symptoms in their patients and planning treatment strategies, often in collaboration with specialist teams.

KEY POINTS

- The site of the neurologic lesion influences the pattern of lower urinary tract dysfunction. Symptoms of an overactive bladder (urinary urgency, increased daytime frequency, nocturia, and, often, incontinence) are the most common presentation.
- The risk of developing upper urinary tract damage is considerably lower in patients with slowly progressive nontraumatic neurologic disorders than in those with spinal cord injury or spina bifida.
- Antimuscarinic agents are the first-line management of urinary incontinence; however, their side effect profile and impact on anticholinergic burden should be considered when prescribing in patients who are susceptible.
- β_3-Receptor agonists are a promising new oral treatment for managing storage symptoms in patients with neurologic diseases.
- IntradetrusorOnabotulinumtoxin A injections are a highly effective and minimally invasive treatment for storage dysfunctions.
- Percutaneous tibial nerve stimulation is a minimally invasive option for managing patients with mild to moderate overactive bladder symptoms and is associated with few adverse effects.
- The postvoid residual should be routinely measured during the workup of every patient with neurologic disease reporting lower urinary tract symptoms.
- A high postvoid residual is important to recognize as it may contribute to storage (overactive bladder) symptoms and can predispose to recurrent urinary tract infections.
- Bowel dysfunction is common in patients with neurologic diseases.
- Bowel dysfunction not only affects patients' quality of life but may also lead to gastrointestinal emergencies.
- Bowel dysfunction is often a combination of slow transit–type constipation (slowed colonic transit time, loss of peristaltic contractions) and anorectal-type constipation (weak strain, anismus on defecation, and large postdefecation residuals).
- Bowel dysfunction should be managed with a combination of diet, exercise, and drugs.
- Collaboration between neurologists, urologists, and gastroenterologists is recommended to maximize the quality of life of patients with neurologic diseases who have lower urinary tract or bowel dysfunction.

Article 11: Skin Biopsy in Evaluation of Autonomic Disorders

Christopher H. Gibbons, MD, MMSc, FAAN; Ningshan Wang, MD, PhD; Jee Young Kim, MD; Marta Campagnolo, MD; Roy Freeman, MBChB. Continuum (Minneap Minn). February 2020; 26 (1 Autonomic Disorders):200–212.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an up-to-date assessment of the role of skin biopsy in the evaluation of autonomic disorders. The standard methodology for completing a skin biopsy, the anatomic structures of interest detected within a skin biopsy, and the disease states in which skin biopsies may provide valuable information are reviewed.

RECENT FINDINGS:

Several recent advances in the studies of hereditary amyloidosis and the various degenerative synucleinopathies have demonstrated that simple skin biopsies can provide valuable pathologic evidence of neurologic disease. In addition to diagnosis of the underlying disorder, skin biopsies provide a quantitative structural measurement of the associated autonomic damage.

SUMMARY:

Skin biopsies are making great inroads into the study of autonomic and peripheral nerve disorders. Complex immunohistochemical staining protocols are challenging to complete, but the rich data derived from these studies in the diagnosis and monitoring of different disease states suggest that the role of skin biopsies in the study of the autonomic nervous system will continue to expand in the years to come.

KEY POINTS

- Standard punch biopsies 3 mm in diameter are used to obtain sections of tissue, generally from the distal leg, distal thigh, and proximal thigh sites.
- Although biopsies are frequently used to evaluate for small fiber neuropathy by quantifying the nerve fibers within the epidermis, autonomic innervation is all contained within the deeper dermal tissue.
- Pilomotor nerve fibers predominantly contain sympathetic adrenergic innervation.
- Sweat glands contain sympathetic cholinergic (also known as sudomotor) nerve fibers. Quantitation of sweat gland density without reporting the area of sweat glands measured is a common error by laboratories and limits the utility of this technique.
- In patients with hereditary amyloidosis, skin biopsy can provide quantitative assessment of neuropathy severity, but it can also provide pathologic confirmation of disease by detection of the presence of amyloid through Congo red staining.
- Skin biopsies are used in research studies to measure phosphorylated α-synuclein to aid in confirming a diagnosis of an α-synucleinopathy such as Parkinson disease, multiple system atrophy, pure autonomic failure, or Lewy body dementia.

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BEHAVIORAL NEUROLOGY AND PSYCHIATRY

ARTICLE 1: CLINICAL APPROACH TO COGNITIVE AND NEUROBEHAVIORAL SYMPTOMS

Meredith Wicklund, MD, FAAN. Continuum (Minneap Minn). December 2021; 27 (6 Behavioral Neurology and Psychiatry):1518–1548.

ABSTRACT

PURPOSE OF REVIEW:

This article provides a framework for the approach to patients with cognitive or neurobehavioral concerns.

RECENT FINDINGS:

Recent advances in structural neuroimaging, functional neuroimaging, and disease biomarkers have greatly expanded knowledge of brain-behavior relationships, neural networks and functional connectivity, and pathophysiologic processes leading to cognitive and neurobehavioral disorders. However, any one of these studies is subject to misinterpretation if not applied in the appropriate clinical context.

SUMMARY:

A systematic approach to the history and examination in patients with cognitive and neurobehavioral symptoms is important in marrying clinical assessments with contemporary diagnostic studies and treatments.

KEY POINTS

- History should be obtained from both the patient and a collateral source who knows the patient well because patients with cognitive and behavioral symptoms may not be able to provide an accurate history.
- Age at onset of the first symptom aids in determining the differential diagnosis because of varying prevalence of diseases in different age groups.
- Education, occupational history, native language, and cultural factors are critical variables to be obtained for interpretation of the mental status examination.
- To develop realistic and appropriate interventions for both the patient and caregiver, the clinician should inquire about the physical, financial, and psychological impact of the patient's illness on family and caregivers and the capacity of those involved to provide practical and psychological support.

- The clinician should query about history of other neurologic disorders (eg, epilepsy, multiple sclerosis, stroke), abnormal movements, traumatic brain injury, and cerebrovascular risk factors (eg, diabetes, hypertension, heart disease) and supplement with review of the electronic medical record, when possible.
- Many patients are unaware of the deleterious cognitive effects of many over-the-counter medications, particularly sleep aids, and do not report use of these medications unless directly asked.
- It is helpful to obtain specific examples from the informant about the presenting symptoms because patients and caregivers may describe any cognitive symptom as "memory loss" or ascribe subtle, early changes to normal aging or psychosocial stressors.
- The clinician should obtain history regarding the first symptom noted, mode of onset (acute, subacute, or chronic), and pace of change (transient, static, progressive, or fluctuating).
- The presence of symptoms in each cognitive and neuropsychiatric and behavioral domain helps define the cognitive profile and aid in the differential diagnosis.
- Obtaining functional capacity of the patient aids in defining the stage of illness, identifying needs for neurorehabilitation, addressing safety concerns, and assessing caregiver burden.
- The mental status examination begins with observation of the patient's appearance and behavior, including assessment of arousal, motivation, mood and affect, thought content and processes, judgment, and insight.
- Screening neurocognitive tests are helpful in obtaining a basic understanding of the patient's cognitive functioning in a short amount of time, but they have inherent weaknesses and should not be used as the sole basis for assessing cognitive dysfunction.
- Attention is a necessary substrate for intact performance in all other cognitive domains; thus, interpretation of performance in other cognitive domains is limited if attention is impaired.
- Working memory is a function of the attentional matrix and not the memory systems. A patient with severe amnesia can have intact working memory.
- Assessment of fluency should be distinguished from difficulties with word finding.
- Deficits in naming show a marked frequency effect; even patients who have severe anomia are able to name familiar, high-frequency objects such as a pen.
- Errors of substitution and omission in repeating longer phrases can be due to deficits in working memory and not necessarily language deficits. Errors can also result from social and cultural factors or from assessing repetition in the non-native language of the patient.
- Individuals with a typical amnestic syndrome display retrograde memory loss with a temporal gradient; events that occurred closer in time to the onset of the memory loss are recalled least well, whereas more remote events are better recalled.
- In assessing delayed recall, the clinician should assess both freely recalled words as well as recognition or cued recall. Individuals who are truly amnestic are impaired on both free and recognition recall, whereas individuals with disorders of memory retrieval have impairment with free recall but no impairment with recognition or cued recall.
- Often, the history obtained from the informant regarding functional abilities such as to plan events and outings, operate appliances and gadgets, and multitask can be as informative, or more so, about the patient's executive function than a formal examination can be.
- Semantic fluency is often better than letter fluency because of the contextual organization offered by the semantic category that is lacking in letter fluency, but semantic fluency will be disproportionately impaired in individuals with semantic naming deficits.
- The cognitive profile is determined by contrasting domains of primary impairment with those in which test failure is secondary to another factor and those in which performance is normal.
- Individuals with primary language impairment tend to show widespread impairment across many cognitive domains, with a discrepancy noted for relative preservation of tasks that are less heavily influenced by verbal instructions and responses.
- Although computerized assessments can be an additional tool to evaluate a patient's mental status, they cannot replace the clinician's examination in its entirety.

- Features of the general neurologic examination can provide important clues as to the etiology of the presenting cognitive or neurobehavioral symptoms.
- Parkinsonism is present in many cognitive and neurobehavioral disorders, but the clinician should not overinterpret subtle findings, such as stooped posture and general slowness of movement, that can be seen in aging individuals.
- Although traditionally thought to signify frontal lobe dysfunction, frontal release signs have little diagnostic value and can be seen in healthy older adults.
- Neuropsychological evaluation represents an extension of the examiner's mental status examination. The goal is to support, or refute, the hypotheses generated by the examiner thus far to aid in refining the differential diagnosis.
- Structural brain imaging with either head CT or MRI is needed in evaluation of cognitive and neurobehavioral disorders. Brain MRI is generally preferred given the greater sensitivity for detection of atrophy patterns, white matter diseases, lacunes, and microhemorrhages.

ARTICLE 2: LANGUAGE AND APHASIAS

Stephen E. Nadeau, MD. Continuum (Minneap Minn). December 2021;
27 (6 Behavioral Neurology and Psychiatry):1549–1561.

ABSTRACT

PURPOSE OF REVIEW:

This article reveals how it is possible for a brain composed of 100 billion highly interconnected, lipid-encased, reticular electrochemical devices to support complex functions such as language and how language disorders can be understood as a reflection of degradation of one or more domains of knowledge.

RECENT FINDINGS:

Ongoing research, building on landmark work regarding parallel distributed processing (PDP), provides the basis for understanding cognitive functions as a manifestation of the activity of populations of millions or billions of neurons in various highly interconnected networks. Population encoding networks have the following intrinsic properties that provide an orderly explanation for normal and degraded language: (1) a capacity for settling into stable "attractor" states; (2) processing occurs in and knowledge (long-term memories) is stored in exactly the same network; (3) a capacity for incorporating statistical regularities of experience, frequency, and age of acquisition; (4) support of content-addressable memory; and (5) graceful degradation, such that lesions increase the probability of errors but do not fundamentally transform network operations. Knowledge in parallel distributed processing networks resides in the strength of connections between units (synapses in the brain). Aphasia, whether stemming from stroke or dementing disorders, can be understood in terms of the degradation of one or more domains of knowledge.

SUMMARY:

Understanding the brain as a population encoding machine incorporating vast interconnectivity provides an orderly explanation for language function, both normal and abnormal.

KEY POINTS

- Our current understanding of language function is fully congruent with the discoveries of the greats of the 19th century, including Wernicke and Lichtheim and their model, and the subsequent work of Norman Geschwind.

- The cross-linguistic aphasia study of Elizabeth Bates and her colleagues has been instrumental to our understanding of the commonalities of all human languages. It clearly established that, although neural networks provide the scaffold for cognitive function, the actual knowledge stored in these networks derives from learning through experience.
- The study of semantic dementia by John Hodges and his colleagues at Cambridge University provided the foundations of our understanding of the neural organization of our knowledge of the world and the objects in it.
- The vast research on parallel distributed processing, in large part deriving from the seminal publication of McClelland and Rumelhart in 1986, has helped us understand how a brain composed of 100 billion neurons enables cognitive functions.
- Representations in the brain are encoded as patterns of activity involving very large numbers of highly interconnected neurons, hence the term *population encoding*.
- Parallel distributed processing models typically employ simple mathematics that, while certainly not capable of capturing all of the subtleties of cortical neural network function, enable these models to account for the key properties of cognition.
- Neural activity in neural networks naturally settles into minimal energy states known as *attractor states*.
- Neural processing consists of the process of settling into constellations of linked attractor states, each state corresponding to a component of the meaning of the concepts in play (eg, the visual and limbic representations of "dog").
- In a parallel distributed processing system, processing occurs in and knowledge (long-term memories) is stored (as connection strengths) in exactly the same network.
- Parallel distributed processing systems have the capacity for incorporating statistical regularities of experience, frequency of experience, and age of acquisition.
- Parallel distributed processing systems support content-addressable memory. Thus, a single feature can elicit an entire concept representation, a phenomenon referred to as *pattern completion*.
- When damaged, parallel distributed processing networks tend to exhibit graceful (incremental) degradation rather than catastrophic collapse because the knowledge is distributed throughout the network.
- Most processing in the brain occurs automatically. What is not automatic is largely the province of the frontal lobes.
- Diaschisis corresponds to transient dysfunction of undamaged neurons caused by a sudden loss of afferent input from acutely damaged regions of the brain. Resolution of diaschisis accounts for much of spontaneous recovery from stroke.
- Knowledge is represented as the connection strengths (synaptic weights) between neurons.
- The characteristic patterns of language dysfunction observed in the aphasias reflect degradation of particular domains of language knowledge.
- The simplification of syntax that is characteristic of Broca aphasia reflects loss of knowledge underlying language-specific habits of sequential ordering and modification of concept representations, loss of the ability to modify sentence plans to fit the unique demands of the particular occasion, and degradation of working memory.
- English-speaking patients with Broca aphasia often leave out small words and endings that convey number, person agreement between nouns and verbs, and tense.
- Wernicke aphasia reflects some combination of damage to the association cortices supporting semantic knowledge, the connections between these association cortices and the perisylvian region, and the perisylvian substrate for phonologic sequence knowledge.
- Conduction aphasia is a disorder related purely to damage to the substrate for phonologic sequence knowledge in the left perisylvian cortex.
- Anomic aphasia can be viewed as a form of Wernicke aphasia in which impairment in phonologic sequence knowledge is inapparent and comprehension is relatively spared. Subtle anomic aphasia may be revealed by poor performance on letter and category fluency tests.

- Impaired repetition or poor performance on letter and category fluency tests, indicating M1 or M2 occlusion, might prioritize intravascular thrombectomy in patients with low National Institutes of Health Stroke Scale scores or those incorrectly thought to have lacunar infarctions.
- Patterns of language impairment in dementia, no less than in stroke, reflect degradation of particular domains of knowledge.
- Speech language therapy, without question, is of enormous benefit to patients who have had a stroke but it has not been proven that it restores language knowledge to an extent that contributes to the ability to converse in everyday life.

ARTICLE 3: MEMORY DYSFUNCTION

Roberto Fernandez-Romero, MD, MPH, PhD; D. Malcolm Spica, PhD. Continuum (Minneap Minn). December 2021; 27 (6 Behavioral Neurology and Psychiatry): 1562–1585.

ABSTRACT

PURPOSE OF THE REVIEW:

This article provides a practical overview of the diagnostic process for patients with memory dysfunction through exploration of the anatomic, physiologic, and psychological aspects of human memory.

RECENT FINDINGS:

As updated methods become available to neurologists, the ability to accurately identify and treat patients with memory disorders evolves. An appreciation of current concepts in the anatomic, physiologic, and psychological aspects of memory, combined with a rational application of everyday tools (such as clinical examination, bedside testing, standardized cognitive screening, and formal neuropsychological examination), allows the clinician to identify possible etiologies and track longitudinal changes in functional memory status. Recent findings regarding the interactions of limbic, anterior temporal, primary sensory, parietal, and dorsal prefrontal structures shed new light on the putative classifications of procedural and declarative memory and their subfunctions.

SUMMARY:

An understanding of memory profiles pertaining to registration, encoding, consolidation, storage, and retrieval, as well as methods to assess those functions, facilitates the clinician's identification of underlying pathology and affected cerebral territories. The memory profile must be appreciated in the context of the entire individual, including possible confounds of comorbid conditions, psychiatric disorders, and normal healthy aging.

KEY POINTS

- Working memory retains information for seconds or minutes, usually while that information is relevant to an ongoing task.
- Long-term memory is divided into episodic and semantic. Episodic memory is characterized by the what, where, and when of a particular episode that is being stored and available for later retrieval. Semantic memory involves the retrieval of facts that may be obtained over a period of time and are not associated with a specific life episode.
- The Papez circuit is crucially involved in the processing and transfer of information for long-term storage. Bilateral lesions to any of its components can cause significant episodic memory deficits and predominantly anterograde amnesia. Injury to the hippocampus will also result in temporally graded retrograde amnesia, where information acquired recently before the lesion will be lost, but more remote memories will remain intact.

- The basolateral limbic system is primarily involved with the processing of emotions, but it also plays a role in the assignment of emotional value to experiences, which can modulate their consolidation. Bilateral injury to the basolateral limbic structures can result in varying degrees of memory dysfunction, often associated with other behavioral symptoms such as hypersexuality, hyperorality, and hyperphagia (Kluver-Bucy syndrome).
- Encoding and consolidation is the set of processes that leads to the establishment of long-term memory. Consolidation requires the reprocessing of acquired information over time and is transiently susceptible to amnestic agents, such as interfering stimuli or distractors.
- Consolidation over hours and days is thought to involve sleep. A period of sleep in the hours after the encoding of new information has been shown to prevent rapid forgetting of the newly acquired material. Slow-wave sleep, in particular, may play a critical role in supporting systems consolidation.
- Lesions in the prefrontal cortex may affect free recall with preservation of cued or recognition memory. Retrograde amnesia that equally affects recent and remote events is most commonly seen in functional amnesias. The more common form, wherein the most recent events are also the hardest to recall, is seen in patients with pathology affecting medial temporal lobes such as Alzheimer disease and medial diencephalic lesions.
- Memory cannot be fully evaluated in isolation from other cognitive domains. The type of memory deficits reported in the clinical history and observed during evaluation and testing should be interpreted in the context of other deficits.
- One should focus on the first memory symptom experienced by the patient or observed by family and determine how it has progressed over time.
- If information is readily recalled with cuing, it may be indicative of problems with retrieval, with possibly preserved encoding and consolidation, and may indicate relative sparing of the limbic system.
- Because memory problems rarely occur in isolation, establishing a timeline of both progression and development of other cognitive and neurologic symptoms can greatly aid in establishing a diagnosis. As diseases progress, different conditions begin to overlap from a clinical perspective, but those same conditions may greatly differ in both onset and progression.
- Working memory can be assessed by having the patient perform mental arithmetic or digit span. Frontal lobes, parietal lobes, and subcortical structures are involved in working memory.
- Episodic memory can be evaluated by asking the patient about recent autobiographic events or recent news. Visual memory can be evaluated by hiding objects in the room while the patient is observing and later asking the patient to recall where the items are. Copying a complex figure and redrawing or recognizing after a latency period is another way to test visual memory. Conditions affecting structures in medial temporal lobes and the Papez circuit can show deficits in these tests.
- Semantic memory is evaluated by assessing the patient's fund of knowledge and should be tailored to the patient's cultural and educational background.
- The Montreal Cognitive Assessment (MoCA) allows discrimination of encoding, storage, and retrieval deficits through its use of repeated presentation of memory targets and cued-recall conditions. Intact cued recall or recognition in the context of poor free recall points to retrieval deficits.
- Standardized cognitive screens provide a rapid assessment of the patient's cognitive function but may not be sufficient to support a diagnosis. Because of their relative brevity, cognitive screens are of important practical use in clinical settings and, if repeated at follow-up visits, may provide some measure of cognitive decline. Although the total score is informative regarding normative data, it is the pattern of deficits that is often most useful when considering a differential diagnosis.
- The initial diagnostic workup for memory dysfunction includes laboratory tests, imaging studies, and more comprehensive neuropsychological testing to further assess the pattern and extent of cognitive deficits and possibly establish a baseline for tracking disease progression.
- In cases in which the cause of a memory disorder remains uncertain, more specialized diagnostic studies can be obtained. These may include fludeoxyglucose positron emission tomography (FDG-PET), amyloid PET, and CSF studies.
- Diagnostic tests performed in patients with memory dysfunction should always be interpreted in the context of history, examination findings, and cognitive test results.

- Neuropsychological testing consists of batteries of well-validated tests assessing multiple neurocognitive domains and produces configurations of strengths and weaknesses that form a neuropsychological "fingerprint" for the patient.
- Neuropsychologists consider the patient's effort, validity, and emotional status when interpreting examination data.
- Each neuropsychological evaluation is a "snapshot" of functioning at a particular point in time; conducting an examination at a different point along the disease progression alters the resultant neuropsychological profile.
- Memory dysfunction is never global, rarely selective for one type of memory (episodic, semantic, working memory, or procedural) or memory process (encoding, consolidation, storage, or retrieval), and seldom occurs in isolation from other cognitive domains.
- Alzheimer disease is the most common age-related neurodegenerative dementia. The amnestic phenotype is the most common presentation and is characterized by deficits in anterograde episodic memory, with variable impairments in semantic and working memory. Deficits in other domains may precede memory impairment and invariably develop over the course of the disease.
- Dementia with Lewy bodies is characterized by a combination of several core features that include fluctuating cognition, recurrent and well-formed visual hallucinations, rapid eye movement (REM) sleep behavior disorder, and parkinsonism. Cognitive tests may show deficits in working memory, encoding, and retrieval that improve with cuing.
- Limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE) is characterized by the deposition of abnormal TDP-43 protein in limbic structures. It is highly prevalent in patients older than 80 years of age who develop memory deficits that mimic the amnestic presentation of Alzheimer disease but often without significant involvement of other cognitive domains. Neuropsychological testing may show major deficits in delayed word list recall, with preserved verbal fluency.
- Ischemic lesions caused by small vessel disease can cause cognitive impairments related to interruption of frontal cortical circuits and disruption of cholinergic pathways. Consequently, memory deficits are related to inattention with retrieval deficits that are worse with free recall but improve with cuing and recognition.
- Normal aging involves decreases in free recall, prospective memory, attention, executive control, and processing speed. Preserved functioning in normal aging has been found for procedural memory, vocabulary, recognition memory, temporal sequencing, and aspects of visual analysis.
- In suspected cases of normal cognitive aging, screener test scores that are normal and stable over time should be reassuring. If cognitive screen results are abnormal, trending down over time, or associated with functional decline in activities of daily living, further evaluation with comprehensive neuropsychological testing and brain imaging is recommended.
- As many as 50% of patients presenting for memory impairment have been found to be functioning within normal limits for their age. For those patients demonstrating impairment on standardized memory testing, confounds such as medication effects, sleep deprivation, low effort, and functional causes should be considered.
- Psychogenic memory dysfunction, caused by emotional rather than physiologic factors, is described as "functional amnesia." Such conditions are often induced by extreme stress, interpersonal conflict, or other nonphysical factors.
- Mood disruption from anxiety and depression interferes with memory encoding and retrieval. In such cases, patients tend to perform below premorbid levels for initial recall of target information but then exhibit minimal decay of the information that was encoded on delayed cued-recognition trials. That is, whatever they learn, they keep.

ARTICLE 4: EXECUTIVE DYSFUNCTION AND THE PREFRONTAL CORTEX

David T. Jones, MD; Jonathan Graff-Radford, MD. Continuum (Minneap Minn). December 2021; 27 (6 Behavioral Neurology and Psychiatry):1586–1601.

ABSTRACT

PURPOSE OF REVIEW:

This article summarizes the cognitive and behavioral functions of the prefrontal cortex with an emphasis on executive cognitive functions and the clinical consequences associated with executive dysfunction. The clinical manifestations of lesions to the lateral prefrontal, orbitofrontal, medial prefrontal, and frontopolar cortex are reviewed.

RECENT FINDINGS:

Traditional lesion studies have emphasized the role of a brain region in controlling a cognitive function. With advances in neurology, neuropsychology, and neuroimaging, the participation of the prefrontal cortex in large-scale networks has been established with recognition that cognitive dysfunction can arise not only from a lesion within a network but also from degenerative disease targeting these large-scale, dynamic neural networks. Although executive dysfunction can result from frontal lobe injury, this article highlights the role of distributed processes subserving executive functions. An atypical phenotype of Alzheimer disease has been described that selectively targets parietal-temporal-frontal networks important for core executive functions.

SUMMARY:

Executive function comprises working memory, cognitive flexibility, and inhibition and depends on top-down (ie, goal-driven) control of distributed processes occurring throughout the brain. The exact behavioral output (ie, function) depends on the content of the processes being controlled. Prefrontal cortex regions serve key cognitive functions related to social, emotional, and motivational aspects of behavior. The dorsal lateral prefrontal cortex plays a role in working memory, goal-driven attention, task switching, planning, problem-solving, and novelty-seeking. The ventral lateral prefrontal cortex plays a role in inhibition, response selection, and monitoring; the medial prefrontal cortex in self-knowledge, motivation, emotional regulation, and updating goal-directed behavior; the orbitofrontal cortex in personality, inhibition, and emotional and social reasoning. Although dysexecutive syndromes have been traditionally associated with dorsolateral prefrontal cortex injury, it is now recognized that they can also result from an impaired parietal-temporal-frontal system, which is targeted in a distinct form of atypical Alzheimer disease. This dysexecutive Alzheimer phenotype is characterized by impaired task performance on a wide battery of neuropsychological tests and simple daily tasks that require executive control. In contrast, dysexecutive syndromes more localized to the frontal lobe involve impaired executive control of social, emotional, and motivational aspects of behavior.

KEY POINTS

- **Executive functions, composed of working memory, cognitive flexibility, and inhibition, depend on top-down control of distributed processes occurring throughout the brain and not exclusively in the frontal lobe.**
- **Because of frontostriatal connections, lesions within the basal ganglia, particularly the caudate, can lead to frontal lobe syndromes.**
- **The dorsolateral prefrontal cortex has been implicated in executive function, including planning, goal-directed behavior, and attentional control.**

- The dorsolateral prefrontal cortex is important for working memory or the online maintenance and manipulation of memory.
- The ventrolateral prefrontal cortex functions are lateralized with the right ventrolateral prefrontal cortex subserving spatial attention and response inhibition and left ventrolateral prefrontal cortex subserving language function; therefore, right-sided lesions result in impaired spatial attention and response inhibition, and left-sided lesions are associated with aphasia.
- Orbitofrontal cortex dysfunction has been associated with personality change and impaired social judgment.
- Normal neuropsychological testing can occur with circumscribed frontal lesions, making history-taking critical to the diagnosis.
- The dorsomedial prefrontal cortex, including the anterior cingulate, has been associated with motivation, conflict monitoring, relating actions with value, and updating goal-directed behavior.
- Medial prefrontal cortex lesions involving the anterior cingulate are associated with impairments in motivation (apathy or abulia) and decreased spontaneous speech or movement.
- *Theory of mind* refers to the ability to attribute and understand one's own mental state and the mental states of others.
- The frontopolar cortex is involved in multitasking and metacognition (which involves the ability to imagine the future), reality monitoring, and theory of mind.
- Alzheimer disease can present as a progressive dysexecutive syndrome without significant behavioral symptoms and with characteristic early involvement of the parietal lobe on neuroimaging.
- The young age of onset, nonamnestic presentation, and relative sparing of medial temporal lobe structures can result in patients with dysexecutive Alzheimer disease receiving a delayed diagnosis.

ARTICLE 5: UPPER LIMB APRAXIA

Kenneth M. Heilman, MD, FAAN. Continuum (Minneap Minn). December 2021; 27 (6 Behavioral Neurology and Psychiatry):1602–1623.

ABSTRACT

PURPOSE OF REVIEW:

Limb apraxia is one of the most common and most disabling disorders caused by brain damage. However, apraxia is one of the least recognized disorders associated with cerebral disease. This article discusses the signs and symptoms of, means of testing for, the pathophysiology of, and possible management of upper limb apraxia.

RECENT FINDINGS:

Upper limb apraxia has four major forms: ideomotor, limb-kinetic, conceptual, and ideational. Although recent findings are included in this article, a full understanding of these disorders, including the means of testing, their possible pathophysiology, and the diseases that may cause these disorders, requires that some older literature is also discussed.

SUMMARY:

This article guides clinicians in testing for and diagnosing the different forms of upper limb apraxia, identifying the underlying diseases that may cause apraxia, managing the different forms of the disorder, and possible forms of rehabilitation.

KEY POINTS

- Limb apraxia is one of the most common and most disabling disorders caused by brain damage and can be caused by a stroke, degenerative dementing diseases, and parkinsonian disorders.

- To diagnose apraxia, the inability to perform skilled movements should not be caused by sensory loss or by elemental motor disorders, such as weakness, rigidity, abnormal postures (eg, dystonia), or abnormal movements (eg, tremor, chorea, ballismus, athetosis, myoclonus, or seizures).
- The four major forms of upper limb apraxia are ideomotor, limb-kinetic, conceptual, and ideational, and all four may cause major disability.
- Testing for ideomotor apraxia includes having patients pantomime transitive actions to verbal command, imitate actions, and use actual tools.
- Patients with ideomotor apraxia may make several types of errors, including using a body part as the tool, moving the incorrect joint, incorrectly coordinating joint movements, and the incorrect spatial directing of their actions, as well as timing errors.
- In right-handed people, apraxia of the left hand can be seen with lesions of the corpus callosum; ideomotor apraxia of both upper limbs can be seen with injury to the left inferior parietal lobe, the left supplementary motor and convexity premotor area of the left hemisphere, or the connections between the premotor cortex and the inferior parietal lobe.
- Patients with ideomotor apraxia should not be allowed to perform any activity that can injure themselves or others.
- When possible, patients with apraxia should undergo behavioral training.
- Limb-kinetic apraxia is the loss of the ability to perform deft-dexterous movements of the hands and fingers.
- The two best methods for assessing patients for limb-kinetic apraxia are the coin rotation test and the grooved pegboard test.
- Injury to the corpus callosum can cause limb-kinetic apraxia of the left hand. In right-handed people, a lesion of the premotor cortex or the sensory-motor cortex can cause limb-kinetic apraxia of both hands. Limb-kinetic apraxia can also be caused by diseases that impair basal ganglia function.
- No treatment for limb-kinetic apraxia is well established, but practicing deft movements may be helpful for patients.
- Conceptual apraxia is the loss of mechanical knowledge, including knowledge of needed mechanical alterations, knowledge about the needed tool, and knowledge about possible alternative tools.
- Conceptual apraxia can be seen in patients with strokes of the left hemisphere and is perhaps most likely with anterior temporal lobe lesions. This disorder is also seen with degenerative dementias such as Alzheimer disease and semantic dementia.
- Ideational apraxia is the loss of the ability to correctly sequence the series of actions needed to completely perform a task.
- Ideational apraxia is often associated with frontal-executive dysfunction and may be caused by disorders such as stroke and vascular dementia.
- Upper limb apraxic disorders are common and disabling disorders that should be assessed in all patients with cerebral dysfunction. When upper limb apraxia is present, patients and caregivers should be made aware of the disability and, when possible, treatment should be obtained.

ARTICLE 6: SPATIAL NEGLECT AND ANOSOGNOSIA AFTER RIGHT BRAIN STROKE

A. M. Barrett, MD, FAAN, FANA, FASNR. Continuum (Minneap Minn). December 2021; 27 (6 Behavioral Neurology and Psychiatry):1624–1645.

ABSTRACT

PURPOSE OF REVIEW:

Up to 80% of survivors of right brain stroke leave acute care without being diagnosed with a major invisible disability. Studies indicate that a generic cognitive neurologic evaluation does not

reliably detect spatial neglect, nor does it identify unawareness of deficit after right brain stroke; this article reviews the symptoms, clinical presentation, and management of these two cognitive disorders occurring after right brain stroke.

RECENT FINDINGS:

Stroke and occupational therapy practice guidelines stress a quality standard for spatial neglect assessment and treatment to reduce adverse outcomes for patients, their families, and society. Neurologists may attribute poor outcomes associated with spatial neglect to stroke severity. However, people with spatial neglect are half as likely to return to home and community, have one-third the community mobility, and require 3 times as much caregiver supervision compared with similar stroke survivors. Multiple randomized trials support a feasible first-line rehabilitation approach for spatial neglect: prism adaptation therapy; more than 20 studies reported that this treatment improves daily life independence. Evidence-based treatment of anosognosia is not as developed; however, treatment for this problem is also available.

SUMMARY:

This article guides neurologists' assessment of right brain cognitive disorders and describes how to efficiently assemble and direct a treatment team to address spatial neglect and unawareness of deficit.

KEY POINTS

- The unsafe behaviors observed as symptoms of spatial neglect can be misattributed to intellectual, reasoning, personality, or generic cognitive problems, which can be devastating to patient dignity.
- Misattribution of spatial neglect symptoms can delay diagnosis of right brain stroke past the window for acute stroke interventions; thus, clinicians should be alert to new spatial bias in patients with stroke risk factors.
- Aiming spatial neglect causes several different movement-related problems. Spatial neglect can cause an ipsilesional turning tendency and disinclination to move in the direction opposite the brain lesion. This symptom is disabling beyond the effects of hemiparesis or awareness problems.
- In-hospital fall risk can be more than 5 times higher in people with spatial neglect than in those without it. Further, active movements that are posturally biased means that the best supervision and guarding by nursing assistants and other personnel may not be effective.
- Line bisection is a simple spatial neglect screening test. Accurate line bisection cannot rule out spatial neglect, but more than 1 cm (0.4 in) of rightward error in bisecting a horizontal line longer than 22 cm (8.7 in) is highly likely to indicate that a patient has spatial neglect.
- Many survivors of stroke benefit from continuing rehabilitation, but most receive no outpatient rehabilitation. Referring patients with spatial neglect for spatial retraining, as endorsed by professional organizations, helps them recover to greater independence and quality of life.
- Ten percent or more of survivors of stroke have chronic spatial neglect years later.
- The degree of unawareness of deficit can be varied; patients with anosognosia may "know what to say," about their deficits and yet they may not believe they are disabled.

ARTICLE 7: BEHAVIORAL AND COGNITIVE ASPECTS OF CONCUSSION

Russell M. Bauer, PhD; Michael S. Jaffee, MD, FAAN. Continuum (Minneap Minn). December 2021; 27 (6 Behavioral Neurology and Psychiatry):1646–1669.

ABSTRACT

PURPOSE OF REVIEW:

This review provides the reader with an overview of concussion and mild traumatic brain injury (TBI). Key aspects of the pathophysiology, signs, and symptoms, treatment and rehabilitation, and recovery from concussion/mild TBI are reviewed with an emphasis on the variety of factors that may contribute to cognitive concerns following injury.

RECENT FINDINGS:

Concussion remains a clinical diagnosis based on symptoms that occur in the immediate aftermath of an applied force and in the hours, days, and weeks thereafter. Although advances have been made in advanced diagnostics, including neuroimaging and fluid biomarkers in hopes of developing objective indicators of injury, such markers currently lack sufficient specificity to be used in clinical diagnostics. The symptoms of concussion are heterogeneous and may be seen to form subtypes, each of which suggests a targeted rehabilitation by the interdisciplinary team. Although the majority of patients with concussion recover within the first 30 to 90 days after injury, some have persistent disabling symptoms. The concept of *postconcussion syndrome*, implying a chronic syndrome of injury-specific symptoms, is replaced by a broader concept of *persistent symptoms after concussion*. This concept emphasizes the fact that most persistent symptoms have their basis in complex somatic, cognitive, psychiatric, and psychosocial factors related to risk and resilience. This framework leads to the important conclusion that concussion is a treatable injury from which nearly all patients can be expected to recover.

SUMMARY:

Concussion/mild TBI is a significant public health problem in civilian, military, and organized athletic settings. Recent advances have led to a better understanding of underlying pathophysiology and symptom presentation and efficacious treatment and rehabilitation of the resulting symptoms. An interdisciplinary team is well-positioned to provide problem-oriented, integrated care to facilitate recovery and to advance the evidence base supporting effective practice in diagnosis, treatment, and prevention.

KEY POINTS

- **Both the American Congress of Rehabilitation Medicine and Concussion in Sport Group definitions make clear the idea that concussion represents a functional, not a structural, disturbance.**
- **Concussion remains a clinical diagnosis that is based on observed alterations of consciousness, reported symptoms, and/or results of neurologic, cognitive, balance, and ocular motor assessments.**
- **Concussion can produce concerns and problems in cognitive function, including reductions in attention, reaction time, processing speed, working memory, memory, and executive functioning.**
- **Assessment of cognitive dysfunction should include interview-based questions focused on the daily course and factors that precipitate the onset of cognitive symptoms, as well as objective measurement of cognitive function.**
- **Given the discrepancy between rates of subjective and objective cognitive disturbance in patients with concussion and that the majority of patients do not report debilitating cognitive disturbance after**

concussion, it may be important to consider the fact that cognition can suffer not only as a primary deficit but also when the patient experiences significant associated emotional/psychiatric or somatic symptoms in the aftermath of a concussion.

- Ocular motor symptoms after concussion can lead to difficulty obtaining, understanding, and processing visual stimuli.
- Vestibular dysfunction is common after concussion and is manifested in abnormalities on tests that involve movement and orientation of the body to space and time.
- Posttraumatic headache is a common symptom that may affect cognition and emotional status after concussion.
- After concussion, many patients report increases in anxiety or depressive symptoms, attributable to both the effects of injury on neuronal function and the injured personâ s reaction to it.
- Sleep disturbance is quite common after concussion, and its presence can modify the degree to which symptoms in other domains are expressed.
- Many patients who have had a concussion present with neck pain, muscle stiffness, and headache, typically localized to the occipital/suboccipital region.
- Regarding diagnosis of TBI itself, no biomarker has been sufficiently validated to justify its use as a diagnostic tool in the individual case.
- The nature of concussion as a transient disturbance of brain function leads to the general expectation that the large majority of concussed individuals have a good prognosis for full recovery. At the same time, clinicians who work with these patients know that the course and rapidity with which recovery occurs can be quite variable. The key management principle is to address postconcussion symptoms and problems as actively and as quickly as feasible to prevent acute symptoms from becoming chronic.
- In this article, the term *persisting symptoms after concussion*, as opposed to *persistent postconcussion syndrome*, is used to make it clear that the discussion focuses on clinical symptoms that remain well after full recovery from the physiologic and functional neurologic effects of concussion has been achieved.
- The etiology of persisting symptoms after concussion is complex and likely reflects neurobiopsychosocial causative pathways that include (1) preinjury medical and psychiatric history, (2) personal characteristics such as age and gender, (3) injury-related factors such as severity and symptom burden, and (4) postinjury factors including interruption of activities, coping style, and other psychosocial circumstance.
- A key concussion management goal is to avoid premature reentry while simultaneously avoiding the deconditioning that often accompanies extended rest periods.
- Following concussion, moderate-intensity physical activities have been shown to reduce symptom duration as compared to either complete rest or high-intensity activity. Research is ongoing to determine the most effective mode and protocol for titrating the intensity of such beneficial physical activity.
- During the early postacute phases, cognitive rehabilitation strategies used rely mostly on compensatory strategies.
- Symptomatically, concussion presents with a heterogeneous admixture of cognitive, vestibular, ocular motor, headache, and neuropsychiatric problems that are frequently accompanied by sleep disturbances and cervical symptoms. Increasing attention is being given to the possibility that these heterogeneous presentations may represent pathophysiologic subtypes, each in need of a separate targeted treatment approach.
- Mismanagement of acute concussion (eg, excessive rest or prolonged prescribed inactivity), preexisting medical or psychiatric problems (eg, migraine, anxiety), as well as current comorbidities (eg, cervical pain, sleep problems) and psychosocial factors (eg, fear-avoidance as a coping strategy), may prolong or complicate recovery well beyond the point that the acute neurometabolic effects of concussion have resolved.

ARTICLE 8: COGNITIVE REHABILITATION

Lindsey Kirsch-Darrow, PhD; Jack W. Tsao, MD, DPhil, FAAN. Continuum (Minneap Minn). December 2021; 27 (6 Behavioral Neurology and Psychiatry):1670–1681.

ABSTRACT

PURPOSE OF REVIEW:

This article provides a definition of and introduction to cognitive rehabilitation. It discusses different approaches to cognitive rehabilitation (ie, restorative, compensatory, and metacognitive). It also reviews types of memory impairment and how they can be distinguished to improve treatment design and implementation.

RECENT FINDINGS:

Neural plasticity as a biological substrate for functional changes from cognitive rehabilitation is an exciting new area of research.

SUMMARY:

This article provides a high-level review of cognitive rehabilitation and presents a complex case example.

KEY POINTS

- Rehabilitation is the process of making patients more "fit" or suited for their environment.
- Rehabilitation of any type involves acquisition, mastery, maintenance, and generalization of new learning. A challenge for cognitive rehabilitation is that patients who need it, such as those with traumatic brain injury, stroke, and other acquired brain injuries, typically have deficits in new learning.
- Systematic instruction is a form of cognitive rehabilitation that takes into account patients' deficits in new learning by using structured training, including explicit models, minimization of errors during initial acquisition, and carefully guided practice.
- Before the design and implementation of cognitive rehabilitation, it is important to complete a thorough neuropsychological assessment.
- Neuropsychological assessment can determine which areas of cognition are preserved and which are impaired; preserved areas can help bolster impaired areas.
- Declarative memory is a type of memory where the knowledge base is consciously known (eg, learning capitals of US states). In contrast, nondeclarative memory does not require conscious awareness (eg, riding a bicycle).
- After completion of neuropsychological assessment, the next steps for cognitive rehabilitation are to provide feedback about test results, educate patients about their injuries and resulting cognitive deficits, and provide systematic instruction to directly improve or compensate for the deficit.
- In addition to neurologists, rehabilitation professionals on the treatment team include physical medicine and rehabilitation specialists, occupational therapists, assistive technologists, speech-language pathologists, and rehabilitation neuropsychologists.
- An important distinction in cognitive rehabilitation is the classification of treatments as either restorative or compensatory.
- Restorative treatment approaches are designed to reduce impairment in a basic cognitive function, whereas compensatory treatment approaches are designed to maximize functioning with or without changing the basic cognitive function.
- Metacognition is a type of compensatory treatment approach that involves monitoring one's thinking and using it to evaluate and regulate one's behavior.
- The structured environmental experience needed for cognitive rehabilitation can be divided into hierarchical stages, which are the (1) acquisition stage, (2) application stage, and (3) adaptation stage.

- The acquisition stage involves patients learning the purpose and procedure of the treatment model and the therapist assessing their level of awareness, the application stage involves patients applying the strategy to simple tasks inside the therapy session, and the adaptation stage involves applying the strategy to everyday tasks outside the clinic.
- Cognitive rehabilitation strategies can be external to the patient, which include patient notebooks, calendars, electronic devices (eg, computers, smartpens, smartphones), and visual cuing such as sticky notes.
- Cognitive rehabilitation strategies can also be internal to the patient and include strategies that are self-generated processes (eg, consciously slowing down to reduce mistakes, using mnemonics for memory aids).
- Making progress in cognitive rehabilitation requires recognizing and treating other aspects that affect cognition such as emotional symptoms, headaches, and poor sleep.
- Neural plasticity can be defined as a change in neuron structure or function directly observed from individual neurons or populations of neurons.
- Cognitive rehabilitation most likely benefits patients because it induces neuroplasticity, detectable as changes in cortical activity in different brain regions in response to a rehabilitation program.

ARTICLE 9: PSYCHOSIS

Parunyou Julayanont, MD; Uma Suryadevara, MD. Continuum (Minneap Minn). December 2021; 27 (6 Behavioral Neurology and Psychiatry):1682–1711.

ABSTRACT

PURPOSE OF REVIEW:

Psychosis can manifest in primary psychotic disorders, neurologic diseases, and medical conditions. This article reviews the definition of psychotic symptoms and the evaluation and management of psychosis in primary psychiatric and neurologic disorders frequently seen in neurologic practice.

RECENT FINDINGS:

Emerging evidence supports significant connections between psychosis and structural and functional brain changes in both primary psychotic and neurologic disorders. In addition to antidopaminergic activity, the mechanism of new-generation antipsychotics shifts to act on serotonin receptors, which potentially contributes to their benefits in the treatment of negative symptoms of psychosis and a lesser frequency of extrapyramidal side effects compared with typical antipsychotics. This is also helpful in the treatment of psychosis in patients who have neurodegenerative diseases and are vulnerable to developing extrapyramidal side effects from typical antipsychotics.

SUMMARY:

Even with significant overlap, management of psychosis in primary psychotic disorders differs from the approach of psychosis in neurologic diseases. This article helps clinicians learn how to practically evaluate psychosis from both psychiatric and neurologic perspectives.

KEY POINTS

- In all the psychotic disorders, abnormalities are noticed in one or more of the five domains: delusions, hallucinations, disorganized thoughts, disorganized behaviors, and negative symptoms. The severity of the symptoms should be sufficient to substantially impair daily functioning to be classified as a disorder.

- Most common psychotic disorders such as schizophrenia and mood disorders with psychosis begin in the second or third decade of life. Delusional disorders are commonly seen in middle age, and psychosis secondary to neurodegenerative disorders usually present at older ages.
- Many hypothetical frameworks are possible for visual hallucinations in neurologic conditions, including impairments of the "top-down" attentional and "bottom-up" perceptual aspects of visual perception, chronic sensory deafferentation and hyperexcitability of the adjacent cortical networks, cortical irritation causing hallucinations in various sensory modalities, and dysfunction of the ascending reticular activating system.
- Some other perceptual disturbances that should be considered for the differential diagnosis of hallucinations include derealization, depersonalization, pseudohallucination, synesthesia, jamais vu, and déjà vu.
- The primary delusion is a direct unmediated phenomenon, whereas the other forms of belief are mediated by thought. They are incomprehensible and ambiguous and may be seen in individuals with schizophrenia, schizoaffective disorder, and other psychotic disorders and cannot be explained by cultural background, education, personality, or other circumstances of life.
- Secondary delusions are understandable in terms of the patient's emotional state, circumstances of life, beliefs of peer group, and personality. They typically present secondary to some other psychopathologic condition.
- Delusional misidentification syndromes represent a group of disorders defined by the misidentification or impairment in recognition of one or more people despite the normally functioning sensory recognition pathways. The four main subtypes are Capgras syndrome, Frégoli syndrome, intermetamorphosis syndrome, and subjective doubles syndrome.
- Neuropsychological testing in patients with misidentification syndromes shows subtle abnormalities in facial recognition with nondominant cerebral compromise.
- The essential feature of brief psychotic disorder is onset of at least one of the following symptoms within the previous 2 weeks: hallucinations, delusions, disorganized speech, and disorganized behavior including catatonia. Brief psychotic disorder has no prodrome, and the symptoms might last for 1 day to 1 month. Once the symptoms resolve, patients are back to their baseline level of functioning.
- The characteristic symptoms of schizophreniform disorder are similar to the symptoms of schizophrenia except for the duration of symptoms, which should last for more than 1 month but less than 6 months. Another unique feature of schizophreniform disorder is it does not require impairment in social or occupational functioning for diagnostic reasons.
- Schizophrenia is hypothesized to be an outcome of a complex interplay of genetic and environmental risk factors that affect the early development of the brain.
- Overwhelming evidence shows eye movement abnormalities including saccade control and smooth pursuit eye movements in patients with schizophrenia and in their biological family members. The abnormalities were proposed to be used as one of the neurophysiologic biomarkers for the disorder.
- Diagnosis of schizoaffective disorder requires an uninterrupted period of active or residual symptoms of psychosis during which the criterion A symptoms of schizophrenia are met, along with a major mood episode. In contrast to mood disorder with psychotic features where psychotic features are present only during the mood episodes, a diagnosis of schizoaffective disorder requires 2 weeks of psychotic features without mood symptoms.
- Delirium-onset dementia with Lewy bodies (DLB) is one of the proposed prodromal subtypes of DLB. When delirium is resolved, clinicians should thoroughly evaluate patients for cognitive impairment and other features of DLB in whom delirium occurs without triggers and in those with prolonged or recurrent delirium after treatment of provoking factors.
- Minor hallucinations, including passage and presence hallucinations, are reported in 42% of drug-naïve patients with Parkinson disease and may manifest months to years before the onset of motor symptoms.
- Because many patients with Parkinson disease may not spontaneously report their experiences of psychotic symptoms, clinicians should always evaluate for any existing or emerging psychotic features during each visit.

- Psychiatric-onset prodromal DLB (late-onset major depressive disorder or late-onset psychosis) may be a solely initial symptom of DLB before subsequent development of parkinsonism or other DLB features.
- Compared with visual hallucinations in Parkinson disease, the characteristics of visual hallucinations in DLB are more well formed (seeing children, people, animals, or scenes), are associated with greater severity of cognitive impairment, and occur earlier in the course of disease.
- Pareidolia, which is the perception of meaningful objects (faces or animals) embedded in visual scenes, is a complex visual illusion in patients with Lewy body diseases, including DLB and Parkinson disease.
- When strokes are unilateral, right hemispheric lesions are associated with poststroke psychosis more than lesions on the left hemisphere.
- A midbrain or thalamic lesion rarely causes peduncular hallucinosis, which consists of naturalistic and vivid visual hallucinations usually associated with preserved insight.
- Strokes on the primary visual cortex can cause simple visual hallucinations (light, colorless, shadow of objects or shapes, etc) on the hemianopic visual field. Visual hallucinations after occipital stroke occur more frequently after focal damage to the striate cortex that spares the extrastriate cortex than a stroke that extensively affects both the striate and extrastriate cortices.
- Poor memory function may manifest as confabulation, which is often not a firm belief and must be distinguished from a fixed belief typically seen in delusion.
- In Alzheimer disease, Capgras delusion and prosopagnosia are secondary to degeneration of the parietotemporal region affecting face recognition systems. Prosopagnosia is not a psychotic symptom, but Capgras delusion is a type of delusional misidentification syndrome found in 10% of patients with Alzheimer disease.
- Psychoses in epilepsy are classified according to the temporal relationship between psychotic symptoms and ictal events into ictal psychosis, postictal psychosis, and interictal psychosis (brief and chronic).
- Chronic interictal psychosis usually manifests with better preserved premorbid personality, lesser negative symptoms (social withdrawal and blunted affect), lesser command hallucinations, and more visual hallucinations than in schizophrenia.
- Geschwind syndrome is a distinct interictal behavioral syndrome observed in patients with temporal lobe epilepsy and characterized by alterations in sexual behaviors, hyperreligiosity, circumstantiality of speech, a tendency to pedantry (mental stickiness, or being overly concerned with minor rules or details), and excessive or compulsive writing and drawing (hypergraphia) with meticulous details. This syndrome can concomitantly occur with or mimic interictal psychosis.
- In patients presenting with late-onset psychosis, it is always the rule to extensively evaluate for an organic etiology before making a diagnosis of primary psychiatric disorders.
- Cognitive screening with the Mini-Mental State Examination or the Montreal Cognitive Assessment is essential because this may assist in the diagnosis of dementia and guide further investigations for dementia-related psychosis.
- For first-episode psychosis, an antipsychotic with a lower risk of extrapyramidal symptoms, weight gain, and metabolic problems would be the preferred choice. If no response is seen in 2 to 4 weeks with a good therapeutic trial of medication, the antipsychotic can be switched to a different one. The new antipsychotic being used should preferably be pharmacologically different from the previous one and can be cross tapered. However, if the patient has no response to two adequate trials of dissimilar antipsychotics, clozapine would then be indicated.
- The typical antipsychotics are further classified into lower-, medium-, or higher-potency agents. The potency is determined by the dopamine receptor affinity, and the side effect profile is based on the degree of cholinergic receptor blockade, α_1-adrenergic blockade, and histaminergic blockade. Lower-potency antipsychotics have prominent cholinergic receptor blockade and, hence, lower extrapyramidal symptom rates.
- The second-generation (atypical) antipsychotics have antagonistic properties at both 5-HT_{2A} and dopamine receptors, hence improving the positive symptoms but causing fewer extrapyramidal symptoms.

- Risperidone is one of the atypical antipsychotics for which D_2 receptor occupancy can be higher, resulting in side effects such as extrapyramidal symptoms or elevated prolactin levels. Clozapine and quetiapine do not have a D_2 receptor occupancy greater than 80% and, hence, have the lowest risk for extrapyramidal symptoms.
- The effective dose ranges for the treatment of psychosis in primary psychotic disorders are significantly higher than the dose ranges used for the treatment of psychosis related to neurologic conditions. Patients with neurodegenerative disorders are particularly vulnerable to developing side effects from antipsychotics. "Start low, go slow" is recommended in managing antipsychotics in this population.
- Antipsychotics with low D_2 antagonistic activity, including quetiapine and clozapine, are preferably used off-label for the treatment of psychosis in DLB, Parkinson disease, and Alzheimer disease because of their low prevalence of extrapyramidal effects.
- Pimavanserin is a newer second-generation antipsychotic approved for the treatment of psychosis associated with Parkinson disease. The mechanism of action is different as it has no affinity for dopamine receptors but instead is a highly selective 5-HT_{2A} inverse agonist; thus, it does not worsen parkinsonism.
- Dystonic reaction is a side effect that is typically seen soon after initiation of an antipsychotic agent. It is uncomfortable and life-threatening if left untreated. Along with hemodynamically supportive treatment, IV or IM anticholinergic agents and antihistamines with potent anticholinergic effects (eg, diphenhydramine) are used for the treatment of dystonic reactions.
- Medications that have been used to treat tardive dyskinesia symptoms include vesicular monoamine transporter type 2 inhibitors such as valbenazine, tetrabenazine, and deutetrabenazine.
- One of the more dangerous side effects of antipsychotics to look for is neuroleptic malignant syndrome in which the patient experiences dystonia, fever, autonomic instability, rigidity, elevated creatine kinase, increased myoglobin in urine, and delirium.
- For clozapine, absolute neutrophil count is monitored frequently to check for agranulocytosis.
- To monitor for life-threatening side effects, patients are enrolled in a registry with routine blood monitoring by the prescriber, in the Clozapine Risk Evaluation and Mitigation Strategy Program. Prescribers must be certified to be able to prescribe clozapine. They are required to obtain an absolute neutrophil count for these patients and submit it directly to the registry. If no absolute neutrophil count is on file for the patient, clozapine dispensation is not authorized.
- The use of antipsychotics in older patients with dementia increases the risk of mortality by 1.6 to 1.7 times compared with placebo, and a boxed warning was issued by the US Food and Drug Administration.

ARTICLE 10: MOOD DISORDERS

Shae Datta, MD; Uma Suryadevara, MD; Josepha Cheong, MD. Continuum (Minneap Minn). December 2021; 27 (6 Behavioral Neurology and Psychiatry):1712–1737.

ABSTRACT

PURPOSE OF REVIEW:

This comprehensive review of mood disorders brings together the past and current literature on the diagnosis, evaluation, and treatment of the depressive and bipolar disorders. It highlights the primary mood disorders and secondary neurologic causes of mood disorders that are commonly encountered in a clinical setting. As the literature and our understanding evolve, recent additions to the current literature are important to bring forth to the readers.

RECENT FINDINGS:

Advancements in clinical medicine have strengthened our understanding of the associations of neurologic and psychiatric diseases. This article highlights the medications frequently used with

newly identified mood disorders and the common side effects of these medications. A paradigm shift has moved toward newer treatment modalities, such as the use of ketamine, repetitive transcranial magnetic stimulation, and complementary and alternative medicine. The risks and benefits of such therapies, along with medications, are reviewed in this article.

SUMMARY:

Mood disorders are extraordinarily complex disorders with significant association with many neurologic disorders. Early identification of these mood disorders can prevent significant morbidity and mortality associated with them. With further expansion of pharmacologic options, more targeted therapy is possible in improving quality of life for patients.

KEY POINTS

- Depressive disorders are exceedingly prevalent and can impair the quality of life. According to data from the National Health Interview Survey in 2019, 18.5% of the general population experienced symptoms of major, moderate, or mild symptoms of depression.
- Bipolar disorder is typically characterized by biphasic mood episodes alternating between depression and mania/hypomania but can also be a single episode of mania. The annual prevalence of bipolar disorders among US adults in 2019 was estimated to be 2.8%.
- When depressive disorders are accompanied by anxious features, treatment response is poor, rates of suicide are higher, and the risk for recurrence is increased.
- Major depressive disorder is an etiologically complex disorder that is globally ranked among the top three in terms of disease burden.
- Heritability for major depression is only around 37%, whereas disorders such as schizophrenia and bipolar disorder have 70% to 80% heritability. Highly intricate genetic differences and psychosocial stressors together are typically the determinants for stress responses and the resiliency or susceptibility for depression.
- Depressive disorders often are chronic and recurring disorders. Remission of a full episode is characterized by the absence of significant symptoms for at least 2 months. However, one-third to one-half of patients with depressive disorders experience another depressive episode within 1year.
- Although bipolar disorder has high genetic loading, it is still considered multifactorial, influenced by environmental factors such as life events.
- Incidence of suicide varies among regions based on the classification of suicide, social and cultural attitudes toward suicide, availability of treatment options, and access to lethal means. Rates are higher in lower socioeconomic sectors and in men between the ages of 45 and 64.
- Current guidelines from the US National Strategy for Suicide Prevention recommend the use of suicide prediction tools. The screening should include a thorough assessment of the predisposing and precipitating factors, including any recent changes in life or triggers.
- Multiple sclerosis is the major cause of nontraumatic neurologic disability in young adults, and the prevalence of depression is higher in these patients. The prevalence in studies has varied from 4.27% to 59.6% due to the heterogeneity of sample size and variations in clinical evaluation styles.
- The American Academy of Neurology supports using treatments such as cognitive-behavioral therapy to help with depression management in patients with multiple sclerosis. Other treatment options including psychopharmacologic approaches and transcranial magnetic stimulations have been studied, but results are not supportive at this point and more research is needed.
- Defining depression in the context of PD is challenging partly because of the overlap of symptoms of both disorders, leading to difficulties in accurately diagnosing depression in PD.
- The risk of suicide in patients with epilepsy and mood disorders is increased almost 32-fold.
- Diagnosis and treatment of poststroke depression in a timely manner may facilitate motor recovery and improve functional independence.

- The most common risk factor for patients to develop substance-induced mood disorders is a prior family history of the disorder (eg, someone in the family with a diagnosis of depression).
- The mood change most frequently seen with the use of prescription medications is depression.
- Risk factors for bipolar disorder include presence of family history of bipolar disorder, early onset of symptoms, atypical features of depression, psychotic symptoms accompanying depression, psychomotor retardation, and severe functional impairment.
- Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are the preferred first-line medication choices for the treatment of depression. Atypical antidepressants like bupropion and mirtazapine can also be used as first-line treatments in certain patient populations.
- First-line monotherapy options for treatment of mania in bipolar disorder include lithium, divalproex sodium, quetiapine, asenapine, aripiprazole, paliperidone, risperidone, and cariprazine.
- For patients with bipolar depression, first-line treatment options include lamotrigine, quetiapine, lurasidone, and lithium.

ARTICLE 11: POSTTRAUMATIC STRESS DISORDER AND ANXIETY-RELATED CONDITIONS

John B. Williamson, PhD; Michael S. Jaffee, MD, FAAN; Ricardo E. Jorge, MD.
Continuum (Minneap Minn). December 2021; 27 (6 Behavioral Neurology and Psychiatry):1738–1763.

ABSTRACT

PURPOSE OF REVIEW:

This article provides a synopsis of current assessment and treatment considerations for posttraumatic stress disorder (PTSD) and related anxiety disorder characteristics. Epidemiologic and neurobiological data are reviewed as well as common associated symptoms, including sleep disruption, and treatment approaches to these conditions.

RECENT FINDINGS:

PTSD is no longer considered an anxiety-related disorder in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* classification and instead is associated with trauma/stressor-related disorders. PTSD symptoms are clustered into four domains including intrusive experiences, avoidance, mood, and arousal symptoms. Despite this reclassification, similarities exist in consideration of diagnosis, treatment, and comorbidities with anxiety disorders. PTSD and anxiety-related disorders are heterogeneous, which is reflected by the neural circuits involved in the genesis of symptoms that may vary across symptom domains. Treatment is likely to benefit from consideration of this heterogeneity.

Research in animal models of fear and anxiety, as well as in humans, suggests that patients with PTSD and generalized anxiety disorder have difficulty accurately determining safety from danger and struggle to suppress fear in the presence of safety cues.

Empirically supported psychotherapies commonly involved exposure (fear extinction learning) and are recommended for PTSD. Cognitive-behavioral therapy has been shown to be effective in other anxiety-related disorders. Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are commonly used in the treatment of PTSD and anxiety disorders in which pharmacologic intervention is supported. Treating sleep

disruption including sleep apnea (continuous positive airway pressure [CPAP]), nightmares, and insomnia (preferably via psychotherapy) may improve symptoms of PTSD, as well as improve mood in anxiety disorders.

SUMMARY:

PTSD has a lifetime prevalence that is close to 10% and shares neurobiological features with anxiety disorders. Anxiety disorders are the most common class of mental conditions and are highly comorbid with other disorders; treatment considerations typically include cognitive-behavioral therapy and pharmacologic intervention. Developing technologies show some promise as treatment alternatives in the future.

KEY POINTS

- Diagnosis of posttraumatic stress disorder (PTSD) requires the experience of a Criterion A event, which is a specific event of exposure to actual or threatened death, sexual violence, or serious injury. Symptoms must persist for at least 1month and have a clinically significant functional impact. Acute stress disorder is the appropriate diagnosis if symptoms are present for less than 1 month.
- The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) articulates four symptom clusters of PTSD: (1) intrusive thoughts, (2) active avoidance, (3) disturbed emotional states, and (4) alterations of arousal and reactivity.
- Comorbidities are common with PTSD and include substance misuse, mood disorders, and chronic pain. In the case of complex PTSD, which is typically associated with childhood abuse, maladaptive personality traits may manifest with associated poor impulse control and the occurrence of self-injurious behaviors. PTSD may contribute to the development of comorbid conditions.
- The gold standard instrument for assessing and diagnosing PTSD is a semistructured interview, the Clinician-Administered PTSD Scale for the *DSM-5* (CAPS-5). Several inventories for quantifying the severity and distribution of PTSD symptoms also exist; the most commonly used is the Posttraumatic Stress Disorder Checklist for the *DSM-5*.
- The experience of Criterion A events is common, with between 50% and 90% of people experiencing at least one in their lifetime. However, of those exposed, between 7% and 12% go on to develop PTSD.
- Sexual-related violence is the preeminent etiology for PTSD among women, and combat-related violence is the more frequent antecedent among men. Women and younger people appear to be more vulnerable to develop PTSD after trauma. PTSD is increasingly recognized in older people.
- Hormonal variations might be an important factor explaining the increased vulnerability of women developing PTSD.
- Autonomic features of PTSD associated with hypothalamic-pituitary-adrenal axis disruption including reduced parasympathetic activity and increased sympathetic responses to stress associated with chronic elevation of noradrenergic tone have significant impact on multiple physiologic systems. Chronic elevation of adrenergic tone is associated with increased cardiovascular risk, sleep disturbance, and the metabolic syndrome.
- Patients with PTSD have difficulty discriminating danger from safety cues and problems suppressing fear in the presence of safety cues. Functional MRI (fMRI) studies show increased amygdala activation resulting from abnormal modulatory activity of the ventromedial prefrontal cortex. This response is heterogeneous with more prominent dissociative symptoms associated with inhibition of the amygdala and less autonomic reactivity to stress.
- PTSD and anxiety-related disorders are both associated with inflammation (systemic and peripheral).
- PTSD is a risk factor for cognitive decline and may contribute to reductions in brain health.
- Reduced hippocampal volumes have been consistently reported among patients with PTSD. Chronic stress may be causal; animal models demonstrate stress impacts neuronal quality and health in the hippocampus.
- Sleep disruption is common in PTSD and anxiety-related disorders. Sleep disruptions in PTSD commonly include nightmares and, although results in the literature are mixed, a meta-analysis of polysomnographic features indicates that patients with PTSD have longer sleep latencies, as well as decreased time in slow-wave sleep and increased time in REM sleep.

- Sleep apnea is a common comorbidity in patients with PTSD and is possibly associated with increased rates of metabolic syndrome. Continuous positive airway pressure (CPAP) adherence may be associated with reduction in nightmare occurrence and overall severity of symptoms of PTSD. CPAP adherence appears to be lower in patients with PTSD compared with those without.
- Both controlled exposure to aversive memories and cognitive reprocessing are efficacious psychotherapies for treatment of PTSD, but they tend to be less effective in combat-related PTSD.
- Medications are modestly more effective than placebo in treating PTSD symptoms. Selective serotonin reuptake inhibitors (SSRIs) are considered a safe initial choice. Psychotherapeutic approaches (image rehearsal therapy for nightmares and cognitive-behavioral therapy for insomnia) are recommended treatments for sleep disruption. Benzodiazepines should be avoided if possible.
- Given the increased risk of cognitive problems in patients with PTSD, it is worthy to note that in older patients benzodiazepines and benzodiazepine receptor agonists used for insomnia ("Z-drugs" such as zolpidem, zaleplon, eszopiclone) are both associated with increased risk of dementia. In addition to concerns with substance use/abuse in PTSD, benzodiazepine use may exacerbate cognitive dysfunction in these patients.
- Pharmacologic modulation of fear conditioning and extinction is an area of active research for the treatment of PTSD. Brain stimulation technologies (eg, repetitive transcranial magnetic stimulation) are also being investigated.

ARTICLE 12: OBSESSIVE-COMPULSIVE DISORDERS

Carol Mathews, MD. Continuum (Minneap Minn). December 2021;
27 (6 Behavioral Neurology and Psychiatry):1764–1784.

ABSTRACT

PURPOSE OF REVIEW:

This article describes the phenomenology and clinical presentation of obsessive-compulsive disorder (OCD), a common but underdiagnosed psychiatric disorder. Guidance for effectively identifying obsessive-compulsive symptoms is provided, and treatment options, including psychotherapy, pharmacologic management, and neuromodulation approaches for treatment-resistant OCD, are discussed.

RECENT FINDINGS:

OCD affects 2% to 3% of adults worldwide and is associated with substantial individual disability and societal costs. Lack of recognition of common OCD symptom types, in addition to shame and fear of stigma on the part of patients, has created an average delay in diagnosis by almost 10 years and a delay in effective treatment (ie, a treatment gap) of nearly 2 years. Cognitive-behavioral therapy (CBT), specifically a form of CBT that includes a type of behavioral intervention called *exposure and response prevention*, remains the most effective form of treatment for OCD. If CBT is not effective or not available, pharmacologic treatment with selective serotonin reuptake inhibitors (SSRIs) or clomipramine, a nonselective serotonin reuptake inhibitor, can also be of benefit. Neuromodulation approaches such as deep brain stimulation and transcranial magnetic stimulation are rapidly emerging as effective treatments for OCD, particularly for patients who have not experienced an adequate response to psychotherapy or pharmacologic management.

SUMMARY:

OCD affects more than one in every 50 adults in the United States but is recognized and adequately treated in fewer than half of those affected. Early intervention and appropriate

treatment can substantially reduce OCD symptom severity, improve quality of life, and minimize the functional disability associated with this chronic and often debilitating illness.

KEY POINTS

- Although obsessions and compulsions are the core features of obsessive-compulsive disorder (OCD), avoidance of situations or events that may trigger obsessions is also common.
- Formal assessment of OCD is typically conducted using standardized assessments, but one or two questions can be effective screening tools in a busy clinical practice.
- The content of obsessions and compulsions can be grouped into several thematic categories (eg, contamination and cleaning or taboo thoughts).
- Obsessions and compulsions regarding symmetry are more common in individuals with co-occurring chronic tic disorders.
- Somatic and hoarding symptoms can occur either in OCD or as a part of other related disorders, such as body dysmorphic disorder, illness anxiety disorder, or hoarding disorder.
- OCD affects approximately 2% to 3% of adults.
- The presence of one or more psychiatric disorders co-occurring with OCD is the rule rather than the exception.
- Early intervention is critical for improving quality of life in OCD and the likelihood of functional remission.
- Obsessive-compulsive symptoms are often missed or misdiagnosed by clinicians, in part because the symptoms are confused with other similar symptoms.
- The most effective form of treatment for OCD is a form of cognitive-behavioral therapy called *exposure and response prevention.*
- The average number of exposure and response prevention sessions needed to attain a desired response is 16 to 20.
- Only one class of medications, the serotonin reuptake inhibitors, which includes clomipramine and the selective serotonin reuptake inhibitors (SSRIs), is effective as a primary treatment for OCD; high doses and long treatment times are needed for maximum benefit.
- Adequate pharmacologic response to treatment cannot be determined until a patient has been on a selective serotonin reuptake inhibitor at an appropriate dose for at least 12 weeks.
- Adjunctive medications such as neuroleptics or the addition of cognitive-behavioral therapy to pharmacologic treatment leads to continued improvement in up to 30% of patients with OCD.
- Deep brain stimulation in brain regions that activate a white matter fiber tract connecting the medial prefrontal cortex to the subthalamic nucleus can lead to substantial symptom improvement in patients with treatment-refractory OCD.
- Transcranial magnetic stimulation targeting the anterior cingulate cortex and the dorsal medial prefrontal cortex is emerging as a noninvasive form of neuromodulation that may also be effective in treating OCD.

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Cerebrovascular Disease

Article 1: Epidemiology and Primary Prevention of Stroke

Karen Furie, MD. Continuum (Minneap Minn). April 2020; 26 (2 Cerebrovascular Disease):260–267.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an update on the epidemiology and prevention of a first stroke. Risk factor modification plays a large role in stroke prevention. Strategies for early intervention, particularly for hypertension, are critical for reducing stroke morbidity and mortality.

RECENT FINDINGS:

Because of the new criteria for hypertension, more people are now classified as hypertensive and can benefit from lifestyle or medical management. Direct oral anticoagulants have made it easier to safely treat patients with atrial fibrillation and are now considered first-line therapy for patients with an additional stroke risk factor.

SUMMARY:

Primary prevention of stroke is essential for maintaining brain health throughout the life span. Adherence to a healthy lifestyle and routine screening for stroke risk factors can promote healthy, stroke-free aging.

KEY POINTS

- Stroke is the fifth leading cause of death in the United States.
- Of those who survive stroke, half have moderate to severe disability.
- Blood pressure should be managed to achieve a goal of <130/80 mm Hg.
- Diabetes mellitus is an independent risk factor for stroke.
- The CHA_2DS_2VASc (congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, stroke, vascular disease, age 65 to 74 years, sex category [female sex]) score is useful for selecting patients with atrial fibrillation who would benefit from anticoagulation.
- The role of cholesterol and its subfractions in first stroke (ie, primary stroke prevention) is complicated, and studies have been inconsistent.
- Neurologists should counsel patients on the importance of smoking cessation and offer therapies proven to achieve abstinence.
- Several trials have demonstrated the protective effect of physical activity in reducing stroke risk.

- The risk of stroke is 5 to 30 times higher in patients with chronic kidney disease, especially in patients on dialysis. Blood pressure control is particularly important to prevent stroke in this population.
- The risk of stroke is higher with abstinence versus low intake of alcohol.

Article 2: Update on Treatment of Acute Ischemic Stroke

Alejandro A. Rabinstein, MD, FAAN. Continuum (Minneap Minn). April 2020; 26 (2 Cerebrovascular Disease):268–286.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an update on the state of the art of the treatment of acute ischemic stroke with particular emphasis on the indications for reperfusion therapy.

RECENT FINDINGS:

In addition to the previously established indications for intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rtPA) within 4.5 hours of stroke symptom onset and endovascular therapy with mechanical thrombectomy for patients with large artery occlusion who can be treated within 6 hours of symptom onset, recent randomized controlled trials have now established new indications for emergency reperfusion in patients with wake-up stroke or delayed presentation (up to 24 hours from last known well in the case of mechanical thrombectomy). Identification of patients who may benefit from acute reperfusion therapy within this extended time window requires screening with perfusion brain imaging or, in the case of IV thrombolysis for wake-up strokes, emergency brain MRI. Collateral status and time to reperfusion remain the primary determinants of outcome.

SUMMARY:

Timely successful reperfusion is the most effective treatment for patients with acute ischemic stroke. Recent evidence supports the expansion of the time window for reperfusion treatment in carefully selected patients.

KEY POINTS

- Prompt reperfusion is the most effective treatment for patients with acute ischemic stroke.
- The three principles of acute stroke therapy are to achieve recanalization of the occluded vessel (and reperfusion of the ischemic tissue), to optimize collateral flow, and to avoid secondary brain injury.
- The ischemic penumbra is the region of hypoperfused brain that can still be viable with prompt recanalization of the occluded artery.
- Collateral flow is responsible for the temporary preservation of the ischemic penumbra.
- No neuroprotective agent has been proven to be beneficial for acute ischemic stroke in clinical trials.
- IV thrombolysis with recombinant tissue plasminogen activator (rtPA)and endovascular thrombectomy with a retrievable stent are both solidly established treatments for appropriate candidates with acute ischemic stroke.
- Time to reperfusion is a major determinant of outcome in acute ischemic stroke.
- Randomized placebo-controlled trials have demonstrated that IV thrombolysis with rtPA is beneficial for patients with acute ischemic stroke up to 4.5 hours from symptom onset.
- Most cases of symptomatic intracerebral hemorrhage are caused by reperfusion injury causing hemorrhagic transformation of an already severe stroke.

- Endovascular therapy with mechanical thrombectomy substantially improves functional outcomes in patients with acute stroke from a proximal intracranial artery occlusion (internal carotid artery or M1 segment) especially when the intervention is performed within 6 hours of symptom onset.
- Some previously cited contraindications for IV thrombolysis have been revisited, thus expanding the pool of patients who can be considered good candidates for this treatment.
- Benefit from IV thrombolysis is much greater in the first 90 minutes from symptom onset.
- Candidates for endovascular stroke therapy are patients with severe neurologic symptoms, no major ischemic changes on the baseline CT scan, good prestroke functional status, and early presentation.
- Mechanical thrombectomy can be attempted when IV thrombolysis does not result in rapid clinical improvement and also in patients who are ineligible for IV rtPA.
- Careful assessment of brain imaging is necessary to exclude a large established infarction (core).
- The optimal radiologic method to select candidates for endovascular therapy is not yet established, but assessment of early ischemic changes on CT, evaluation of collaterals on CT angiography, and CT perfusion or MRI diffusion/perfusion are all available options.
- Patients with wake-up strokes and those with stroke of unknown time of onset presenting within 24 hours of the last time when they were known to be well should be treated with endovascular thrombectomy if they have a large intracranial artery occlusion and evidence of salvageable tissue on perfusion imaging.
- It is prudent not to administer IV thrombolysis in patients taking the novel oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban) because readily available tests in the emergency department cannot quantify the degree of active anticoagulation.
- Patients with mild or rapidly improving strokes who present within the time window for IV thrombolysis and still have disabling symptoms at the time of the evaluation should probably be offered treatment with rtPA.
- Patients with minor, nondisabling stroke symptoms should not be currently considered candidates for IV thrombolysis.
- Although patients with basilar artery occlusion were not included in the randomized controlled trials of IV thrombolysis or mechanical thrombectomy, these patients should be treated with acute reperfusion therapies because of their dismal prognosis if recanalization cannot be achieved.
- Mobile stroke units have been shown to provide a safe way to start thrombolysis in the prehospital setting.

Article 3: Neuroimaging in Acute Stroke

Bijoy K. Menon, MD, DM, MSc, FRCPC. Continuum (Minneap Minn). April 2020; 26 (2 Cerebrovascular Disease):287–309.

ABSTRACT

PURPOSE OF REVIEW:

This article describes how imaging can be used by physicians in diagnosing, determining prognosis, and making appropriate treatment decisions in a timely manner in patients with acute stroke.

RECENT FINDINGS:

Advances in acute stroke treatment, including the use of endovascular thrombectomy in patients with large vessel occlusion and, more recently, of IV thrombolysis in an extended time window, have resulted in a paradigm shift in how imaging is used in patients with acute stroke. This paradigm shift, combined with the understanding that "time is brain," means that imaging must be fast, reliable, and available around the clock for physicians to make appropriate clinical decisions. CT has therefore become the primary imaging modality of choice. Recognition of a large vessel occlusion using CT angiography has become essential in identifying patients for

endovascular thrombectomy, and techniques such as imaging collaterals on CT angiography or measuring blood flow to predict tissue fate using CT perfusion have become useful tools in selecting patients for acute stroke therapy. Understanding the use of these imaging modalities and techniques in dealing with an emergency such as acute stroke has therefore become more important than ever for physicians treating patients with acute stroke.

SUMMARY:

Imaging the brain and the blood vessels supplying it using modern tools and techniques is a key step in understanding the pathophysiology of acute stroke and making appropriate and timely clinical decisions.

KEY POINTS

- As time is of the essence in the management of patients with acute stroke, clinical assessment and imaging interpretation must happen quickly.
- Imaging is used in acute stroke to help determine diagnosis, prognosis, and appropriate treatment selection.
- CT is the workhorse of acute stroke imaging because of its speed and ease of acquisition, 24/7 availability, lower cost, and relative absence of contraindications when compared to MRI.
- The primary purpose of noncontrast CT in patients with acute stroke is to rule out a hemorrhagic stroke and to identify imaging features that may suggest the presence of an ischemic stroke.
- The classic radiologic signs of early ischemic change seen on noncontrast CT are obscuration of the lentiform nucleus, the insular ribbon sign (loss of gray-white matter differentiation at the insula), and the cortical ribbon sign (loss of gray-white matter differentiation at the surface cortex).
- The two most widely used methods to assess the extent of early ischemic changes in brain supplied by the middle cerebral artery are the one-third middle cerebral artery rule and the Alberta Stroke Program Early CT Score (ASPECTS).
- On noncontrast CT, brain regions that are darker than the contralateral normal-appearing white matter are a marker of increased risk of hemorrhage with thrombolysis. The presence of these regions does not mean that thrombolysis is absolutely contraindicated, but they do mean that clinicians should proceed with caution after weighing the risks and benefits of thrombolysis.
- The primary modality used to image blood vessels supplying the brain is CT angiography (CTA). It is best to acquire a head and neck CTA (aortic arch to vertex) to visualize all extracranial and intracranial arteries supplying the brain.
- CTA is a useful tool to help understand the etiology of any intracranial hemorrhage and to identify underlying pathologies, such as intracranial aneurysms, arteriovenous malformations, dural arteriovenous fistulas, and any other vascular malformations.
- On CTA, the spot sign is a serpiginous or linear contrast density located within the parenchymal hemorrhage. The presence of a spot sign suggests hemorrhage that is likely to grow over time.
- CTA is an essential tool in the management of patients with acute ischemic stroke. It helps in detecting thrombi within arteries and their extent, collateral status beyond occlusive thrombus, and any other associated pathologies. The tool also helps in determining the risk of recurrent strokes and in planning acute endovascular treatment and surgical management of carotid stenosis.
- Multiphase CTA is an excellent tool to assess collateral status. On the three time-resolved phases of the multiphase CTA, arteries distal to the blocked artery are assessed for extent of arterial contrast, delay in filling of contrast, and impaired washout of contrast when compared to arteries on the contralateral side.
- Head and neck CTA is an important tool in planning acute endovascular thrombectomy. Assessment of the aortic arch and large artery anatomy helps in choosing the type of catheter to be used during the procedure. In addition, the location and extent of thrombus within the arterial tree also helps determine the device type and profile used for mechanical thrombectomy.

- CT perfusion (CTP) involves acquiring multiple scans of the brain over time; summating these time-resolved images of contrast filling in and washing out from brain using mathematical formulas; and generating estimates of cerebral blood flow, blood volume, and transit time within brain tissue.
- Current CTP techniques are prediction tools. They help predict the probability of brain tissue being dead or alive by estimating the degree of blood flow within that tissue.
- Brain tissue with very low blood flow on CTP is likely to infarct early. By detecting regions of very low blood flow (or blood volume) or regions of brain with increased blood-brain barrier permeability, CTP can help predict brain regions with increased risk of hemorrhage after acute stroke treatment.
- Subacute-appearing changes on noncontrast CT or regions of the brain with changes seen on diffusion-weighted images (DWI) and fluid-attenuated inversion recovery (FLAIR) images (no DWI-FLAIR mismatch) may also help clinicians predict the risk of hemorrhage with acute treatment.

Article 4: Endovascular Treatment of Acute Ischemic Stroke

Gisele S. Silva, MD, MPH, PhD; Raul G. Nogueira, MD. Continuum (Minneap Minn). April 2020; 26 (2 Cerebrovascular Disease):310–331.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the actual indications for mechanical thrombectomy in patients with acute ischemic stroke and how the opportunities for endovascular therapy can be expanded by using the concept of clinical-imaging or perfusion-imaging mismatch (as a surrogate for salvageable tissue) rather than time of ischemia.

RECENT FINDINGS:

Six randomized controlled trials undoubtedly confirmed the benefits of using endovascular thrombectomy on the clinical outcome of patients with stroke with large vessel occlusion within 6 hours from symptom onset compared with those receiving only standard medical care. In a meta-analysis of individual patient data, the number needed to treat with endovascular thrombectomy to reduce disability by at least one level on the modified Rankin Scale for one patient was 2.6. Recently, the concept of "tissue window" versus time window has proved useful for selecting patients for mechanical thrombectomy up to 24 hours from symptom onset. The DAWN (DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention) trial included patients at a median of 12.5 hours from onset and showed the largest effect in functional outcome ever described in any acute stroke treatment trial (35.5% increase in functional independence). In DEFUSE 3 (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 3), patients treated with mechanical thrombectomy at a median of 11 hours after onset had a 28% increase in functional independence and an additional 20% absolute reduction in death or severe disability.

SUMMARY:

For patients with acute ischemic stroke and a large vessel occlusion in the proximal anterior circulation who can be treated within 6 hours of stroke symptom onset, mechanical thrombectomy with a second-generation stent retriever or a catheter aspiration device should be indicated regardless of whether the patient received treatment with intravenous (IV) recombinant tissue plasminogen activator (rtPA) in patients with limited signs of early ischemic changes on neuroimaging. Two clinical trials completely disrupted the time window concept in

acute ischemic stroke, showing excellent clinical outcomes in patients treated up to 24 hours from symptom onset. Time of ischemia is, on average, a good biomarker for tissue viability; however, the window of opportunity for treatment varies across different individuals because of a range of compensatory mechanisms. Adjusting time to the adequacy of collateral flow leads to the concept of tissue window, a paradigm shift in stroke reperfusion therapy.

KEY POINTS

- Although IV recombinant tissue plasminogen activator (rtPA) is safe and effective in reducing disability in patients with acute ischemic stroke, several limitations prevent its more widespread use, including its narrow therapeutic time window and poor effect in the recanalization of large vessels.
- An essential premise in the development and optimization of endovascular therapies for acute ischemic stroke is the notion of the ischemic penumbra, essentially described as the area of brain tissue that is still viable but is critically hypoperfused and will progress to infarct in the absence of timely reperfusion.
- The different behaviors relative to the time–ischemia construct are now better delineated, allowing for the possibility of improving the selection of patients for acute reperfusion therapies.
- The duration of the penumbra in humans varies substantially, depending on factors such as degree of collateral blood flow supply, cerebral perfusion pressure, susceptibility of tissue to ischemia and ischemic preconditioning, location of the vessel occlusion, and other specific factors such as hyperglycemia, body temperature, and oxygen delivery capacity.
- In patients with proximal cerebral artery occlusions, no single practical and reliable imaging biomarker predicts infarct growth into the surrounding penumbra; however, the principles of clinical-imaging mismatch and perfusion-imaging mismatch have revolutionized the evaluation of patients with acute ischemic stroke.
- Cerebral collaterals can be broadly divided into the short bypass segments at the circle of Willis and the elongated leptomeningeal anastomotic routes able to deliver retrograde perfusion to adjacent vascular territories.
- The natural history of proximal intracranial arterial occlusion is usually that of poor outcomes. However, clinical severity at presentation (eg, baseline National Institutes of Health Stroke Scale [NIHSS] score) and the presence of collateral flow seem to be more important than the level of proximal intracranial arterial occlusion in determining the prognosis.
- An accurate assessment of the cerebral collateral circulation is a very important prerequisite for the appropriate management of patients with acute ischemic stroke.
- The success of the pivotal clinical trials demonstrating the efficacy of endovascular stroke therapy is mostly attributable to the use of next-generation mechanical thrombectomy devices, resulting in better recanalization rates, and to more rigid neuroimaging criteria for the choice of endovascular treatment candidates.
- CT perfusion might be helpful in choosing patients with higher chances of benefiting from the treatment. However, clinicians should be aware that CT perfusion may cause significant delays in workflow due to the longer acquisition and processing times, and it does not invariably provide accurate information, resulting in both overestimation and underestimation of ischemic core.
- Several studies have shown that automated processing of CT perfusion and MRI can provide a quantitative mismatch classification even among inexperienced neuroimaging centers.
- Recently, two clinical trials completely disrupted the time window concept in acute ischemic stroke, showing excellent clinical outcomes in patients treated up to 24 hours from symptom onset; effectiveness of late-window thrombectomy was maintained across all subgroups, including those defined by time, age, mode of presentation, and the Alberta Stroke Program Early CT Score (ASPECTS).
- Outcomes after mechanical thrombectomy seem to depend on the interaction of several variables including infarct volume, regional eloquence, age, and baseline functional status.
- The safety profile in the late time window seems to be similar to mechanical thrombectomy performed in up to 6 hours from symptom onset.

Article 5: Cerebral Small Vessel Disease

Natalia S. Rost, MD, MPH, FAAN, FAHA; Mark Etherton, MD, PhD. Continuum (Minneap Minn). April 2020; 26 (2 Cerebrovascular Disease):332–352.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the clinical significance and neuroimaging characteristics of cerebral small vessel disease and the impact on neurologic disease and current and potential therapeutic approaches.

RECENT FINDINGS:

Cerebral small vessel disease is increasingly prevalent and highly heterogeneous in neuroimaging and clinical presentation. Small subcortical infarcts, lacunes, cerebral microbleeds, cortical microinfarcts, and white matter hyperintensity of presumed vascular origin represent the major neuroimaging markers of small vessel disease. Increasing small vessel disease burden is associated with risk of incident stroke and dementia, as well as other neuropsychiatric symptoms. Current research strategies are targeting elucidation of the mechanisms of small vessel disease pathogenesis and pursuing clinical trials of therapeutic agents to reduce the clinical manifestations of cerebral small vessel disease.

SUMMARY:

Cerebral small vessel disease is common in aging adults and represents a major risk factor for multiple acute and chronic neurologic diseases. Increased awareness of cerebral small vessel disease as a modifiable risk factor holds potential for reducing neurologic disease morbidity and mortality across diverse populations in the United States and worldwide.

KEY POINTS

- Small vessel disease is prevalent among healthy aging adults and patients diagnosed with acute ischemic stroke or intraparenchymal hemorrhage.
- Small vessel disease is a multifaceted cerebrovascular syndrome that is composed of distinct clinical, neuropathologic, and neuroimaging findings.
- Brain MRI plays an essential role in the diagnosis and characterization of the small vessel disease spectrum.
- White matter hyperintensity is known to be one of the most well-characterized features of the small vessel disease neuroimaging spectrum; it is a validated biomarker and an established risk factor for stroke and intraparenchymal hemorrhage (incident and recurrent), vascular cognitive impairment and dementia, mortality, and functional disability among healthy aging adults and in patients with acute ischemic stroke.
- In cerebral amyloid angiopathy, several hemorrhagic manifestations, including acute intraparenchymal hemorrhage, subclinical macrohemorrhages, cerebral microbleeds, cortical subarachnoid hemorrhage, and cortical superficial siderosis, have been described.
- Cortical microinfarcts are silent and usually undetectable on conventional neuroimages.
- Small vessel disease is the most common cause of vascular cognitive impairment and dementia.
- Small vessel disease represents a significant risk factor for ischemic stroke, specifically small vessel occlusive mediated infarcts (lacunar stroke), and hemorrhagic stroke.
- In adults older than 55 years of age, cerebral amyloid angiopathy represents the most common etiology of spontaneous, nontraumatic lobar intraparenchymal hemorrhage.
- Apathy, depression, parkinsonism, anxiety, hallucinations, and sleep disturbances have all been reported in patients with small vessel disease.
- Intensive treatment of hypertension seems promising for treatment of small vessel disease.

- Given the multifactorial benefits of smoking cessation, diet, and aerobic exercise in secondary stroke prevention, these lifestyle modifications should be emphasized in all patients with stroke regardless of small vessel disease burden.

Article 6: The Evolving Concept of Cryptogenic Stroke

Hooman Kamel, MD. Continuum (Minneap Minn). April 2020; 26 (2 Cerebrovascular Disease):353–362.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses cryptogenic stroke and the results of recent randomized trials that can inform its evaluation and management.

RECENT FINDINGS:

Most cryptogenic strokes appear embolic, leading to the term *embolic stroke of undetermined source*. It was previously thought that embolic stroke of undetermined source was a single, therapeutically relevant entity, the underlying sources of which would respond to anticoagulant therapy; however, two large randomized trials found no benefit with anticoagulation compared to antiplatelet therapy for secondary stroke prevention after embolic stroke of undetermined source. A single antiplatelet drug remains the recommended long-term antithrombotic treatment for secondary stroke prevention in embolic stroke of undetermined source. However, three caveats should be considered with regard to cryptogenic stroke. First, those with minor stroke symptoms presenting early after onset should receive 3 weeks of dual antiplatelet therapy. Second, all patients with cryptogenic stroke should be monitored for atrial fibrillation. Third, patients 60 years of age or younger with a patent foramen ovale (PFO) should be carefully evaluated to determine whether the PFO may have caused the stroke and whether they might benefit from PFO closure.

SUMMARY:

More personalized strategies may soon be available to guide treatment of cryptogenic stroke. In the meantime, it is hoped that the application of recent findings from clinical trials will reduce stroke recurrence in this important population.

KEY POINTS

- It is important to elucidate the underlying mechanism of stroke because such knowledge informs treatment to prevent recurrent stroke.
- About one-fourth of ischemic strokes are cryptogenic, and one-sixth meet the definition of embolic stroke of undetermined source.
- The minimum evaluation of ischemic stroke involves a transthoracic echocardiogram, imaging of the cervical and intracranial arteries, a 12-lead ECG, and at least 24 hours of continuous heart-rhythm monitoring.
- Based on two high-quality randomized clinical trials, it is clear that an empiric strategy of anticoagulation for all cases of cryptogenic stroke is not effective and may be harmful. Therefore, a single antiplatelet agent remains the recommended long-term antithrombotic treatment for secondary stroke prevention.
- Patients with cryptogenic stroke with minor stroke symptoms presenting early after onset should be treated with a 3-week course of dual antiplatelet therapy.
- Patients with cryptogenic stroke should be monitored for atrial fibrillation.

- Patients with cryptogenic stroke with a patent foramen ovale (PFO) should be carefully evaluated to determine whether the PFO may have been responsible for the stroke and whether they might benefit from PFO closure.

Article 7: Stroke in Women

Hanne Christensen, MD, PhD, DMSci; Cheryl Bushnell, MD, MHS. Continuum (Minneap Minn). April 2020; 26 (2 Cerebrovascular Disease):363–385.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews sex differences in stroke risk and presentation, with a particular emphasis on the unique risk factors women experience throughout the lifespan.

RECENT FINDINGS:

Although prior studies suggested women have worse outcomes after stroke, it is now clear that age, prestroke functional status, and comorbidities explain many of the differences between men and women in stroke severity, functional outcomes, and mortality. Several meta-analyses and large cohort studies have evaluated the risk factors for women related to reproductive factors and found that fewer years between menarche and menopause, pregnancy complications (preeclampsia/eclampsia, preterm delivery, and stillbirth), oophorectomy, hormone replacement therapy use, and younger age at menopause all increase the risk of stroke. Although the nonreproductive risks of stroke overlap between men and women, those with greater impact on women include age, hypertension, atrial fibrillation, socioeconomic status, and depression.

SUMMARY:

Significant sex differences are observed in risk factors of stroke and stroke outcome. Including this information in the clinical assessment of the individual patient may support development of more effective prevention plans.

KEY POINTS

- Although the incidence of stroke up to 2010 appeared to be decreasing overall, this trend is driven by a decrease in incidence in men, not women.
- Age at menarche at 10 years of age or younger increases the risk of stroke later in life by about 25%.
- Women with preeclampsia have an increased risk of both ischemic and hemorrhagic stroke in the peripartum and postpartum periods, and this risk increases with additional comorbidities such as atrial fibrillation, migraine, or congenital heart disease.
- Pregnant women with an acute stroke may be candidates for either IV thrombolysis or thrombectomy; referral to a center with multidisciplinary expertise is essential for these treatment decisions.
- Hypertensive disorders of pregnancy increase the risk of multiple vascular complications later in life, including hypertension, stroke, heart disease, heart failure, and cerebral microvascular disease.
- A reproductive lifespan of less than 30 years (age of menarche subtracted from the age at menopause) is associated with an increased risk of stroke.
- Women have strokes at older ages and tend to have lower levels of education than men, so it is important to tailor necessary resources accordingly.
- Compared to men, women have a higher prevalence of hypertension over age 65, and women with stroke are more likely to have hypertension, probably due to older age of stroke onset.

- Atrial fibrillation has a higher impact on the risk of stroke in women compared to men. This can be explained by the more advanced age in women at the time of stroke, that atrial fibrillation carries twice the risk of stroke in women in comparison to men, and, further, women have more severe stroke presentations than men in stroke related to atrial fibrillation.
- Women are more likely to present with nontraditional stroke symptoms and mimics than men.
- Women have worse outcomes after stroke than men, a result of older age at the time of stroke onset, worse prestroke functional status, and multiple comorbidities in women.
- Women are underrepresented in many clinical trials of stroke treatments, limiting the full understanding of both benefits and harm in women.

Article 8: Ischemic Stroke in Young Adults

Jukka Putaala, MD, PhD, MSc. Continuum (Minneap Minn). April 2020; 26 (2 Cerebrovascular Disease):386–414.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews current knowledge on epidemiology, risk factors and causes, diagnostic considerations, management, and prognosis of ischemic stroke in young adults (those 55 years old and younger).

RECENT FINDINGS:

The incidence of ischemic stroke in young adults has been increasing since the 1980s, which has occurred in parallel with increasing prevalence of vascular risk factors and substance abuse among the younger population. Young adults have a considerably wider range of risk factors than older patients, including age-specific factors such as pregnancy/puerperium and oral contraceptive use. Behavioral risk factors such as low physical activity, excess alcohol consumption, and smoking are factors as well. More than 150 identified causes of early-onset ischemic stroke exist, including rare monogenic disorders. Several recent advances have been made in diagnosis and management of stroke in young adults, including molecular characterization of monogenic vasculitis due to deficiency of adenosine deaminase 2 and transcatheter closure of patent foramen ovale for secondary prevention. Compared with the background population of the same age and sex, long-term mortality in patients remains fourfold higher with cardiovascular causes underlying most of the deaths. The cumulative rate of recurrent stroke extends up to 15% at 10 years. Patients with atherosclerosis, high-risk sources of cardioembolism, and small vessel disease underlying their stroke seem to have the worst prognosis regarding survival and recurrent vascular events. Young stroke survivors also often have other adverse outcomes in the long term, including epilepsy, pain, cognitive problems, and depression.

SUMMARY:

Systematic identification of risk factors and causes and the motivation of patients for long-term prevention and lifestyle changes are of utmost importance to improve the prognosis of early-onset ischemic stroke.

KEY POINTS

- Of great public health importance, the incidence of ischemic stroke at younger ages has been increasing worldwide from the 1980s to 2010s.

- In the large Stroke in Young Fabry Patients study, the most common risk factors were abdominal obesity, tobacco smoking, physical inactivity, and hypertension.
- Migraine with aura is a risk factor for early-onset ischemic stroke.
- The risk for ischemic stroke or myocardial infarction increases with higher doses of estrogen and is doubled for women taking pills containing at least 50 mcg of estrogen compared with nonusers.
- Ischemic stroke complicates fewer than 20 per 100,000 pregnancies. The risk is highest during the third trimester, around delivery, and in the postpartum period.
- The association of patent foramen ovale and ischemic stroke appears stronger for younger (approximately fivefold risk) than older individuals (approximately twofold risk) when compared with stroke-free individuals or patients with known stroke causes.
- The Risk of Paradoxical Embolism (RoPE) score may be helpful when estimating the probability of a patent foramen ovale causing the stroke. In the RoPE score, younger age, cortical infarct, and a lack of vascular risk factors give more points and a greater probability of stroke-related patent foramen ovale.
- Both recent and long-term heavy drinking, including binge drinking, have been shown to increase the risk of ischemic stroke at younger ages.
- The route and mode of illicit drug administration modulate the risk and affect the possible pathophysiologic mechanisms of ischemic stroke.
- Malignancy is a risk factor for ischemic stroke in young adults.
- Antiphospholipid syndrome can be diagnosed with two positive blood test results at least 12 weeks apart showing the presence of antiphospholipid antibodies—most commonly lupus anticoagulant, anticardiolipin antibodies, or anti–β2 glycoprotein-I antibodies—reacting against proteins that bind to phospholipids on plasma membranes.
- In most young patients with ischemic stroke, anticardiolipin antibodies or anti–β2 glycoprotein-I antibodies are only modestly elevated, and often on one occasion only, and so criteria for antiphospholipid syndrome are not met.
- Rare causes, eg, noninflammatory and inflammatory vasculopathies, hematologic causes, and monogenic disorders, together cause up to 22% of ischemic strokes in young adults.
- The most frequent singular cause of ischemic stroke in young adults is carotid artery dissection, causing up to one-fifth of all events. In the largest series, etiology of stroke remained undetermined in up to 40%.
- One recent finding in young patients with otherwise cryptogenic stroke is the presence of carotid webs, which are seen on CT angiography and defined as intimal variants of fibromuscular dysplasia appearing as a shelflike lesion on the posterior aspect of the carotid bulb.
- A routine 12-lead ECG is a first-line investigation that can reveal occult atrial fibrillation and hints from other high-risk sources of embolism. For example, P terminal force in lead V_1 appeared strongly associated with a final diagnosis of cardioembolism in young patients.
- Cardiac MRI and CT can be used as complementary studies, especially when further information is needed on intracardiac masses, congenital heart disease, valvular disease, or when transesophageal echocardiography is contraindicated or resulted in suboptimal findings.
- Discontinuation of antiplatelets and antihypertensives and poor adherence to antihypertensives are associated with a heightened risk of recurrent stroke, other vascular events, and mortality.
- Three positive trials compared transcatheter closure of patent foramen ovale with medical treatment. A meta-analysis of these and two earlier completed trials concluded that patent foramen ovale closure reduces the risk of recurrent ischemic stroke with an odds ratio of 0.43 (95% CI, 0.21 to 0.90) and a number needed to treat of 46. However, a significant increase in new-onset atrial fibrillation was associated with transcatheter closure with an odds ratio of 5.15 (95% CI, 2.18 to 2.15), although atrial fibrillation episodes in most patients may have been transient.
- In carotid artery dissection, a randomized trial found no difference between antiplatelets and anticoagulants in prevention of recurrent stroke.
- The risk of recurrence remains high for years after the index ischemic event, with cumulative risk for stroke around 10% at 5 years and 15% at 10 years.

- One study followed young patients with ischemic stroke and transient ischemic attack and age-matched controls for 11 years and observed that up to 50% of the patients had a decline in their cognitive skills even if the motor symptoms were mild.
- A substantial proportion of young patients with ischemic stroke are not able to return to work, and this proportion increases over time.

Article 9: Recovery After Stroke

Steven C. Cramer, MD, MMSc, FAHA, FAAN. Continuum (Minneap Minn). April 2020; 26 (2 Cerebrovascular Disease):415–434.

ABSTRACT

PURPOSE OF REVIEW:

This article describes restorative therapies to improve patient outcomes after stroke. These therapies contrast with acute stroke treatments such as recombinant tissue plasminogen activator (rtPA) and thrombectomy that target clots, aim to salvage threatened brain tissue to limit injury, and have a time window measured in hours. Restorative therapies target the brain, aim to promote plasticity within surviving brain tissue, and have a time window measured in days to weeks or longer.

RECENT FINDINGS:

A number of drugs are under study. Preclinical studies are providing attractive therapeutic candidates for translation, such as the C-C chemokine receptor 5 inhibitor maraviroc. Some drug studies have used a pragmatic approach, which is premature for the nascent field of neural repair. Substantial data support the utility of activity-dependent therapies, including constraint-induced movement therapy, with recent studies supporting the need for very high doses to generate the best functional gains. While stem cell therapies are at an early stage, mounting preclinical evidence supports the efficacy of mesenchymal stem cells; some initial human studies are supportive. Several types of brain stimulation have been examined, and in some cases initial studies are promising.

SUMMARY:

Improved insights into stroke recovery and its treatment have the potential to reduce disability in a large segment of stroke survivors.

KEY POINTS

- A stroke also triggers numerous cellular and molecular cascades that facilitate spontaneous repair and recovery.
- In contrast to acute stroke treatments such as recombinant tissue plasminogen activator (rtPA) and thrombectomy, recovery treatments target surviving brain tissue with the goal of promoting neural repair.
- Evidence exists that a very high dose of rehabilitation therapy results in large improvements in functional status.
- The physiologic state of the brain evolves rapidly and substantially during the weeks that follow a stroke, and this carries with it varying receptivity and vulnerability to interventions at different time points during this period.
- As with all restorative therapies, studying the mechanism of action in humans will increase the likelihood that the target population can be identified and that methods can be devised to stratify patients according to the likelihood that treatment will provide benefit.
- Therapeutic targets of stroke recovery vary over time.

- Increasing evidence suggests that the best results derived from a restorative therapy occur when the therapy is paired with concomitant training.
- It is useful to understand the sites of brain injury and details of brain function perturbation that have occurred consequent to the infarct to optimize clinically useful neural plasticity.
- When treating the brain after stroke to promote neural plasticity, treatment will be maximally effective when patients are stratified on the basis of assessments that identify target patient subgroups.
- Restorative therapies benefit patients by improving the function of specific neural systems. Improvement is seen in neural systems with sufficient surviving substrate that are amenable to repair.

Article 10: Medical Management for Secondary Stroke Prevention

Anthony S. Kim, MD, MAS. Continuum (Minneap Minn). April 2020; 26 (2 Cerebrovascular Disease):435–456.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the evidence base and recommendations for medical management for secondary stroke prevention.

RECENT FINDINGS:

Recent developments for secondary stroke prevention include evidence to support the use of short-term dual antiplatelet therapy after minor stroke and transient ischemic attack, direct oral anticoagulants for nonvalvular atrial fibrillation, reversal agents for direct oral anticoagulant–associated hemorrhage, and aspirin rather than presumptive anticoagulation with a direct oral anticoagulant for embolic stroke of undetermined source.

SUMMARY:

Most strokes are preventable. The mainstays of medical management for secondary stroke prevention include antihypertensive therapy; antithrombotic therapy, with antiplatelet agents for most stroke subtypes or anticoagulants such as warfarin or a direct oral anticoagulant for cardioembolic stroke specifically; cholesterol-lowering therapy, principally with statins, but with potential roles for ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitors in selected patients; and glycemic control to prevent microvascular complications from diabetes mellitus or pioglitazone in selected patients with insulin resistance but not diabetes mellitus.

KEY POINTS

- Prevention of recurrent stroke requires an early and aggressive approach.
- Most strokes are preventable.
- Medical management is but one component of a comprehensive approach to stroke secondary prevention that may include surgical or procedural options, behavioral interventions, and addressing the social determinants of health.
- The choice of antihypertensive agents used should be individualized with a focus on the degree of blood pressure reduction achieved.
- For secondary stroke prevention, a blood pressure target of <140/90 mm Hg is justified, and a more stringent goal of <130/80 mm Hg is reasonable for selected patients.
- Aspirin 325 mg should be administered initially for most patients with stroke or transient ischemic attack.

- A loading dose of clopidogrel followed by 21 days of treatment with aspirin and clopidogrel is reasonable when initiated up to 3 days after minor stroke and transient ischemic attack.
- Chronic use of combination aspirin and clopidogrel therapy is not recommended for stroke secondary prevention.
- Triple antiplatelet therapy with aspirin, clopidogrel, and dipyridamole for secondary stroke prevention is not recommended.
- Cilostazol and ticagrelor are investigational antiplatelet agents, and their precise role in treatment of stroke is unclear.
- Anticoagulation with warfarin or direct oral anticoagulants is indicated for secondary stroke prevention for cardioembolic stroke including nonvalvular atrial fibrillation and valvular heart disease.
- Statins are a first-line treatment for dyslipidemia after stroke.
- Ezetimibe can be considered with statin intolerance or when the response to statins is inadequate.
- Proprotein convertase subtilisin/kexin type 9 inhibitors can result in dramatic reductions of low-density lipoprotein levels but are costly and require subcutaneous injections.
- Intensive glycemic control may have benefits for microvascular disease, but intensive management of glucose levels after acute stroke or for chronic secondary stroke prevention may have limited benefits over standard therapy.
- Pioglitazone may have benefits for secondary prevention in patients with documented insulin resistance, but this is partially outweighed by adverse events.

Article 11: Surgical Approaches to Stroke Risk Reduction

Michael F. Waters, MD, PhD, FAAN, FAHA. Continuum (Minneap Minn). April 2020; 26 (2 Cerebrovascular Disease):457–477.

ABSTRACT

PURPOSE OF REVIEW:

Surgical vascular intervention is an important tool in reducing the risk of stroke. This article examines the evidence for using the available options.

RECENT FINDINGS:

Carotid endarterectomy is an effective treatment option for reducing the risk of stroke in appropriately selected patients. Patients should be stratified for future stroke risk based on both the degree of stenosis and the presence of symptoms referable to the culprit lesion. Carotid stenting is also useful in reducing stroke risk, again in carefully selected patients. Because of the publication of significant data regarding both carotid endarterectomy and carotid artery stenting in the last several years, selection can be far more personalized and refined for individual patients based on demographics, sex, patient preference, and medical comorbidities. Routine extracranial-intracranial bypass surgery remains unproven as a therapeutic option for large vessel occlusion in reducing the incidence of ischemic stroke although some carefully screened patient populations remaining at high risk may benefit; procedural risks and pathology related to alterations in blood flow dynamics are challenges to overcome. Indirect revascularization remains an appropriate solution for carefully selected patients with cerebral large vessel steno-occlusive disease, and multiple variations of surgical technique are patient specific. Indirect revascularization may benefit from clinical trials with larger patient populations for validation in specific pathologies and offers the advantages of lower surgical complication rates and reduced risk of pathologic responses to altered cerebral flow dynamics.

SUMMARY:

Surgical solutions to reduce stroke risk provide important alternatives in appropriately selected patients and should be considered in addition to medical management and lifestyle modification for optimizing patient outcomes.

KEY POINTS

- In select patients, carotid endarterectomy remains an effective and durable solution to reducing the risk of stroke.
- For optimal care, patients should be risk stratified by both the degree of carotid stenosis and symptomatic status.
- Carotid artery stenting is an appropriate alternative to endarterectomy in a subset of patients, depending on certain aspects of the patient's overall health and demographic profile.
- Patients presenting with asymptomatic internal artery stenosis greater than 70% should be referred for potential enrollment into the CREST-2 clinical trial.
- Intensive medical management remains an important adjuvant for stroke risk reduction irrespective of the decision regarding surgical risk reduction with revascularization by either carotid endarterectomy or carotid artery stenting procedures.
- Multiple large, multicenter trials comparing surgical with medical management have failed to demonstrate an advantage for surgical revascularization in patients with symptomatic, intracranial steno-occlusive arterial disease. Routine extracranial-intracranial bypass surgery remains unproven as a therapeutic option for large vessel occlusion in reducing the incidence of ischemic strokes, although some carefully screened patient populations remaining at high risk may benefit.
- The majority of risk in extracranial-intracranial bypass surgeries is immediate to the periprocedural timeframe and not secondary to patency failure of the revascularization bypass.
- Patients with refractory, symptomatic, intracranial steno-occlusive arterial disease and ongoing ischemic events, who are carefully selected with multimodal diagnostic testing, may benefit from surgical revascularization.
- Intensive medical management remains an important adjuvant for risk reduction in patients with symptomatic, intracranial steno-occlusive arterial disease.
- Indirect surgical revascularization may represent an appropriate alternative to reduce the incidence of stroke in patients with symptomatic intracranial atherosclerotic disease.
- Randomized clinical trials are needed to validate the appropriateness and efficacy of indirect revascularization in mitigating stroke risk in patients with symptomatic intracranial atherosclerotic disease.

Article 12: Management of Unruptured Cerebral Aneurysms and Arteriovenous Malformations

Ynte M. Ruigrok, MD, PhD. Continuum (Minneap Minn). April 2020; 26 (2 Cerebrovascular Disease):478–498.

ABSTRACT

PURPOSE OF REVIEW:

Unruptured intracranial aneurysms and brain arteriovenous malformations (AVMs) may be detected as incidental findings on cranial imaging. This article provides a practical approach to the management of unruptured intracranial aneurysms and unruptured brain AVMs and reviews

the risk of rupture, risk factors for rupture, preventive treatment options with their associated risks, and the approach of treatment versus observation for both types of vascular malformations.

RECENT FINDINGS:

For unruptured intracranial aneurysms, scoring systems on the risk of rupture can help with choosing preventive treatment or observation with follow-up imaging. Although the literature provides detailed information on the complication risks of preventive treatment of unruptured intracranial aneurysms, individualized predictions of these procedural complication risks are not yet available. With observation with imaging, growth of unruptured intracranial aneurysms can be monitored, and prediction scores for growth can help determine the optimal timing of monitoring. The past years have revealed more about the risk of complications of the different treatment modalities for brain AVMs. A randomized clinical trial and prospective follow-up data have shown that preventive interventional therapy in patients with brain AVMs is associated with a higher rate of neurologic morbidity and mortality compared with observation.

SUMMARY:

The risk of hemorrhage from both unruptured intracranial aneurysms and brain AVMs varies depending on the number of risk factors associated with hemorrhage. For both types of vascular malformations, different preventive treatment options are available, and all carry risks of complications. For unruptured intracranial aneurysms, the consideration of preventive treatment versus observation is complex, and several factors should be included in the decision making. Overall, it is recommended that patients with unruptured asymptomatic brain AVMs should be observed.

KEY POINTS

- Rupture of an aneurysm leads to a subarachnoid hemorrhage, which has devastating effects; one-third of patients die, and one-third are rendered dependent.
- The PHASES (Population, Hypertension, Age, Size of aneurysm, Earlier subarachnoid hemorrhage from another aneurysm, and Site of aneurysm) score provides absolute estimates for the 5-year risk of rupture of unruptured intracranial aneurysms based on the presence of these different risk factors.
- Depending on the number of different risk factors present, the 5-year risk of rupture of unruptured intracranial aneurysms ranges from 0.25% to more than 15%.
- Patient-related risk factors for rupture of unruptured intracranial aneurysms in addition to the PHASES score are smoking and, possibly, a positive family history of intracranial aneurysms.
- In addition to the PHASES score, aneurysm-related risk factors for unruptured intracranial aneurysm rupture are irregular shape and possibly aspect ratio (the ratio of aneurysm neck-to-dome length to aneurysm neck width) and height to width ratio.
- Unruptured intracranial aneurysms can be preventively treated by surgical clipping or endovascular coiling. Both treatments have a risk of complications, and different factors associated with an increased risk have been identified.
- When deciding whether to preventively treat unruptured intracranial aneurysms, several factors should be considered, including the life expectancy of the patient, the estimated risk of rupture, the risk of complications of preventive treatment, and the level of anxiety of the patient with regard to the knowledge of having an unruptured intracranial aneurysm.
- If an unruptured intracranial aneurysm is not preventively treated by surgery or endovascular treatment, patients are often advised to undergo serial follow-up imaging to detect aneurysm growth.
- The risk of rupture of unruptured intracranial aneurysms that grew during follow-up is higher than in unruptured intracranial aneurysms that remained stable. In the case of growth, the decision not to preventively treat the unruptured intracranial aneurysm should be reconsidered.

- Hypertension should be treated in patients with an unruptured intracranial aneurysm, and these patients should be advised to quit smoking.
- The mortality rate after hemorrhage from a brain arteriovenous malformation has a wide range from 12% to 67%, and, of the patients who survive the hemorrhage, approximately 45% have severe deficits.
- The risk of hemorrhage from a previously unruptured brain arteriovenous malformation is 1% to 3% per year, and the risk varies depending on the number of risk factors associated with brain arteriovenous malformation hemorrhage.
- Risk factors associated with brain arteriovenous malformation hemorrhage are previous hemorrhage, race, age, deep brain location, and exclusive deep venous drainage.
- Brain arteriovenous malformations can be preventively treated by microsurgery, endovascular embolization, and stereotactic radiosurgery. Each treatment has a risk of complications, and different factors associated with an increased risk have been identified.
- The main goal of treatment is to prevent hemorrhage from the brain arteriovenous malformation, but treatment to control seizures or stabilization of progressive neurologic deficits caused by the brain arteriovenous malformation may also be considered.
- Microsurgery, endovascular embolization, and stereotactic radiosurgery are often combined to optimally treat brain arteriovenous malformations.
- Follow-up imaging can take place after treatment of a brain arteriovenous malformation to ensure that it is completely obliterated. This imaging is certainly indicated after embolization and radiosurgery.
- Patients with brain arteriovenous malformations have a higher rate of neurologic morbidity and mortality after preventive interventional therapy compared with observation. These data indicate that patients with unruptured asymptomatic brain arteriovenous malformations should be observed. However, in the case of unruptured symptomatic arteriovenous malformations, treatment may be considered to reduce epileptic seizures or neurologic deficits caused by the arteriovenous malformations.
- Evidence to support the use of imaging to screen and monitor patients with unruptured brain arteriovenous malformations is lacking.
- No medical treatment is available to treat brain arteriovenous malformations or to reduce the risk of hemorrhage from them.

CONTINUUM
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Genetic Diagnostics for Neurologists

Laura Silveira-Moriyama, MD, PhD; Alex R. Paciorkowski, MD. Continuum (Minneap Minn). February 2018; 24 (1 Child Neurology):18–36.

Abstract

Purpose of Review:

This article puts advances in the field of neurogenetics into context and provides a quick review of the broad concepts necessary for current practice in neurology.

Recent Findings:

The exponential growth of genetic testing is due to its increased speed and decreasing cost, and it is now a routine part of the clinical care for a number of neurologic patients. In addition, phenotypic pleiotropy (mutations in the same gene causing very disparate phenotypes) and genetic heterogeneity (the same clinical phenotype resulting from mutations in different genes) are now known to exist in a number of conditions, adding an additional layer of complexity for genetic testing in these disorders.

Summary:

Although the growing complexity of technical knowledge in the ordering and interpretation of genetic tests makes it necessary for neurologists to consult medical geneticists, limitations in the availability of such professionals often means neurologists will be on the front line dealing with suspected or confirmed neurogenetic conditions. The growing availability of broad genetic testing through chromosomal microarray and next-generation sequencing and the expanded phenotypic spectrum of many conditions has implications for genetic counseling and medical management. This article discusses the various forms of genetic variability and how to test for each of them. It also provides an update on the most common forms of neurologic presentations of genetic disease and a review of testing strategies.

Key Points

- The growing complexity of technical knowledge involved in ordering and interpreting genetic tests makes the opinion of a medical genetics specialist desirable in the many cases of suspected neurogenetic conditions.
- The shortage of medical genetics specialists makes it necessary for neurologists to be familiar with basic concepts in medical genetics that will enable handling some cases and referring when appropriate.

- Before and after genetic testing, it is imperative to conduct appropriate genetic counseling. It is ideal to have a specialized genetic counselor provide this service, but in many limited-resource settings, this responsibility lies with the neurologist.
- Genetic counseling for massive gene sequencing (such as whole-exome sequencing) should include the expected and unexpected outcomes of testing, the likelihood and type of incidental findings, and which results will or will not be disclosed.
- Knowledge about the relationship between genotype (what the DNA looks like) and phenotype (what the patient looks like) has changed dramatically in the past decade.
- Mutations in various different genes can cause very similar phenotypes. This is called *genetic heterogeneity*.
- Most genes are now believed to be associated with varied phenotypes (phenotypic pleiotropy).
- Genetic variability may be normal, predispose the patient to medical conditions (risk variants), cause medical conditions (pathogenic variants), or need further studies to clarify its nature (variant of unknown significance). Interpretation of variants of unknown significance requires the opinion of a medical genetics specialist.
- Multiplex ligation-dependent probe amplification detects dose changes within a gene, chromosomal microarray detects dose changes affecting a small part of the chromosome (greater than 100,000 base pairs), while karyotyping only detects large changes (greater than 5,000,000 base pairs).
- Dosage abnormalities can affect only a single gene or a whole region of the chromosome or be in the form of an increased number of repeats in a given sequence that normally is repeated up to a certain number.
- Southern blot detects an increased number of repeats in a particular sequence. It is specific for the sequence examined, so if more than one gene with repeats can cause the phenotype observed, a panel of Southern blot for various genes can be requested (eg, testing for various spinocerebellar ataxias at the same time).
- In addition to gene sequence and gene dose, other factors affect the production of proteins (epigenetic factors). An important factor affecting gene expression as a disease mechanism is methylation of DNA.
- The majority of neurogenetic conditions described thus far are caused by sequence abnormalities that can be detected by DNA sequencing.
- Genomic data, including the sequence and dose of genes, needs to be analyzed and interpreted to yield any meaningful clinical result. Interpretation of these results requires the expertise of bioinformaticians and geneticists.
- Most pathogenic genetic variability is caused by variation of sequence or dose of the DNA. The techniques used to detect these types of abnormalities are very different, so ordering the correct test is as important as targeting the right gene.
- Genomic data can be stored indefinitely and reanalyzed as the knowledge about genomics evolves.
- Given the rapidity with which new genetic causes of neurologic conditions are being discovered, exome sequencing is probably the most cost-effective approach to diagnosis in phenotypes with great genetic heterogeneity without a high chance of chromosomal events, but many exceptions exist.
- Global developmental delay, intellectual disability, autism spectrum disorder, and epileptic encephalopathies are frequently caused by chromosomal-level events, so chromosomal microarray and karyotype are likely to be helpful.
- Autism, intellectual disability, and epileptic encephalopathy are all conditions with great genetic heterogeneity, and each can be caused by mutations in more than 50 known genes.

- In neurodegeneration, movement disorders, and neuromuscular disorders, excluding compatible metabolic causes is paramount. Often, the opinion of a subspecialist is necessary before genetic testing.

Testing for Inborn Errors of Metabolism

Jennifer M. Kwon, MD, MPH, FAAN. Continuum (Minneap Minn). February 2018; 24 (1 Child Neurology):37–56.

Abstract

Purpose of Review:

This article provides an overview of genetic metabolic disorders that can be identified by metabolic tests readily available to neurologists, such as tests for ammonia, plasma amino acids, and urine organic acids. The limitations of these tests are also discussed, as they only screen for a subset of the many inborn errors of metabolism that exist.

Recent Findings:

Advances in next-generation sequencing and the emerging use of advanced metabolomic screening have made it possible to diagnose treatable inborn errors of metabolism that are not included in current newborn screening programs. Some of these inborn errors of metabolism are especially likely to present with nonspecific neurologic phenotypes, such as epilepsy, ataxia, or intellectual disability. However, cost may be a barrier to obtaining these newer tests. It is important to keep in mind that common metabolic testing may lead to treatable diagnoses. Resources are available to guide neurologists in diagnosing genetic metabolic conditions.

Summary:

This article introduces the clinical presentations of treatable inborn errors of metabolism that are important for neurologists to consider in patients of all ages. Inborn errors of metabolism are rare, but they can present with neurologic symptoms. Newborns are now screened for many treatable metabolic disorders, but these screening tests may miss milder presentations of treatable inborn errors of metabolism that present later in life. These patients may present to adult neurologists who may be less likely to consider metabolic genetic testing.

Key Points

- There must be a low threshold for considering an inborn error of metabolism since presentations are nonspecific.
- Inborn errors of metabolism often present with symptoms that suggest sepsis or gastrointestinal illness accompanied by weakness, developmental delay, and poor growth. If the history suggests decline or an attack of illness associated with increased catabolism or increased protein intake, consider testing for metabolic disorders.
- Neurologists should recognize the highly specialized nature of diagnosing and treating metabolic disorders and involve a metabolic geneticist in the diagnosis and care of patients with inborn errors of metabolism.
- Almost all inborn errors of metabolism are autosomal recessive disorders. Genetic counseling must be provided to families learning of a diagnosis of an inborn error of metabolism.

- Prior to delivery, infants are protected from toxic effects of metabolite accumulation by placental clearance, which is why a symptom-free period often occurs right after birth.
- In the setting of acute encephalopathy (eg, where a lumbar puncture would be considered an appropriate test), remember to check an ammonia level.
- Elevated ammonia levels can cause vomiting, encephalopathy, cerebral edema, and hyperventilation.
- Urea cycle defects can present as a catastrophic neonatal illness or during childhood or teenage years, often after significant stress (eg, pregnancy, steroids, excessive protein ingestion.)
- Although ornithine transcarbamoylase deficiency is X-linked, men may present later in life.
- Hyperammonemia is seen in organic acid disorders because the accumulating acids inhibit the urea cycle.
- Treatable cobalamin defects may present in adulthood with brain and spinal cord abnormalities suggestive of myelin disorders.
- Serum methylmalonic acid and homocysteine, commonly used to identify vitamin B12 and folate deficiency, will also help screen for treatable cobalamin defects.
- The organic acid disorders methylmalonic acidemia and propionic acidemia can selectively damage basal ganglia and white matter.
- Late-onset organic acid disorders may be treatable and are relatively easy to screen for with urine studies; their identification may prevent permanent brain injury.
- Elevated phenylalanine acts as a neurotoxin, which is why the phenylalanine-restricted diet for phenylketonuria is a diet for life.
- Untreated homocystinuria is associated with strokes, lens dislocation, and skeletal abnormalities.
- The clinical presentation of maple syrup urine disease, with metabolic crisis and coma, is similar to the organic acid disorders, but there may be no metabolic acidosis or hypoglycemia.
- Pyridoxine-dependent epilepsy used to be a clinical diagnosis but now biochemical (plasma and urine α-aminoadipic semialdehyde) and molecular (*ALDH7A1* gene) tests are available.
- Diagnosis of glucose transporter type 1 deficiency requires documentation of low CSF glucose values in the setting of normal blood glucose. Mutational testing of the *SLC2A1* gene can also be performed.
- Patients with glucose transporter type 1 deficiency can be treated with the ketogenic diet.

Hypoxic-Ischemic Encephalopathy and Other Neonatal Encephalopathies

Hannah C. Glass, MDCM, MAS. Continuum (Minneap Minn). February 2018; 24 (1 Child Neurology):57–71.

Abstract

Purpose of Review:

Neonatal encephalopathy is the most common condition in neonates encountered by child neurologists. The etiology is most often global hypoxia-ischemia due to failure of cerebral perfusion to the fetus caused by uterine, placental, or umbilical cord compromise prior to or

during delivery. Other etiologies of neonatal encephalopathy include ischemic stroke and intracranial hemorrhage, infection, developmental anomalies, and inborn errors of metabolism.

Recent Findings:

Therapeutic hypothermia is standard of care for the treatment of neonatal encephalopathy presumed to be caused by hypoxia-ischemia. The number needed to treat is approximately 6 to 7 to prevent one child from either death or disability at age 18 to 22 months. EEG monitoring and MRI are important tools in determining the etiology of encephalopathy and prognosis of the infant.

Summary:

Neonatal encephalopathy is a heterogeneous disorder that is characterized by alterations in mental status, hypotonia, seizures, and abnormalities in feeding and respiration. The most common cause of neonatal encephalopathy is hypoxic-ischemic encephalopathy, for which treatment with 72 hours of therapeutic hypothermia is associated with reduced death or disability.

Key Points

- The hallmark signs of neonatal encephalopathy are altered mental status (eg, irritability, lethargy, coma), seizures, hypotonia, abnormal primitive reflexes, apnea, feeding disturbance, and abnormal cry.
- Neonatal encephalopathy that is caused by an intrapartum event leading to perinatal hypoxia-ischemia (sometimes called perinatal *asphyxia*) has historically been called *hypoxic-ischemic* encephalopathy; however, some prefer the term neonatal encephalopathy given that the exact pathogenesis is often not known.
- While a well-defined hypoxic-ischemic event (eg, placental abruption, uterine rupture, cord prolapse) is the cause of encephalopathy in many infants, other causes of altered mental status or seizures in a neonate include ischemic or hemorrhagic stroke, infection, brain malformation, genetic conditions, and inborn errors of metabolism.
- In addition to a comprehensive neurologic examination, neonates with encephalopathy should be carefully evaluated for signs of abnormal fetal development, including dysmorphic craniofacial features, birthmarks, and congenital anomalies of the internal organs and skeleton.
- The American Clinical Neurophysiology Society recommends neurophysiologic monitoring using continuous EEG or amplitude-integrated EEG to determine the presence of electrographic seizures and to establish the severity of encephalopathy.
- MRI is recommended for all neonates with encephalopathy or seizures to assist with identifying the etiology of encephalopathy, as well as for assisting with prognosis.
- Optimized care involves active management of temperature (including therapeutic hypothermia for neonates with encephalopathy due to hypoxia-ischemia and avoiding hyperthermia for all brain-injured neonates), oxygenation/ventilation, and glucose (especially avoiding hypoglycemia, which can cause de novo injury and may exacerbate underlying hypoxic-ischemic injury).
- Therapeutic hypothermia to 33.5°C (92.3°F) for 72 hours is standard of care for neonates who are at least 36 weeks gestational age and who have neonatal encephalopathy that is due to suspected or confirmed hypoxia-ischemia.
- Eligibility criteria in clinical trials for therapeutic hypothermia for neonatal encephalopathy varied slightly between trials and typically involved some combination of gestational age, indicator of perinatal distress, and moderate to severe encephalopathy.

- Therapeutic hypothermia should be implemented within 6 hours after birth, and evidence from preclinical studies and the randomized controlled trials suggests that earlier implementation leads to better outcomes.
- Continuous brain monitoring, preferably with continuous video-EEG, is recommended for all neonates undergoing hypothermia.
- The risk of seizures in neonates undergoing hypothermia is approximately 50%.
- Normal or mildly abnormal EEG (eg, mild excess discontinuity) or early recovery of severe abnormalities within the first 24 to 48 hours after birth portends good prognosis, whereas severe (and especially persistently severe) abnormalities (eg, burst suppression, depressed and undifferentiated tracing, extremely low voltage) are associated with brain injury, death, and disability.
- The predominant patterns of injury in neonates with hypoxic-ischemic encephalopathy are (1) basal ganglia/thalamus (with extension to rolandic cortex, hippocampus, and brainstem in severe cases, which is seen predominantly in the setting of acute profound disruption in placental perfusion), and (2) watershed areas (with injury to the watershed zones of the anterior, middle, and posterior cerebral arteries), which occurs in the setting of partial prolonged injuries.
- Developmental care by occupational and physical therapists and lactation experts can begin during the inpatient admission to assess and manage positioning, oral feeding readiness and preparation, and behavioral state regulation and to optimize tone, strength, and ability to deal with environmental stimuli.
- Since survivors of neonatal encephalopathy are at high risk for long-term disabilities, children should be followed longitudinally by a high-risk program or a child neurologist as recommended by the American Academy of Pediatrics.

Nervous System Malformations

John Gaitanis, MD; Tomo Tarui, MD. Continuum (Minneap Minn). February 2018; 24 (1 Child Neurology):72–95.

Abstract

Purpose of Review:

This article provides an overview of the most common nervous system malformations and serves as a reference for the latest advances in diagnosis and treatment.

Recent Findings:

Major advances have occurred in recognizing the genetic basis of nervous system malformations. Environmental causes of nervous system malformations, such as perinatal infections including Zika virus, are also reviewed. Treatment for nervous system malformations begins prior to birth with prevention. Folic acid supplementation reduces the risk of neural tube defects and is an important part of health maintenance for pregnant women. Fetal surgery is now available for prenatal repair of myelomeningocele and has been demonstrated to improve outcomes.

Summary:

Each type of nervous system malformation is relatively uncommon, but, collectively, they constitute a large population of neurologic patients. The diagnosis of nervous system

malformations begins with radiographic characterization. Genetic studies, including chromosomal microarray, targeted gene sequencing, and next-generation sequencing, are increasingly important aspects of the assessment. A genetic diagnosis may identify an associated medical condition and is necessary for family planning. Treatment consists primarily of supportive therapies for developmental delays and epilepsy, but prenatal surgery for myelomeningocele offers a glimpse of future possibilities. Prognosis depends on multiple clinical factors, including the examination findings, imaging characteristics, and genetic results. Treatment is best conducted in a multidisciplinary setting with neurology, neurosurgery, developmental pediatrics, and genetics working together as a comprehensive team.

Key Points

- Ambulation is one of the most important clinical concerns in patients with myelomeningocele. Antigravity function of the iliopsoas and quadriceps muscles is required for walking, but ambulation can be impaired in all children with spina bifida, even those with low neurosegmental lesions.
- Hydrocephalus is seen in approximately 90% of patients with myelomeningocele affecting the lumbar region. Newborns can be asymptomatic without recognizable clinical signs of increased intracranial pressure.
- Prenatal surgery for myelomeningocele is associated with lower rates of shunt placement and improvements in mental development and motor function.
- Oral supplementation with folic acid before conception and during early pregnancy substantially reduces the recurrence of neural tube defects in women who previously had a child with such a condition. All women of childbearing age are recommended to consume 0.4 mg of folic acid daily to prevent neural tube defects. Women who have had a child with a neural tube defect are recommended to consume 4 mg of folic acid daily.
- The etiology of holoprosencephaly is heterogeneous with both genetic and environmental causes. Gestational diabetes mellitus is the most common environmental cause and carries a 1% risk of holoprosencephaly. Chromosomal abnormalities account for approximately 25% to 50% of holoprosencephaly cases.
- Both partial and complete isolated agenesis of the corpus callosum can have broad neurodevelopmental presentations from mild to severe impairments.
- Septooptic dysplasia presents with visual impairment in infancy (congenital nystagmus or poor visual engagement), hypopituitarism, or both.
- Primary microcephaly is a heterogeneous condition and can be caused by destructive processes (hypoxia-ischemia, intrauterine infections) or from a genetically determined reduction in neuronal proliferation. Mutations associated with primary microcephaly alter neuroprogenitor cell proliferation through cell cycle regulation, centrosome function, cell proliferation, mitotic spindle formation, or DNA repair.
- All patients with hemimegalencephaly have epilepsy. Hemispherectomy is often required to treat intractable epilepsy, although some patients' seizures may be controlled medically.
- In the brain, characteristic features of tuberous sclerosis include cortical and subcortical hamartomas, subependymal nodules, and subependymal giant cell astrocytomas.
- Patients with tuberous sclerosis complex may develop progressive cognitive impairment. Seizures in children younger than 2 years of age, infantile spasms, and a high burden of cortical tubers are associated with a high risk for cognitive impairment. Autism is commonly seen in patients with tuberous sclerosis complex, especially in patients with temporal tubers, seizure onset before 3 years of age, or infantile spasms.

- Focal cortical dysplasia is highly associated with medically refractory epilepsy and often requires epilepsy surgery to control the seizures.
- Focal cortical dysplasia type I may be radiographically occult as its anatomic alterations are so subtle and can only be detected at the microscopic level. Focal cortical dysplasia type I may be found in nonlesional specimens resected in epilepsy surgery.
- Most patients with periventricular nodular heterotopia have normal intelligence, and some patients may develop epilepsy, commonly in the middle teenage years.
- Patients with classic lissencephaly have severe reduction in gyral formation manifesting either as agyria (a total absence of gyri) or pachygyria (a reduced number of abnormally large gyri).
- Most children with lissencephaly have relatively severe cognitive and motor disabilities and seizures. Clinical severity is related to the degree of structural abnormality, with greater gyral simplification resulting in greater clinical impairment. Epilepsy is universal, and infantile spasms are a particularly common seizure type.
- *LIS1* mutations are commonly seen in cases with a posterior greater than anterior gradient of agyria. Almost all patients have de novo heterozygous mutations of *LIS1*. The recurrence risk of having a second affected child is very low. A microdeletion syndrome affecting this region manifests as Miller-Dieker syndrome, with other congenital anomalies (craniofacial, renal, cardiac, or gastrointestinal malformations).
- Cobblestone malformations are sometimes associated with congenital muscular dystrophy and eye abnormalities. These disorders result from an impairment of glycosylation of α-dystroglycan, affecting the brain, nerve, and skeletal muscle.
- Bilateral perisylvian polymicrogyria results in a clinical syndrome manifested by mild cognitive impairment, epilepsy, and pseudobulbar palsy. In childhood, the pseudobulbar palsy results in expressive speech delay and feeding difficulty.
- Child neurologists play a central role in providing prenatal diagnosis and counseling to pregnant women and families in collaboration with a multidisciplinary team consisting of maternal fetal medicine, radiologists, neurosurgeons, geneticists, and neonatologists. Child neurologists are essential in formulating a diagnostic plan, assessing prognosis, and providing postnatal care to affected children.

Neurocutaneous Disorders

Tena Rosser, MD. Continuum (Minneap Minn). February 2018; 24 (1 Child Neurology):96–129.

Abstract

Purpose of Review:

This article presents an up-to-date Summary of the genetic etiology, diagnostic criteria, clinical features, and current management recommendations for the most common neurocutaneous disorders encountered in clinical adult and pediatric neurology practices.

Recent Findings:

The phakomatoses are a phenotypically and genetically diverse group of multisystem disorders that primarily affect the skin and central nervous system. A greater understanding of the genetic and biological underpinnings of numerous neurocutaneous disorders has led to better clinical characterization, more refined diagnostic criteria, and improved treatments in neurofibromatosis

type 1, Legius syndrome, neurofibromatosis type 2, Noonan syndrome with multiple lentigines, tuberous sclerosis complex, Sturge-Weber syndrome, and incontinentia pigmenti.

Summary:

Neurologists require a basic knowledge of and familiarity with a wide variety of neurocutaneous disorders because of the frequent involvement of the central and peripheral nervous systems. A simple routine skin examination can often open a broad differential diagnosis and lead to improved patient care.

Key Points

- Plexiform neurofibromas occur in approximately 30% of individuals with neurofibromatosis type 1 and are the cause of significant morbidity.
- The lifetime risk of malignant transformation of plexiform neurofibromas is approximately 10%.
- Warning signs of malignancy include rapid plexiform growth, significant pain, new neurologic deficit, and change to a hard texture.
- Optic pathway gliomas are present in 15% to 20% of young children with neurofibromatosis type 1 but often have an indolent course, becoming symptomatic in only 33% to 50% of those affected.
- Children under 6 years of age are most at risk for developing optic pathway gliomas.
- Optic pathway gliomas present with decreased visual acuity, pupillary abnormalities, color vision abnormalities, and proptosis. Endocrinopathies may signal associated chiasmatic and hypothalamic involvement.
- While still a controversial issue, evidence-based medicine does not support the use of screening brain MRIs for optic pathway gliomas in pediatric patients with neurofibromatosis type 1, but regular vision screening is imperative.
- Any child with neurofibromatosis type 1 who has vision deterioration, endocrine abnormalities, significant headaches, seizures, marked increase in head size, or other concerning neurologic symptoms should undergo a brain MRI with and without contrast.
- Legius syndrome is caused by a mutation in the *SPRED1* gene.
- Approximately 5% of individuals with Legius syndrome will meet the National Institutes of Health diagnostic criteria for neurofibromatosis type 1.
- Individuals with Legius syndrome do not have many of the clinical features seen in neurofibromatosis type 1, including dermal or plexiform neurofibromas, Lisch nodules, optic pathway gliomas, or tibial dysplasia.
- Adults with neurofibromatosis type 2 typically present in the second or third decade of life with hearing loss, tinnitus, or disequilibrium.
- Children with neurofibromatosis type 2 commonly present with nonvestibular-related symptoms due to other brain tumors, spinal cord tumors, and ophthalmic abnormalities.
- Schwannomatosis is a rare third form of neurofibromatosis with clinical and genetic overlap with neurofibromatosis type 2.
- Individuals with schwannomatosis typically present in their twenties to thirties with chronic pain and symptoms relatable to nerve sheath tumors in the central and peripheral nervous systems.
- Schwannomatosis does not cause vestibular schwannomas as seen in neurofibromatosis type 2, but other cranial nerves can be involved.
- Intracranial neurofibromatosis type 2–related tumors include vestibular schwannomas, other cranial nerve schwannomas, and meningiomas.

- The spinal tumors most often found in neurofibromatosis type 2 include schwannomas, extramedullary meningiomas, and intramedullary ependymomas.
- A high rate of mosaicism exists in neurofibromatosis type 2, which can complicate confirmation of a diagnosis and screening of family members.
- If genetic testing in blood lymphocytes is negative for the *NF2* mutation, testing of a tumor sample can be helpful, particularly in sporadic cases.
- Noonan syndrome with multiple lentigines is a rare multisystem RASopathy with three known causative genes (*PTPN11, RAF1, BRAF*).
- Hypertrophic cardiomyopathy is the most common cardiac anomaly in Noonan syndrome with multiple lentigines and can be a cause of morbidity and mortality. A variety of cardiac arrhythmias and valvular defects are also frequently identified.
- In tuberous sclerosis complex, mutations in the *TSC1* and *TSC2* genes map to different chromosomes but produce essentially the same clinical syndrome with variable expressivity.
- *TSC1* mutations occur more often with a familial inheritance pattern and produce a milder phenotype, while *TSC2* mutations arise more frequently in sporadic cases and result in more severe clinical manifestations.
- The most common cutaneous findings in tuberous sclerosis complex include hypomelanotic macules, facial angiofibromas, fibrous cephalic plaques, shagreen patches, confetti lesions, and ungual fibromas.
- Subependymal giant cell astrocytomas occur in approximately 5% to 20% of young patients with tuberous sclerosis complex.
- Subependymal giant cell astrocytomas are a pediatric phenomenon and rarely develop de novo after 20 to 25 years of age.
- Subependymal giant cell astrocytomas are benign tumors that arise from subependymal nodules located at the foramen of Monro and can cause acute and chronic obstructive hydrocephalus as they enlarge.
- Epilepsy with multiple different seizure types occurs in 80% of individuals with tuberous sclerosis complex.
- Infantile spasms present in 40% to 50% of infants with tuberous sclerosis complex.
- Vigabatrin has shown superior efficacy to adrenocorticotropic hormone in infants with tuberous sclerosis complex and infantile spasms; thus, it is recommended as first-line treatment. Patients taking vigabatrin require regular monitoring for potential retinal toxicity and associated vision loss.
- The comprehensive term tuberous sclerosis–associated neuropsychiatric disorders is now used to describe the numerous behavioral and psychiatric symptoms that can arise in individuals with tuberous sclerosis complex.
- Lymphangioleiomyomatosis occurs both in tuberous sclerosis complex and sporadically.
- The incidence of tuberous sclerosis complex–associated lymphangioleiomyomatosis is 1% to 4%, and it primarily affects women.
- Lymphangioleiomyomatosis commonly presents with pulmonary symptoms, including dyspnea, hemoptysis, recurrent pneumothorax, and chylothorax, but extrapulmonary features also occur.
- Discovery of the GNAQ gene has clarified that Sturge-Weber syndrome represents the severe end of a clinical spectrum that also includes more benign isolated port-wine birthmarks.
- A facial port-wine birthmark and an intracranial leptomeningeal angioma (often in the parietooccipital region) are typically required to make a diagnosis of Sturge-Weber syndrome.
- A child with a facial port-wine birthmark who is older than 1 year of age with a normal contrastenhanced brain MRI is unlikely to develop brain involvement.

- In Sturge-Weber syndrome, a facial port-wine birthmark is usually ipsilateral to the intracranial lesion.
- The most common neurologic complications of Sturge-Weber syndrome include epilepsy, strokelike episodes, headaches, and developmental disabilities.
- Hemiparesis and visual field cuts can develop over time in Sturge-Weber syndromeand are thought to be due to chronic ischemia associated with the leptomeningeal vascular malformation.
- Glaucoma associated with Sturge-Weber syndrome does not always correspond to the trigeminal distribution of the facial lesion.
- The use of low-dose aspirin has been used to prevent seizures and strokelike episodes in Sturge-Weber syndrome but remains controversial.
- Incontinentia pigmenti is a rare X-linked dominant disorder that primarily affects females.
- Central nervous system, dental, nail, hair, and ocular anomalies are commonly seen in incontinentia pigmenti.
- In incontinentia pigmenti, cutaneous hyperpigmented markings follow the lines of Blaschko and develop in four stages.
- Rare cases of acute disseminated encephalomyelitis have been reported in infants with incontinentia pigmenti.
- Neurologic complications of incontinentia pigmenti include ischemic stroke and cerebral dysgenesis, which can clinically result in epilepsy, cerebral palsy, developmental delays, and intellectual disability.

Leukodystrophies

Amy T. Waldman, MD, MSCE. Continuum (Minneap Minn). February 2018; 24 (1 Child Neurology):130–149.

Abstract

Purpose of Review:

The leukodystrophies, typically considered incurable neurodegenerative disorders, are often diagnosed after irreversible central and peripheral nervous system injury has occurred. Early recognition of these disorders is imperative to enable potential therapeutic interventions. This article provides a Summary of the symptoms of and diagnostic evaluation for leukodystrophies, along with the currently available therapies and recent advances in management.

Recent Findings:

The leukodystrophies are a rapidly expanding field because of advances in neuroimaging and genetics; however, recognition of the clinical and biochemical features of a leukodystrophy is essential to accurately interpret an abnormal MRI or genetic result. Moreover, the initial symptoms of leukodystrophies may mimic other common pediatric disorders, leading to a delay in the recognition of a degenerative disorder.

Summary:

This article will aid the clinician in recognizing the clinical features of leukodystrophies and providing accurate diagnosis and management.

Key Points

- The leukodystrophies comprise a heterogeneous group of disorders predominantly affecting the glial cell or myelin sheath.
- Genetic leukoencephalopathies include metabolic disorders and primary neuronal diseases that affect the white matter through mechanisms other than glial pathology.
- X-linked adrenoleukodystrophy should be considered in school-aged boys with the recent onset of attention and behavioral difficulties, especially for those who demonstrate regression in cognition, fine motor skills, or speech. While MRI may be helpful in confirming cerebral involvement, the test of choice to confirm or exclude X-linked adrenoleukodystrophy is measurement of plasma very-long-chain fatty acids.
- The adrenal function of boys with X-linked adrenoleukodystrophy should be monitored routinely by an endocrinologist.
- Very-long-chain fatty acids, especially C26:0 and the ratios of C26:C22 and C26:C24, are elevated in all clinical phenotypes of X-linked adrenoleukodystrophy, and these abnormalities may be detected at birth, facilitating a diagnosis prior to symptom onset.
- Infantile Krabbe disease should be considered in a child 6 months of age or younger with irritability, sterile pyrexia, and elevated CSF protein. Other symptoms in this age group include extremity stiffness, fisted hands, and decreased oral intake.
- The biochemical abnormality in Krabbe disease is an abnormal galactosylceramidase level (typically 0% to 5% of normal values) in white blood cells or cultured fibroblasts.
- Metachromatic leukodystrophy should be considered in a toddler with regression in gross motor skills, a peripheral neuropathy, or gall bladder polyps.
- Gall bladder disease should be considered in patients with metachromatic leukodystrophy who experience feeding intolerance.
- Arylsulfatase A pseudodeficiency is common; therefore, the diagnosis of metachromatic leukodystrophy is confirmed by low arylsulfatase A activity along with an elevation in the urinary excretion of sulfatides.
- Aicardi-Goutières syndrome should be considered in young children with developmental regression, acquired microcephaly, spasticity, and dystonia. Chilblains, glaucoma, cardiomyopathy, stroke, and comorbid autoimmune conditions are present, with variability in the presence and frequency of these symptoms by genetic mutation.
- In Aicardi-Goutières syndrome, a CT scan may be performed to demonstrate calcium deposits in the basal ganglia and other areas of the brain.
- Patients with Aicardi-Goutières syndrome may have a CSF lymphocytic pleocytosis, elevated interferon alfa, or elevated neopterin or biopterin.
- Infants with persistent jaundice or chronic diarrhea and children with bilateral cataracts should be tested for cerebrotendinous xanthomatosis, even in the absence of neurologic symptoms, through measurement of serum cholestanol and urine and serum bile alcohols.
- Cholic acid is a US Food and Drug Administration–approved treatment for cerebrotendinous xanthomatosis and, when initiated early, delays the onset of neurologic symptoms.

Evaluation and Acute Management of Ischemic Stroke in Infants and Children

Catherine Amlie-Lefond, MD. Continuum (Minneap Minn). February 2018; 24 (1 Child Neurology):150–170.

Abstract

Purpose of Review:

This article provides an overview of stroke in neonates, infants, and children.

Recent Findings:

Arterial ischemic stroke and cerebral venous sinus thrombosis are increasingly recognized in childhood as important causes of lifelong morbidity and mortality. Diagnosis of arterial ischemic stroke is frequently delayed, as acute neurologic deficits can be challenging to detect in the young child, and stroke is often not considered in the differential diagnosis. Neurologic sequelae following stroke are common, and strategies to minimize stroke size and optimize recovery are being developed. Recurrent arterial ischemic stroke is not uncommon, particularly in children with cerebral arteriopathy. Cerebral venous sinus thrombosis causes obstruction of venous outflow leading to venous infarcts. Complications include hemorrhagic conversion of infarcts and increased intracranial pressure. Without treatment, thrombus extension with increased symptoms is common. Robust guidelines of care that exist for adults do not exist for children, particularly for children with arterial ischemic stroke.

Summary:

The approach to stroke in infants and children can be informed by clinical experience in pediatric stroke and cerebral venous sinus thrombosis, the extensive literature on pediatric thrombosis, and extrapolation from data from adult patients.

Key Points

- Diagnosis of arterial ischemic stroke is often delayed because of the infrequency of stroke in children relative to adults and the frequency of stroke mimics, such as seizure, migraine, encephalitis, demyelination, and functional neurologic disorders.
- Congenital and acquired cardiac diseases account for approximately 30% of cases of childhood arterial ischemic stroke, presumably due to cardioembolic events.
- Up to one-half of all childhood arterial ischemic stroke is associated with cerebral arteriopathy, which is also a risk factor for recurrent stroke.
- Approximately one-fourth of arteriopathies in childhood arterial ischemic stroke are focal cerebral arteriopathy, which is a narrowing of the artery that usually involves large- and medium-sized arteries.
- Cervicocephalic arterial dissection accounts up to 20% of childhood arterial ischemic stroke and one-half of posterior circulation childhood arterial ischemic stroke.
- Congenital and acquired thrombophilias are associated with childhood arterial ischemic stroke, especially if multiple thrombophilias or other risk factors are present.
- When possible, MRI is the optimal study for diagnosis of acute childhood arterial ischemic stroke.
- The goals of acute care of childhood arterial ischemic stroke are to limit injury, salvage the penumbra, prevent stroke extension, treat complications, and prevent recurrent stroke.
- To decrease metabolic demands on the brain, fever should be avoided and aggressively treated in patients with childhood arterial ischemic stroke; excess clothing and blankets should be removed, and acetaminophen should be administered.

- The child with acute arterial ischemic stroke should have nothing by mouth in the event that sedation is needed for procedures and pending clearance for safe swallowing on swallowing evaluation.
- Following arterial ischemic stroke, recurrence occurs in one-fifth of children, and it can occur in the immediate poststroke period.
- Headache is the most common presenting symptom of cerebral venous sinus thrombosis, although it is nonspecific and frequently seen in other childhood illnesses.
- In most children presenting with cerebral venous sinus thrombosis, underlying risk factors can be identified and usually involve venous stasis, dehydration, hypercoagulable states, and direct injury to the vessel from trauma or infection.
- Brain MRI (particularly contrast-enhanced T1-weighted sequences) is the optimal study to diagnose cerebral venous sinus thrombosis as well as associated venous congestion and venous stroke.
- Children with acute symptomatic cerebral venous sinus thrombosis require intensive care monitoring, as they are at risk of declining neurologic status and death, especially if the deep venous system is involved.
- Death due to cerebral venous sinus thrombosis is rare; however, neurologic sequelae including encephalopathy and seizures are common.

Epileptic Encephalopathies

Shaun A. Hussain, MD, MS. Continuum (Minneap Minn). February 2018; 24 (1 Child Neurology):171–185.

Abstract

Purpose of Review:

This article reviews the manifestations and treatment of the epileptic encephalopathies, which are a heterogeneous group of disorders characterized by both seizures and neurocognitive impairment.

Recent Findings:

Next-generation (exome- and genome-based) sequencing technologies are revolutionizing the identification of single-gene causes of epileptic encephalopathy but have only had a modest impact on patient-specific treatment decisions. The treatment of most forms of epileptic encephalopathy remains a particularly challenging endeavor, with therapeutic decisions chiefly driven by the electroclinical syndrome classification. Most antiseizure drugs are ineffective in the treatment of these disorders, and treatments that are effective often entail significant risk and cost.

Summary:

The epileptic encephalopathies continue to pose a major challenge in diagnosis and treatment, with most patients experiencing very poor outcomes, although a significant minority of patients respond to, or are even cured by, specific therapies.

Key Points

- The term *epileptic encephalopathy* refers to disorders in which epileptic activity threatens cognition above and beyond what would be expected from pathology alone.

- Early infantile epileptic encephalopathy is interictally characterized by the suppression-burst pattern.
- Genetic associations with all forms of epileptic encephalopathy are numerous, with a list of single-gene mutations that is likely to grow substantially as modern approaches to exome and genome sequencing are implemented on a wider scale.
- Early myoclonic encephalopathy bears great resemblance to early infantile epileptic encephalopathy but is more often caused by inborn errors of metabolism.
- The hallmark of epilepsy of infancy with migrating focal seizures is frequent, long seizures with multifocal origin and migration (as opposed to spread).
- *KCNT1* mutations have emerged as the most frequent cause of epilepsy with migrating focal seizures, and manipulation of potassium currents is a prime target of emerging therapeutic approaches.
- Prompt diagnosis of infantile spasms is a critical prerequisite for successful treatment.
- The seizures (spasms) that characterize infantile spasms are highly variable in appearance, but they typically occur in clusters and often commence upon awakening.
- Although often a dramatic interictal abnormality, hypsarrhythmia is often relatively subtle or absent; the absence of hypsarrhythmia neither excludes the diagnosis of infantile spasms nor warrants less aggressive treatment.
- The age of onset of Lennox-Gastaut syndrome is usually later than other forms of epileptic encephalopathy and typically occurs between the ages of 1 and 6 years.
- Drop seizures are a common manifestation of Lennox-Gastaut syndrome and pose disproportionate harm given the potential for physical injury.
- Reports of seemingly miraculous success accompanying the use of cannabidiol-enriched cannabis extracts for treatment of seizures in Lennox-Gastaut syndrome have been balanced by concerns of reporting bias and the possibility that the perception of favorable efficacy is confounded by drug interaction with clobazam.
- Landau-Kleffner syndrome and the syndrome of continuous spike and wave in sleep exhibit similar EEG patterns but clearly distinct phenotypes.
- Electrical status epilepticus in slow sleep is frequently missed on routine EEGs, as activation of epileptiform discharges occurs most often in slow-wave sleep.
- Although uncommon in epileptic encephalopathy, meaningful response, or even a cure, requires prompt diagnosis and treatment.

Epilepsy Syndromes in Childhood

Phillip L. Pearl, MD, FAAN. Continuum (Minneap Minn). February 2018; 24 (1 Child Neurology):186–209.

Abstract

Purpose of Review:

Epilepsy syndromes are an important clinical construct in pediatric epilepsy, as they encompass recognizable patterns seen in patients with epilepsies, whether of the more benign variety or associated with encephalopathy.

Recent Findings:

Syndromes may be organized by age of onset: neonatal, infantile, childhood, or adolescent. The assignment of a syndrome has specific implications for diagnosis, management, and

prognostication. The 2010 revised classification of the epilepsies by the International League Against Epilepsy preserved the syndrome approach, while progress in genetics continues to advance our understanding of the pathophysiology and overlap of the epilepsy syndromes.

Summary:

Given that mutations of the same gene may cause both encephalopathic and relatively benign epilepsies, an understanding of the pediatric epilepsy syndromes remains vital to patient care.

Key Points

- The previous classification of the epilepsies as idiopathic, symptomatic, and cryptogenic has been replaced by the terms *genetic, structural-metabolic, and unknown*; these terms have overlap with the previous terms but are not identical.
- The electroclinical clusters known as epilepsy syndromes continue to represent a clinically useful approach to evaluating, managing, and counseling patients and families with pediatric epilepsy, even if their elucidation with ongoing discoveries will naturally lead to revisions of the syndromes over time.
- Benign familial neonatal epilepsy was among the first epilepsy syndromes for which the causative genes were identified, although the range of phenotypes now associated with *KCNQ2* mutations has broadened to include severe epileptic encephalopathies, thus representing the complexity of genotype-phenotype correlation.
- Early-onset epileptic encephalopathies include early myoclonic encephalopathy, with a burst-suppression EEG pattern that becomes prominent during sleep, and early infantile epileptic encephalopathy (Ohtahara syndrome), with a combination of tonic seizures, burst-suppression EEG pattern throughout wakefulness and sleep, and more often an association with a structural brain anomaly.
- Benign myoclonic epilepsy of infancy includes myoclonic seizures in otherwise developmentally healthy infants and typically has a reflex component.
- Benign familial infantile epilepsy is often associated with *PRRT2* mutations, medication responsiveness, and a good outcome, although also associated with other paroxysmal disorders such as paroxysmal kinesigenic dyskinesia and familial hemiplegic migraine.
- Hemiconvulsion-hemiplegia-epilepsy syndrome may present as prolonged unilateral convulsions during a febrile illness, followed by hemiparesis, progressive cerebral hemiatrophy, and epilepsy that may become intractable over time.
- West syndrome comprises the triad of infantile spasms, hypsarhythmia on EEG, and neurodevelopmental arrest or regression.
- Dravet syndrome, or severe myoclonic epilepsy of infancy, is caused by heterozygous mutations of the sodium channel *SCN1A* in at least 80% of affected patients.
- Patients with Dravet syndrome frequently present in infancy with prolonged hemiclonic seizures and are sensitive to elevated temperatures.
- Sodiumchannel blockers should be avoided in Dravet syndrome, although they are effective in *SCN2A*- and *SCN8A*-related epilepsies.
- Myoclonic epilepsies in nonprogressive disorders may be medically refractory and associated with developmental decline (as seen in genetic etiologies such as Angelman, Rett, Prader-Willi, or Wolf-Hirschhorn [4p-] syndromes), underlying malformations of cortical developmental (eg, polymicrogyria), or remote injury (eg, prenatal or perinatal hypoxic-ischemic encephalopathy).

- Genetic epilepsy with febrile seizures plus is often associated with *SCN1A* mutations and may overlap with Dravet (severe myoclonic epilepsy of infancy) and Doose (myoclonic-astatic epilepsy) syndromes in the same families.
- Panayiotopoulos syndrome (early-onset childhood occipital epilepsy) has a relatively young age of onset (3 to 6 years), prominent autonomic symptoms (especially prolonged vomiting), and long-term remission.
- Myoclonic-atonic epilepsy, or Doose syndrome, has been associated with a number of genes, including mutations of sodium channels and the γ-aminobutyric acid-A receptor, and may be particularly responsive to the ketogenic diet.
- Benign epilepsy with centrotemporal spikes (benign rolandic epilepsy) accounts for nearly 25% of the childhood epilepsies, has a peak age of onset of 7 to 8 years, and has anticipated long-term remission by 14 to 16 years of age.
- The late-onset form of benign childhood occipital epilepsy (Gastaut type) is associated with occipital spike-wave discharges that are activated by eye closure and attenuate upon eye opening. No structural pathology is associated with this form of epilepsy, and long-term remission is anticipated in about half of patients.
- Lennox-Gastaut syndrome is composed of the combination of mixed generalized seizures that are predominantly tonic, slow spike-and-wave discharges (1.5 Hz to 2.5 Hz) on EEG, and cognitive impairment, often with regression.
- Continuous spike and wave in slow sleep is an electroclinical syndrome with an epileptic encephalopathy characterized by mixed generalized seizures, cognitive deterioration, and the EEG pattern of electrical status epilepticus in slow sleep. While the terms continuous spike and wave in slow sleep and electrical status epilepticus in slow sleep are sometimes used interchangeably, some authors prefer to use the former for the epilepsy and the latter for the EEG pattern.
- Acquired epileptic aphasia (Landau-Kleffner syndrome) is an acquired epileptic aphasia characterized classically by an auditory agnosia and electrical status epilepticus in slow sleep on EEG.
- Childhood absence epilepsy is associated with seizure freedom and long-term remission in up to 75% of patients, with positive prognostic factors being normal neurodevelopmental status, absence of generalized tonic-clonic seizures, and negative family history of epilepsy. Yet a serious risk of accidents and increased comorbidities, including learning and attentional disabilities, exists.
- Juvenile myoclonic epilepsy has a mixed prognosis, with seizure freedom expected but long-term remission not anticipated.
- Epilepsy with generalized tonic-clonic seizures alone has onset in adolescence or young adulthood and is associated with generalized 3 Hz to 4 Hz spike-and-slow-wave paroxysms on EEG and pharmacoresponsiveness but a lifelong predisposition to seizures.
- Progressive myoclonus epilepsies (eg, Unverricht-Lundborg disease, Lafora body disease, myoclonic epilepsy with ragged red fibers, and neuronal ceroid lipofuscinosis) manifest by myoclonus (cortical and subcortical), cognitive regression, and generalized spike or polyspike and wave on EEG with a photoparoxysmal response.
- Reflex epilepsies are characterized by seizures exclusively or predominantly triggered by a variety of stimuli, most commonly of visual, auditory, or tactile phenomena.

Pediatric Sleep Disorders

Kiran Maski, MD, MPH; Judith Owens, MD, MPH. Continuum (Minneap Minn). February 2018; 24 (1 Child Neurology):210–227.

Abstract

Purpose of Review:

This article provides an overview of the clinical features, diagnosis, and treatment of insomnia, restless legs syndrome, periodic limb movements of sleep, parasomnias, narcolepsy, and sleep-related breathing disorders among children and adolescents.

Recent Findings

Pediatric presentations of sleep disorders differ from adult presentations, making diagnosis challenging. Specific clinical syndromes, such as cataplexy in children with narcolepsy type 1, can have an altogether different presentation compared to adult-onset symptoms, contributing to diagnostic delays and potential misdiagnoses. More broadly, research shows strong associations between sleep and daytime cognition, mood, and behavior among children with and without neurologic conditions and thus suggests a need to identify and treat sleep problems to optimize daytime functioning.

Summary:

Addressing sleep problems in children with neurologic conditions and neurodevelopmental disorders improves quality of life for patients and their families and, in many cases, reduces neurologic disease burden.

Key Points

- The incidence of narcolepsy peaks in the second decade of life.
- Delayed diagnosis and misdiagnosis are common in patients with narcolepsy, with a median time to diagnosis of 10.5 years.
- Narcolepsy type 1 can present with atypical cataplexy in pediatric populations with constant cataplexy (not emotionally triggered) and positive motor phenomena.
- Narcolepsy type 1 is caused by loss of hypocretin neurons in the lateral hypothalamus.
- Insomnia is the most common sleep disorder among children and has an especially high prevalence in children with neurologic disorders such as attention deficit hyperactivity disorder and autism spectrum disorder.
- Disrupted sleep is associated with poorer adaptive functioning and verbal skills in children with autism spectrum disorder.
- Insomnia may reflect a state of heightened cortical, autonomic, and somatic arousal.
- Behavioral counseling is the foundation for management of insomnia in children.
- Early-onset restless legs syndrome has a strong genetic component.
- Non–rapid eye movement parasomnias are disorders of episodic arousal from sleep that take several forms, including confusional arousals, sleep terrors, and sleepwalking.
- Non–rapid eye movement parasomnias typically occur in the first few hours of nocturnal sleep.
- Management of non–rapid eye movement parasomnias should first include reassurance and education of the family regarding the benign and self-limited nature of the disorder.
- Certain populations, such as children with Down syndrome, Prader-Willi syndrome, neuromuscular disorders, cerebral palsy, and epilepsy, have a higher prevalence of obstructive sleep apnea.
- Daytime neurobehavioral problems can result from sleep-related breathing disorder, including alterations in mood (irritability, emotional dysregulation), behavior

(hyperactivity, oppositional and disruptive behavior), and cognitive function (inattention, impaired executive functions, poor academic progress).
- The most common causes of pediatric obstructive sleep apnea syndrome are obesity and adenotonsillar hypertrophy.
- No consensus exists regarding the need for intervention in children with mild obstructive sleep apnea (an apnea-hypopnea index between 1 and 5 per hour).

Evaluation of the Child With Developmental Impairments

Clara D. M. van Karnebeek, MD, PhD. Continuum (Minneap Minn). February 2018; 24 (1 Child Neurology):228–247.

Abstract

Purpose of Review:

This article discusses the diagnostic evaluation of intellectual developmental disorder, comprising global developmental delay and intellectual disability in children.

Recent Findings:

With a prevalence of 1% to 3% and substantial comorbidity, high lifetime costs, and emotional burden, intellectual developmental disorder is characterized by limitations in both intellectual functioning (IQ less than 70) and adaptive behavior starting before 18 years of age. Pinpointing the precise genetic cause is important, as it allows for accurate genetic counseling, avoidance of unnecessary testing, prognostication, and tailored management, which, for an increasing number of genetic conditions, targets the pathophysiology and improves outcomes.

Summary:

The etiology of intellectual developmental disorder is heterogeneous, which mandates a structured approach that considers family situation, test costs, yield, and potential therapeutic tractability of the identified condition. Diagnosis of an underlying genetic cause is increasingly important with the advent of new treatments. Still, in many cases, the cause remains unknown, and research is needed to elucidate its complex molecular basis.

Key Points

- Pinpointing the precise genetic cause of intellectual developmental disorder is important, as it allows for proper genetic counseling, avoidance of unnecessary tests, prognostication, and tailored management, which, for an increasing number of genetic conditions, targets the pathophysiology and improves outcomes.
- The etiology of intellectual developmental disorder is extremely heterogeneous, which mandates a structured diagnostic approach, taking into account family situation and burden as well as test costs, yield, and potential therapeutic tractability of the identified condition.
- The first important step in evaluating intellectual developmental disorder is confirmation of the type and severity of developmental delay (and domains affected), including

intellectual disability. Screening for medical and psychological comorbidities should be performed.
- Loss of skills is an alarming symptom and requires expedited workup.
- A complete medical evaluation should be done for every child with intellectual developmental disorder.
- Chromosomal microarray and metabolic testing for treatable conditions are first-tier tests for intellectual developmental disorder and should be considered in all children with unexplained intellectual developmental disorder. Additional testing includes neuroimaging, neurophysiology, single-gene tests, and specialist evaluations.
- Inborn errors of metabolism constitute a class of single-gene disorders involving impaired biochemical or cellular processes. The majority are due to defects in genes that typically affect the synthesis or breakdown of molecules, leading to accumulation of toxic molecules or deficiency of cellular energy or required substrates for many important intracellular processes.
- In a 2011 practice parameter, the American Academy of Neurology and the Child Neurology Society state that neuroimaging is a recommended part of the diagnostic evaluation, particularly if there are abnormal findings on examination (eg, microcephaly, macrocephaly, focal motor findings, pyramidal or extrapyramidal signs).
- Whole-exome and whole-genome sequencing (genomics) are becoming more readily available in the clinical arena.
- For meaningful interpretation of genomic data, careful clinical phenotyping with a differential diagnosis or hypotheses for involved pathways are essential, along with close communication between the clinical and bioinformatics team.
- If the diagnostic workup is negative, the clinician should reevaluate the patient a few years later. New diagnostic clues may have arisen, and new human disease genes related to intellectual developmental disorder are increasingly being identified.
- The number of rare conditions underlying intellectual developmental disorder that are amenable to treatment is steadily increasing, and, for many indications, therapies are still under development.
- Genome sequencing is likely to become the first-tier diagnostic test for intellectual developmental disorder as soon as it becomes clinically available and affordable. This genetic testing will require appropriate counseling, and any incidental findings will need to be assessed without compromising a child's right to an open future.

Evaluation and Management of the Child With Autism Spectrum Disorder

Nicole Baumer, MD, MEd; Sarah J. Spence, MD, PhD. Continuum (Minneap Minn). February 2018; 24 (1 Child Neurology):248–275.

Abstract

Purpose of Review:

Autism spectrum disorder is a neurodevelopmental disorder defined by deficits in social communication and the presence of restricted and repetitive behaviors and interests. This article provides the tools to diagnose and manage patients with autism spectrum disorder.

Recent Findings:

Autism spectrum disorder is a heterogeneous condition with varying presentations, multiple etiologies, and a number of comorbidities that impact the course and management of the disorder. This article defines the core features of social communication deficits, including problems with social reciprocity, decreased nonverbal communication, and difficulties in developing and maintaining relationships. The second domain of repetitive behaviors and restricted interests, which includes the presence of stereotyped behaviors or speech, insistence on sameness and behavioral rigidity, intense or out of the ordinary interests, and unusual responses to sensory stimulation, is also delineated. Comorbidities commonly seen with autism spectrum disorder include medical, neurologic, and psychiatric conditions. Despite intense research efforts, the etiology of autism spectrum disorder remains unknown in most cases, but it is clear that a strong genetic component exists that interacts with various environmental risk factors. Current research is identifying overlapping neurobiological pathways that are involved in pathogenesis. Treatment involves intensive behavioral therapy and educational programming along with traditional ancillary services, such as speech/language, occupational, and physical therapies. Psychopharmacologic treatments are also used to target certain symptoms and comorbid conditions.

Summary:

Neurologists can play an important role in diagnosing autism spectrum disorder according to clinical criteria through a comprehensive evaluation that includes a thorough medical and developmental history, behavioral and play observations, and a review of standardized cognitive and language evaluations. Neurologists are also responsible for investigating etiologies, recommending and advocating for appropriate behavioral and educational interventions, and identifying and often managing comorbidities.

Key Points

- What is now termed autism spectrum disorder was historically made up of multiple distinct disorders (ie, autistic disorder, pervasive developmental disorder–not otherwise specified, and Asperger disorder). In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, all of these are combined into one, termed autism spectrum disorder.
- Current diagnostic criteria for autism spectrum disorder focus on two domains of function: deficits in social communication and the presence of restricted interests and repetitive behaviors.
- Given the single diagnostic label in DSM-5, specifiers were added to better characterize the particular profile of any one patient with autism spectrum disorder. It is important for clinicians to indicate whether associated cognitive impairment or language disorder exists.
- Large population-based studies suggest that approximately 20% of individuals with autism spectrum disorder will develop epilepsy in their lifetime. Risk factors include syndromic autism, intellectual disability, and female sex. All seizure types can occur, and the age of onset appears to have a bimodal distribution, with peaks in early childhood or adolescence/early adulthood.
- Previously, behavioral issues were only attributed to the autism spectrum disorder itself; however, it is now recognized that comorbid psychiatric conditions occur in children with autism spectrum disorder, and *DSM-5* explicitly allows the diagnosis of co-occurring psychiatric conditions as a specifier.
- The evaluation for autism spectrum disorder involves three primary components: a detailed developmental and behavioral history from primary caregivers, direct clinical

observations, and review of data and impressions from other child care providers or teachers, especially with regard to peer interactions and behaviors. It is important to include a detailed and thorough assessment of early and previous developmental functioning to assess for past behaviors consistent with autism spectrum disorder.

- The Centers for Disease Control and Prevention's Act Early Campaign website has resources on developmental milestones, including checklists for typical social and communication milestones from 2 months to 5 years of age, photo/video libraries of developmental milestones, and an autism case training curriculum for health care professionals.
- Behavioral observations must be made throughout the entirety of the clinic visit. Observations begin in the waiting room with observation of the child with other children and assessment of greetings and transition to the examination room; passive observations continue throughout the visit while obtaining the developmental history with caregivers and through assessment during evaluator-directed play and interactions with the child.
- Observations must be considered in the context of the overall developmental history and corroborative information and within the context of the social and cultural convention for the child's age group and cultural/ethnic status.
- By *DSM-5* diagnostic criteria, no standardized tools are required for diagnosing autism spectrum disorder. However, a number of tools, such as standardized questionnaires and rating scales, parent interviews, and direct assessments (including autism spectrum disorder–specific tools), can help clarify the diagnostic profile.
- An accurate diagnosis of autism spectrum disorder requires standardized assessments of cognition, adaptive skills, and speech and language skills to help clinicians distinguish global delays from deficits limited or targeted to language and social communication skills.
- Formal audiologic evaluation should be completed in all children with language delay and diagnosis (or suspicion) of autism spectrum disorder.
- Lead testing should be done for all children with developmental delays and those still in an oromotor stage of development or with pica.
- The neurologist has an important role in identifying possible neurogenetic or metabolic syndromes in individuals diagnosed with autism spectrum disorder and should be aware of phenotypes that may be suggestive of specific syndromes.
- The yield of genetic testing for autism spectrum disorder is higher in those who have syndromic features, dysmorphology, or presence of intellectual disability. Additional etiologic testing, including gene mutation analyses, should be considered for children if concerns exist for a specific neurogenetic or metabolic syndrome or if the child has a history of developmental regression.
- The evaluator must determine whether social and communication difficulties and repetitive behaviors are best explained by autism spectrum disorder or another medical or neurodevelopmental disorder.
- Behavioral and educational therapies are the mainstay of treatment for autism spectrum disorder.
- The National Research Council Recommendations for Educating Children With Autism include at least 25 hours of total service time, maximal individualized instruction with a low teacher to student ratio, and parent/family involvement.
- Applied behavior analysis, a methodology based on learning theory principles that teaches skills and decreases maladaptive behaviors through repetition and reinforcement, is currently considered the gold-standard treatment for autism spectrum disorder.
- Currently, no medications are US Food and Drug Administration approved for the treatment of the core symptoms of autism spectrum disorder; however, risperidone and aripiprazole are approved specifically for treating the symptoms of irritability and aggression in children.

- Co-occurring behavioral or psychiatric disorders are common in autism spectrum disorder. Medications used in other psychiatric disorders can be effective in individuals with autism spectrum disorder as well.
- Children with autism spectrum disorder tend to experience more side effects from medications; therefore, medication dosing trials should ''start low and go slow.''

Transition From Pediatric to Adult Neurologic Care

Ann H. Tilton, MD, FAAN; Claudio Melo de Gusmao, MD. Continuum (Minneap Minn). February 2018; 24 (1 Child Neurology):276–287.

Abstract

Purpose of Review:

With advances in medical care, the number of youths surviving with medically complex conditions has been steadily increasing. Inadequate transition planning and execution can lead to gaps in care, unexpected emergency department visits, and an increase in health care costs and patient/caregiver anxiety. Many barriers that prevent adequate transition have been identified, including insufficient time or staff to provide transition services, inadequate reimbursement, resistance from patients and caregivers, and a dearth of accepting adult providers.

Recent Findings:

Transition is distinct from transfer of care. Transition is a planned multistage process, while transfer refers to a point in time where responsibility of care shifts from one provider to another. Key differences exist between the pediatric and adult models of care. A successful transition should empower the patient to understand and take responsibility in managing his or her condition; foster independent functioning to the extent that is possible; integrate educational, legal, and community resources in the care plan; and identify appropriate adult health care providers at the time of transfer. Different models have been proposed to streamline the transition process, with improvement in patients' knowledge of their condition, self-efficacy, and confidence.

Summary:

Neurologists have a key role in supporting their patients in the transition to adulthood. This article reviews basic tenets and provides tools to assist in navigating the complex transition process. These tenets are intended to improve quality of care and decrease clinician burden and remain an active area of research.

Key Points

- Every year, about 750,000 youths require transfer from pediatric to adult care; unfortunately, less than 40% meet nationally defined transition core outcomes.
- In many pediatric-onset neurologic conditions, such as epilepsy, the burden of disability may be present even if patients are in clinical remission.

- The distinction between child-centered and adult-centered care is important.
- Adult medicine carries an expectation that knowledge and management of disorders should be assigned to the patient, but these skills are not necessarily fostered during pediatric care.
- Transition should be viewed distinctly from transfer of care. Transition is a planned multistage process, while transfer refers to a point in time where responsibility of care shifts from one provider to another.
- Inadequate, unplanned, or incomplete transition may cause significant morbidity. Often, entry to the adult care system for neurologic patients occurs at a time of crisis and with significant gaps in care. Even in patients with complex chronic conditions, this interval can be longer than 1 year, with potential for lapses in care and increased high-acuity emergency department visits.
- Transition is best viewed as not only being composed of philosophical tenets but also of well-defined steps that provide the details necessary for implementation.
- It is best that the youth and caregivers have a clear expectation that a transition into the adult health care system will be scheduled.
- The initial discussion of transition with patient and caregivers should raise awareness of upcoming changes in the care model through adolescence, including private sessions between the youth and health care provider, the expectation of knowledge of the neurologic condition, the gradual increase in responsibility for managing health care needs (to the extent possible), and the differing health care needs of adults.
- A regular review of the patient's self-management skills is important so that gaps in the patient's knowledge base can be identified and remedied before transition.
- Individuals with intellectual disabilities should not be excluded from the self-management assessment process, as many may be able to develop limited self-management skills. In particular, individuals with mild intellectual disability may be able to exert some decision-making capacity and often can become responsible for knowing their diagnosis, taking medication independently, and participating in their own care.
- Some patients with cognitive limitations will require legal guardianship, and starting the discussion by the age of 14 allows adequate planning before the patient's 18th birthday (the age of majority in most states).
- In the United States, if no process has determined otherwise, competency is automatically assumed at majority, regardless of the degree of the individual's disability. This directly impacts the young adult and those providing care, as legally removing competency is a lengthy and potentially expensive process.
- Some state courts require a clinical team report to assist them in making decisions establishing competency or lack thereof. This report often consists of evaluations performed by a physician, psychologist, and social worker within a certain period of time, so advance planning is key.
- The child neurology team is essential in identifying and collaborating with an adult neurologist or other appropriate medical caregivers as the plans are made to transfer the patient to adult services.
- A major tool in the transfer to an adult health care provider is the transfer packet, which should include the transition care plan and a medical Summary with relevant medical information, such as imaging studies, electrophysiologic test results, recent laboratory studies, and other pertinent data.
- Child neurologists and child neurology teams have a key role in supporting their patients in their transition to adulthood.

Neurologic Complications in the Pediatric Intensive Care Unit

Mark S. Wainwright, MD, PhD. Continuum (Minneap Minn). February 2018; 24 (1 Child Neurology):288–299.

Abstract

Purpose of Review:

All critical care is directed at maintaining brain health, but recognizing neurologic complications of critical illness in children is difficult, and limited data exist to guide practice. This article discusses an approach to the recognition and management of seizures, stroke, and cardiac arrest as complications of other critical illnesses in the pediatric intensive care unit.

Recent Findings:

Convulsive and nonconvulsive seizures occur frequently in children after cardiac arrest or traumatic brain injury and during extracorporeal membrane oxygenation. Seizures may add to neurologic morbidity, and continuous EEG monitoring is needed for up to 24 hours for detection. Hypothermia has not been shown to improve outcome after cardiac arrest in children, but targeted temperature management with controlled normothermia and prevention of fever is a mainstay of neuroprotection.

Summary:

Much of brain-directed pediatric critical care is empiric. Recognition of neurologic complications of critical illness requires multidisciplinary care, serial neurologic examinations, and an appreciation for the multiple risk factors for neurologic injury present in most patients in the pediatric intensive care unit. Through attention to the fundamentals of neuroprotection, including maintaining or restoring cerebral perfusion matched to the metabolic needs of the brain, combined with anticipatory planning, these complications can be prevented or the neurologic injury mitigated.

Key Points

- Neurologic management of the patient in the pediatric or cardiac intensive care unit (ICU) requires an interdisciplinary team involving neurologists, intensivists, neurosurgeons, and allied disciplines, including physical medicine and rehabilitation and psychiatry.
- Neuroprotection aims to match cerebral perfusion with the metabolic requirements of the injured brain.
- Electrographic seizures and electrographic status epilepticus have been associated with increased risk for neurologic morbidity after neurologic insults.
- Electrographic seizures may cause secondary injury and worsen outcome in critical illness.
- Continuous EEG monitoring for nonconvulsive seizures should be obtained for at least 12 to 24 hours in children with persistent altered mental status following generalized convulsive status epilepticus or other clinically evident seizures and after supratentorial brain injury with altered mental status.

- Many children in the intensive care unit have risk factors for ischemic or hemorrhagic stroke.
- Empiric neuroprotective measures for suspected ischemic stroke may include positioning the head of the bed flat, increasing IV fluid rate, reducing antihypertensive dosing, allowing blood pressure at the upper limit of normal for age, and targeted temperature management, with a goal temperature lower than 37°C (98.6°F).
- Early recognition of stroke, meticulous control of blood pressure and temperature, and anticipatory planning are the key steps for neuroprotection in patients in the intensive care unit.
- Unlike adults, cardiac arrest in children is most often due to progressive tissue hypoxia and acidosis resulting from respiratory failure and circulatory shock.
- While hypothermia has not been shown to improve outcome after cardiac arrest in children, targeted temperature management to maintain temperature of 36.8°C (98.2°F) for at least 48 hours should be considered standard care.
- Nonconvulsive seizures are common during extracorporeal membrane oxygenation, and continuous EEG may be considered a standard practice.
- Young age and fever are risk factors for neurologic deterioration in children with acute liver failure.
- Intensive care unit–acquired weakness occurs in children but the precise impact on morbidity is uncertain because there is no consensus on the criteria for diagnosis in children.
- Before beginning treatment for sympathetic hyperarousal, other treatable medical conditions should be investigated.

Pediatric Traumatic Brain: Injury and Concussion

Meeryo Choe, MD; Karen M. Barlow, MD. Continuum (Minneap Minn). February 2018; 24 (1 Child Neurology):300–311.

Abstract

Purpose of Review:

This article summarizes the impact and complications of mild traumatic brain injury and concussion in children and outlines the recent evidence for its assessment and early management. Useful evidence-based management strategies are provided for children who have a typical recovery following concussion as well as for those who have persistent postconcussion syndrome. Cases are used to demonstrate the commonly encountered pathologies of headache, cognitive issues, and mood disturbances following injury.

Recent Findings:

A clinical risk score using risk factors for poor recovery (eg, female sex, adolescence, previous migraine, and a high degree of acute symptoms) can be used to help the clinician plan follow-up in the community. Prolonged periods of physical and cognitive rest should be avoided. Multidisciplinary treatment plans are often required in the management of persistent postconcussion syndrome.

Summary:

A paucity of research exists for the treatment of postconcussion syndrome. Current treatments target individual symptoms.

Key Points

- Alteration in brain function due to an external force is the hallmark of traumatic brain injury.
- The symptoms and signs of traumatic brain injury and concussion should not be better explained by another medical or psychological condition.
- Traumatic brain injury is the leading cause of death and neurologic morbidity in children.
- Mild traumatic brain injury and concussion are often sustained during sports participation.
- Removal from sport-related activities decreases early repeat injury and speeds recovery.
- After a short period of rest following a concussion, a graduated reentry into normal activities is encouraged.
- Early involvement with a specialized concussion clinic should be considered in those children at risk of delayed recovery.
- Management of concussion is targeted to the problematic symptoms while gradually increasing participation in activities of daily life.
- Preexisting conditions can exacerbate symptoms and lead to delayed recovery.
- Preinjury and postinjury psychological factors are often present in those with prolonged recovery times. Psychological support is a key strategy in healthy recovery.
- Avoid overuse of analgesics in posttraumatic headaches

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Dementia

Article 1: Late-onset Alzheimer Disease

Gil D. Rabinovici, MD. Continuum (Minneap Minn). February 2019; 25 (1 Dementia):14–33.

ABSTRACT

PURPOSE OF REVIEW:

Alzheimer disease (AD) is the most common cause of late-onset dementia. This article describes the epidemiology, genetic and environmental risk factors, clinical diagnosis, biomarkers, and treatment of late-onset AD, defined by age of onset of 65 years or older.

RECENT FINDINGS:

An estimated 5.7 million Americans are living with AD dementia, with the number of affected individuals growing rapidly because of an aging population. Vascular risk factors, sleep disorders, and traumatic brain injury are associated with an increased risk of AD, while increased cognitive and physical activity throughout the lifespan reduce the risk of disease. The primary genetic risk factor for late-onset AD is the apolipoprotein E (*APOE*) ε4 allele. AD typically presents with early and prominent episodic memory loss, although this clinical syndrome is neither sensitive nor specific for underlying AD neuropathology. Emerging CSF and imaging biomarkers can now detect the key neuropathologic features of the disease (amyloid plaques, neurofibrillary tangles, and neurodegeneration) in living people, allowing for characterization of patients based on biological measures. A comprehensive treatment plan for AD includes use of symptomatic medications, optimal treatment of comorbid conditions and neuropsychiatric symptoms, counseling about safety and future planning, and referrals to community resources.

SUMMARY:

AD is very common in older neurologic patients. Neurologists should set the standard for the diagnosis and care of patients with AD and should be familiar with emerging biomarkers that have transformed AD research and are primed to enter the clinical arena.

KEY POINTS

- **Alzheimer disease is the most common cause of dementia, affecting an estimated 5.7 million Americans. The number of affected individuals is expected to triple by 2050 because of an aging population.**
- **Vascular risk factors, sleep disturbances, and traumatic brain injury increase the risk of Alzheimer disease. Increased years of education and greater cognitive and physical activity throughout the lifespan decrease the risk of Alzheimer disease.**
- **The estimated heritability of late-onset Alzheimer disease is approximately 60% to 80%. The primary genetic risk factor for sporadic late-onset Alzheimer disease is the apolipoprotein E (*APOE*) ε4 allele.**

- The clinical evaluation of patients with cognitive symptoms should first and foremost exclude reversible causes based on history, examination, and laboratory testing.
- Mild cognitive impairment is defined as objectively confirmed cognitive decline that does not interfere with independent function. When cognitive decline interferes with independent function, patients meet criteria for dementia.
- Late-onset Alzheimer disease typically presents with progressive decline in episodic memory, with variable involvement of other cognitive domains. Progressive memory impairment can also be caused by other neurodegenerative processes affecting the medial temporal lobes.
- Common neuropsychiatric symptoms in Alzheimer disease include depression, anxiety, mild apathy, irritability, and sleep disturbances.
- MRI findings in Alzheimer disease include medial temporal lobe and posterior-predominant cortical atrophy. Iron-sensitive sequences should be performed to assess for hemorrhages associated with cerebral amyloid angiopathy.
- The neuropathology of Alzheimer disease is defined by the presence of senile amyloid plaques and tau neurofibrillary tangles. The burden and distribution of these two lesions define the degree of Alzheimer disease neuropathologic changes.
- Late-life dementia is often associated with multiple brain pathologies. The most common are Alzheimer disease, Lewy bodies, vascular brain injury, hippocampal sclerosis, and TDP-43 inclusions.
- Amyloid plaques and tau tangles can be detected in living people based on changes in CSF levels of amyloid-β and phosphorylated tau or by using positron emission tomography radiotracers that selectively bind amyloid-β or tau aggregates.
- A comprehensive care plan for patients with Alzheimer disease includes treatment with Alzheimer disease–specific medications, treatment of relevant comorbid conditions, counseling about safety and future planning, and referrals to community resources.
- Acetylcholinesterase inhibitors are approved for the treatment of mild to severe Alzheimer disease dementia. Memantine is approved for the treatment of moderate to severe Alzheimer disease dementia.
- Difficult behaviors in Alzheimer disease should be addressed primarily with nonpharmacologic approaches, use of Alzheimer disease symptomatic drugs, and judicious use of antidepressants. Use of neuroleptics should be avoided, if possible, because of increased morbidity and mortality.

Article 2: Early-onset Alzheimer Disease and Its Variants

Mario F. Mendez, MD, PhD, FAAN. Continuum (Minneap Minn). February 2019; 25 (1 Dementia):34–51.

ABSTRACT

PURPOSE OF REVIEW:

Early-onset Alzheimer disease (AD) is defined as having an age of onset younger than 65 years. While early-onset AD is often overshadowed by the more common late-onset AD, recognition of the differences between early- and late-onset AD is important for clinicians.

RECENT FINDINGS:

Early-onset AD comprises about 5% to 6% of cases of AD and includes a substantial percentage of phenotypic variants that differ from the usual amnestic presentation of typical AD. Characteristics of early-onset AD in comparison to late-onset AD include a larger genetic predisposition (familial mutations and summed polygenic risk), more aggressive course, more

frequent delay in diagnosis, higher prevalence of traumatic brain injury, less memory impairment and greater involvement of other cognitive domains on presentation, and greater psychosocial difficulties. Neuroimaging features of early-onset AD in comparison to late-onset AD include greater frequency of hippocampal sparing and posterior neocortical atrophy, increased tau burden, and greater connectomic changes affecting frontoparietal networks rather than the default mode network.

SUMMARY:

Early-onset AD differs substantially from late-onset AD, with different phenotypic presentations, greater genetic predisposition, and differences in neuropathologic burden and topography. Early-onset AD more often presents with nonamnestic phenotypic variants that spare the hippocampi and with greater tau burden in posterior neocortices. The early-onset AD phenotypic variants involve different neural networks than typical AD. The management of early-onset AD is similar to that of late-onset AD but with special emphasis on targeting specific cognitive areas and more age-appropriate psychosocial support and education.

KEY POINTS

- Early-onset Alzheimer disease, which makes up about 5% to 6% of all cases of Alzheimer disease, is distinct from late-onset Alzheimer disease in a number of clinical, genetic, neurobiological, and management features.
- Early-onset Alzheimer disease is the most common cause of early-onset neurodegenerative dementia.
- Many clinical, neuropathologic, and management differences exist between early-onset and late-onset Alzheimer disease.
- One major difference between early-onset and late-onset Alzheimer disease is that one-third or more of patients with early-onset Alzheimer disease present with language, visuospatial, or other phenotypes rather than the usual amnestic disorder seen in late-onset Alzheimer disease.
- MRI of patients with early-onset Alzheimer disease shows more widespread cortical atrophy, particularly in the parietal cortex, compared to the more limited atrophy affecting temporal regions in patients with late-onset Alzheimer disease.
- Fludeoxyglucose positron emission tomography shows greater parietal hypometabolism in early-onset Alzheimer disease compared to greater bilateral temporal hypometabolism in late-onset Alzheimer disease.
- Amyloid positron emission tomography is positive in most patients with early-onset Alzheimer disease who would not be expected to have age-associated brain amyloid deposition and can be useful in diagnosis of the disorder.
- Tau positron emission tomography has promise for future use in early-onset Alzheimer disease, particularly in correlating localization of changes with clinical symptoms.
- CSF analysis in early-onset Alzheimer disease is similar to late-onset Alzheimer disease, showing the characteristic low amyloid-$\beta_{1\text{-}42}$ and high total tau and phosphorylated tau levels but with some variations.
- The vast majority of patients with early-onset Alzheimer disease have a nonfamilial, or sporadic, form.
- Only 11% or less of those with early-onset Alzheimer disease (about 0.6% of the total of all patients with Alzheimer disease of any age) have familial Alzheimer disease associated with one of the three known autosomal dominant mutations in *APP*, *PSEN1*, or *PSEN2*.
- An active area of genetic research is the recognition of a polygenic risk for sporadic early-onset Alzheimer disease from a number of susceptibility genes.
- On neuropathology, patients with early-onset Alzheimer disease (especially with the variants) are more likely to have hippocampal sparing with increased neocortical tau pathology, particularly in the parietal cortex and, to a lesser extent, the frontal cortex, than patients with late-onset Alzheimer disease.
- On neuropathology, tau and neurofibrillary tangles, more than amyloid-$\beta_{1\text{-}42}$ and neuritic plaques, correspond with the features of early-onset Alzheimer disease, with a relatively greater tau burden in early-onset Alzheimer disease than in late-onset Alzheimer disease.

- Phenotypic variants of early-onset Alzheimer disease include those that present with language impairment (known as *logopenic variant primary progressive aphasia*), those that present with visuospatial or visuoperceptual impairments (known as *posterior cortical atrophy*), frontal or behavioral/executive variants, a number of parietal syndromes (such as the acalculia variant of early-onset Alzheimer disease), and a subgroup of patients with corticobasal syndrome.
- Phenotypic variants of early-onset Alzheimer disease may involve alternative frontoparietal neural networks rather than the posterior default mode network implicated in late-onset Alzheimer disease.
- Logopenic variant primary progressive aphasia, the most common nonamnestic phenotypic variant of early-onset Alzheimer disease, presents with a progressive decline in language with relatively spared memory and cognition due to focal Alzheimer neuropathology in temporoparietal language areas in the left hemisphere, especially the superior/midtemporal gyrus, angular gyrus, and midfrontal cortex.
- In logopenic variant primary progressive aphasia, neuroimaging and CSF studies usually reveal abnormalities consistent with early-onset Alzheimer disease, including focal atrophy and decreased metabolism in the left temporoparietal junction.
- Posterior cortical atrophy, the second most common early-onset Alzheimer disease variant, presents with progressive and disproportionate loss of visuospatial or visuoperceptual functions, usually due to Alzheimer neurodegeneration of posterior visual cortical regions.
- The frontal variant of Alzheimer disease, now known as *behavioral/dysexecutive Alzheimer disease*, presents with features suggestive of frontotemporal lobar degeneration but most commonly with apathy or abulia.
- Less common phenotypic variants of early-onset Alzheimer disease may have prominent parietal lobe symptoms and signs, exemplified by the acalculia variant from early Alzheimer neuropathology in the left inferior parietal lobule, particularly the intraparietal sulcus.
- Acetylcholinesterase inhibitors, such as donepezil, galantamine, and rivastigmine, are indicated in the management of patients with early-onset Alzheimer disease, with the usual precautions and titration schedules.
- The management of early-onset Alzheimer disease may differ from late-onset Alzheimer disease when targeting the management of specific cognitive and behavioral deficits.
- Management of patients with early-onset Alzheimer disease must also consider providing genetic counseling if patients are to be evaluated for familial Alzheimer disease when the family history is suggestive of an autosomal dominant disorder.
- The provision of age-appropriate psychosocial support is important in the management of early-onset Alzheimer disease.

Article 3: Posterior Cortical Atrophy

Jonathan M. Schott, BSc, MD, FRCP, FEAN, SFHEA; Sebastian J. Crutch, PhD, CPsych.
Continuum (Minneap Minn). February 2019; 25 (1 Dementia):52–75.

ABSTRACT

PURPOSE OF REVIEW:

This article presents an overview of the clinical syndrome of posterior cortical atrophy (PCA), including its pathologic underpinnings, clinical presentation, investigation findings, diagnostic criteria, and management.

RECENT FINDINGS:

PCA is usually an atypical form of Alzheimer disease with relatively young age at onset. New diagnostic criteria allow patients to be diagnosed on a syndromic basis as having a primary visual (pure) form or more complex (plus) form of PCA and, when possible, on a disease-specific basis using biomarkers or underlying pathology. Imaging techniques have demonstrated that some

pathologic processes are concordant (atrophy, hypometabolism, tau deposition) with clinical symptoms and some are discordant (widespread amyloid deposition). International efforts are under way to establish the genetic underpinnings of this typically sporadic form of Alzheimer disease. In the absence of specific disease-modifying therapies, a number of practical suggestions can be offered to patients and their families to facilitate reading and activities of daily living, promote independence, and improve quality of life

SUMMARY:

While rare, PCA is an important diagnostic entity for neurologists, ophthalmologists, and optometrists to recognize to allow for early accurate diagnosis and appropriate patient management. PCA provides an important opportunity to investigate the causes of selective vulnerability in Alzheimer disease.

KEY POINTS

- A striking feature of posterior cortical atrophy is that the majority of affected individuals have an unusually early age at disease onset, typically presenting between 50 and 65 years of age.
- Most patients with posterior cortical atrophy have underlying Alzheimer disease.
- The core features of posterior cortical atrophy include visuospatial and perceptual deficits as well as features of Gerstmann syndrome (acalculia, left-right disorientation, finger agnosia, and agraphia), Balint syndrome (ocular motor apraxia, optic ataxia, and simultanagnosia), alexia, and apraxia.
- Patients with posterior cortical atrophy may have a history of repeated visits to optometrists and ophthalmologists and multiple unsuccessful changes in eyeglasses or surgical procedures in an attempt to correct acuity.
- Over time, difficulties with reading emerge in the vast majority of patients with posterior cortical atrophy.
- Patients with posterior cortical atrophy often become anxious about riding on escalators, particularly when going down; can be cautious when crossing the road because of difficulties in judging the speed of traffic; and can have difficulty with revolving doors.
- Combinations of visual problems and dyspraxia in patients with posterior cortical atrophy have significant functional consequences, including difficulty in getting dressed; cooking; and using cell phones, remote controls, and computers.
- Simultanagnosia (the inability to interpret the entirety of a visual scene) can often be demonstrated by asking an individual to describe a complex picture; rather than describing it in its entirety, individuals with posterior cortical atrophy will often hone in on specific features and fail to see the picture as a whole.
- A particularly striking and very common feature of posterior cortical atrophy is the presence of an apperceptive agnosia.
- Visual disorientation (likely reflecting combinations of simultanagnosia and optic ataxia), when present, is a striking sign in patients with posterior cortical atrophy.
- When performing neuropsychological testing in posterior cortical atrophy, it is important that the testing psychologist is aware of the patient's difficulties with vision, ensuring that test material is, whenever possible, presented in verbal rather than visual form.
- In the presence of a typical history for posterior cortical atrophy, the absence of marked parietooccipital volume loss should not exclude the diagnosis.
- Fludeoxyglucose positron emission tomography may be extremely valuable in demonstrating hypometabolism within the parietooccipital cortices.
- While amyloid positron emission tomography has a role in confirming the presence or absence of amyloid pathology, it is not useful in distinguishing between Alzheimer disease syndromes.
- Tau positron emission tomography, which is currently only available in a research setting, often shows very striking posterior cortical deposition of tau pathology.
- Posterior cortical atrophy due to Alzheimer disease is a sporadic condition, and routine testing for the autosomal dominant forms of the disease is not usually indicated.

- For most patients with posterior cortical atrophy due to Alzheimer disease, treatment with acetylcholinesterase inhibitors or memantine, as would be standard treatment for Alzheimer disease, is appropriate.
- The mainstay of management of patients with posterior cortical atrophy (as with typical Alzheimer disease) is the provision of practical and psychological support to affected patients and their caregivers.
- Most patients with posterior cortical atrophy will not be fit to drive. Establishing driving safety is of paramount importance.

Article 4: Behavioral Variant Frontotemporal Dementia

William W. Seeley, MD. Continuum (Minneap Minn). February 2019; 25 (1 Dementia):76–100.

ABSTRACT

PURPOSE OF REVIEW:

This article describes the clinical, anatomic, genetic, and pathologic features of behavioral variant frontotemporal dementia (bvFTD) and discusses strategies to improve diagnostic accuracy, emphasizing common pitfalls to avoid. Key aspects of management and the future of diagnosis and care for the disorder are highlighted.

RECENT FINDINGS:

BvFTD is a clinical syndrome, not a disease. Patients with the syndrome share core symptoms that reflect degeneration within the most consistently affected brain regions, but accompanying features vary and reflect the precise topography of regional degeneration. The clinician must distinguish a bvFTD syndrome from psychiatric illness and other neurodegenerative syndromes that feature a prominent behavioral component. Antemortem prediction of pathologic diagnosis remains imperfect but improves with careful attention to the clinical details. Management should emphasize prevention of caregiver distress, behavioral and environmental strategies, symptom-based psychopharmacology, and genetic counseling.

SUMMARY:

BvFTD is an important and challenging dementia syndrome. Although disease-modifying treatments are lacking, clinicians can have a profound impact on a family coping with this disorder. Treatment trials are under way for some genetic forms of bvFTD. For sporadic disease, pathologic heterogeneity remains a major challenge, and ongoing research seeks to improve antemortem molecular diagnosis to facilitate therapeutic discovery.

KEY POINTS

- Behavioral variant frontotemporal dementia (bvFTD) is an important disorder than can be difficult to recognize, in part because of the wide normative variation in social-emotional functions and the long list of disorders that affect those functions.
- BvFTD is a syndrome, not a disease, and clinicians who diagnose bvFTD should generate a differential diagnosis.
- BvFTD presents with slowly progressive decline in social and emotional functions.
- BvFTD core diagnostic features reflect degeneration of networked structures, typically including the anterior insula, anterior cingulate and adjacent medial prefrontal cortices, amygdala, striatum, and thalamus.
- Features that develop less frequently in patients with bvFTD reflect variable involvement of additional brain regions.

- Patients with bvFTD often develop prominent motor deficits of various types later in the course of the syndrome.
- BvFTD is the result of a known pathogenic variant in 15% to 20% of patients.
- Expansions in *C9orf72* are the most common genetic cause of bvFTD and are commonly accompanied by motor neuron disease.
- BvFTD results from a diverse array of neuropathologic entities, most of which are classified as frontotemporal lobar degeneration.
- Accurate bvFTD diagnosis requires a methodical stepwise approach that relies heavily on the clinical history.
- Both neurodegenerative and non-neurodegenerative causes should be considered in all patients with bvFTD.
- Structural MRI and, increasingly, molecular biomarkers play a key role in predicting pathology in patients with a bvFTD syndrome.
- Occasionally, patients with bvFTD have severe early memory loss or a normal MRI.
- Executive dysfunction is common in bvFTD but also in other disorders and should not be used as an indicator of bvFTD unless accompanied by signature social-emotional features.
- Model care for bvFTD involves contributions from a multidisciplinary team that supports both patient and caregiver.
- BvFTD caregivers are at high risk for burnout.
- Nonpharmacologic approaches are often the best way to manage troublesome behavioral symptoms in bvFTD.
- Pharmacologic management of bvFTD should target specific symptoms, such as overeating, compulsivity, severe agitation, or psychosis.
- Selective serotonin reuptake inhibitors are first-line therapy for overeating and compulsivity symptoms in bvFTD.
- Acetylcholinesterase inhibitors have shown no benefit in bvFTD and may worsen behavioral symptoms.

Article 5: Primary Progressive Aphasias and Apraxia of Speech

Hugo Botha, MBChB; Keith A. Josephs, MD, MST, MSc. Continuum (Minneap Minn). February 2019; 25 (1 Dementia):101–127.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews two of the primary progressive aphasias (PPAs), disorders characterized by the early and predominant impairment of language, and primary progressive apraxia of speech, a degenerative motor speech disorder that is closely related to PPA. An outline of the history and controversy surrounding how these disorders are classified is provided before the article focuses on each disorder's clinical and imaging features.

RECENT FINDINGS:

Over the past decade, the classification of degenerative speech and language disorders has been refined. Clinical, imaging, and pathologic evidence suggests that primary progressive apraxia of speech is a distinct degenerative disorder. Furthermore, multiple lines of evidence have highlighted issues with nonfluent/agrammatic variant PPA, which complicates the diagnosis, prognosis, and study of this disorder. Semantic variant PPA, while not without controversy, remains one of the most well-defined disorders, with good clinicopathologic correlation.

SUMMARY:

Accurate classification and diagnosis of these degenerative speech and language disorders is crucial in clinical practice and ongoing research efforts. For nonfluent/agrammatic variant PPA, the authors suggest emphasizing agrammatism as the core inclusion criterion and taking care not to include patients with isolated or predominant apraxia of speech. Isolated apraxia of speech can be the manifestation of a degenerative disease and, based on the different prognosis, should be recognized as distinct from PPA. Finally, it is important to recognize that some patients with semantic dementia, despite sharing the same pathologic associations, may not meet criteria for PPA.

KEY POINTS

- *Primary progressive aphasia* refers to a group of neurodegenerative diseases characterized by early and prominent language impairment occurring in the relative absence of cognitive impairment, behavioral disturbance, or motor symptoms.
- Three canonical variants of primary progressive aphasia (PPA) are recognized, of which two (nonfluent/agrammatic variant PPA and semantic variant PPA) are classified as frontotemporal dementia syndromes while the other (logopenic variant PPA) is most commonly viewed as an atypical variant of Alzheimer disease.
- Apraxia of speech is a motor speech disorder thought to result from impaired planning and programming of the movements required for speech production.
- The most widely accepted current classification scheme and diagnostic criteria for primary progressive aphasia consists of two stages. First, a root diagnosis of primary progressive aphasia is considered. Second, criteria for the three main variants are considered, each with a set of mandatory and supportive features.
- While motor speech disorders such as dysarthria and apraxia of speech often co-occur with aphasia, these are clearly not language impairments that would, on their own, qualify a patient for a diagnosis of primary progressive aphasia.
- The relative dominance of phonetic impairment (sound level errors, such as distorted substitutions or additions) or prosodic impairment (such as slow rate or segmented speech) is the primary source of heterogeneity in apraxia of speech.
- Primary progressive apraxia of speech refers to cases in which apraxia of speech is the sole initial manifestation of a neurodegenerative disease.
- In primary progressive apraxia of speech, it is crucial to ask about writing or typing, as preservation of these forms of communication is often striking despite severe speech impairment.
- Cases in which apraxia of speech dominates over aphasia appear to have clinical and imaging features that are more like those seen in primary progressive apraxia of speech than nonfluent/agrammatic variant primary progressive aphasia.
- Patients with primary progressive apraxia of speech typically score well within the normal range on bedside cognitive testing and may continue to do so in the later disease stages, provided written responses are allowed.
- The most helpful parts of the speech examination for primary progressive apraxia of speech are those that demand the production of motorically complex utterances: conversational or narrative speech, alternating motion rates, sequential motor rates, and repetition of increasingly complex words and sentences.
- About two-thirds of patients with primary progressive apraxia of speech have a coexisting nonverbal oral apraxia, which can be assessed at the bedside by asking the patient to perform simple movements such as smacking their lips, clicking their tongue, coughing, or blowing.
- Gray and white matter atrophy of the motor, premotor, and supplementary motor areas bilaterally has been reported in primary progressive apraxia of speech at group level, but it is worth noting that this may be fairly asymmetric at the single patient level.

- Approximately 40% of patients with primary progressive apraxia of speech develop a progressive supranuclear palsy/corticobasal syndrome–like disorder, which has been termed *progressive supranuclear palsy–apraxia of speech*, approximately 5 years into their illness.
- The overwhelming majority of autopsied cases of primary progressive apraxia of speech reported in the literature were found to have an underlying 4-repeat tauopathy, with corticobasal degeneration pathology being the most common.
- While some patients or informants may volunteer examples of impaired grammar or syntax, focused questioning is often necessary to reveal early problems.
- When assessing language ability, it is important to bear in mind that aphasia typically involves all aspects of language to varying degrees, and thus the primary progressive aphasia classification depends on the relative impairment.
- When evaluating patients for nonfluent/agrammatic variant primary progressive aphasia, it is helpful to review samples of written language, such as emails, as they frequently contain errors involving word order or functional morphemes.
- The rest of the neurologic examination is typically unrevealing in nonfluent/agrammatic variant primary progressive aphasia, although mild ideomotor apraxia and parkinsonism are possible.
- The anterior portions of the language network appear to be most vulnerable in nonfluent/agrammatic variant primary progressive aphasia, including Broca areas 44 and 45.
- The subset of nonfluent/agrammatic variant primary progressive aphasia cases with apraxia of speech are more likely to have underlying 4-repeat tau.
- Semantic dementia results from a breakdown in semantic memory, the amodal and time-independent knowledge store, in contrast to the episodic memory system, which is involved with recall of specific events or experiences.
- About 70% of cases of semantic dementia have predominant left-sided involvement (ie, would be viewed as semantic variant primary progressive aphasia), while the remaining 30% present with predominant right-sided involvement.
- Nouns are typically most difficult for patients with semantic variant primary progressive aphasia, which may result in circumlocution, the use of a more general or category label, or the use of nonspecific filler words.
- Testing for prosopagnosia is usually done by showing patients pictures of celebrities or other famous people and asking them to either identify the famous face among distractors or to provide some information to prove that they have correctly recognized the person.
- Whereas patients with nonfluent/agrammatic variant or logopenic variant primary progressive aphasia typically benefit greatly from cueing on unnamed items, patients with semantic variant primary progressive aphasia often fail to choose the correct word from a small list.
- A supportive, albeit not specific, feature of semantic variant primary progressive aphasia is trouble with reading (surface dyslexia) and writing {surface dysgraphia) of irregularly spelled words, such as *yacht*, *colonel*, and *debt*.
- Focal anterior temporal pole involvement is characteristic of semantic dementia.
- Semantic dementia appears to be the frontotemporal dementia syndrome with the lowest risk of an underlying genetic cause.
- The majority (>80%) of semantic dementia cases are associated with the accumulation of TDP-43 Type C.
- Even in unclassified or mixed cases of primary progressive aphasia, the presence of certain features (eg, apraxia of speech) may still influence management and can still be predictive of the underlying pathology.
- The lack of pharmacologic options to treat speech and language disorders should not dissuade the physician or patient from seeking therapeutic options, and referral to a speech and language pathologist is highly recommended when a degenerative speech and language disorder is considered.

Article 6: Lewy Body Dementias

Melissa J. Armstrong, MD, MSc, FAAN. Continuum (Minneap Minn). February 2019; 25 (1 Dementia):128–146.

ABSTRACT

PURPOSE OF REVIEW:

This article describes current diagnostic criteria relating to the diagnosis of Lewy body dementia, highlights diagnostic controversies, and reviews treatment approaches.

RECENT FINDINGS:

Clinical diagnostic criteria for both Parkinson disease and dementia with Lewy bodies have been recently updated. These criteria result in overlap between individuals diagnosed with Parkinson disease and those with dementia with Lewy bodies. Although clinical features and symptomatic treatment overlap, differences remain in epidemiology and expected progression. The high prevalence of cognitive impairment in Parkinson disease supports regular screening for cognitive changes and counseling patients and families regarding what to expect. Treatment for Lewy body dementia involves avoiding medications that may cause or exacerbate symptoms; prescribing pharmacologic agents to address bothersome cognitive, behavioral, movement, and other nonmotor symptoms; recommending physical exercise and therapy; and providing education, counseling, caregiver support, and palliative care.

SUMMARY:

Lewy body dementia includes both dementia with Lewy bodies and Parkinson disease dementia, overlapping clinicopathologic entities with differences relating to diagnosis and expected progression. Treatment is symptomatic and thus largely overlapping for the two conditions.

KEY POINTS

- Lewy body dementia is an umbrella term that includes the clinical diagnoses of both Parkinson disease dementia and dementia with Lewy bodies.
- According to current diagnostic criteria from the Dementia With Lewy Bodies Consortium, probable dementia with Lewy bodies is diagnosed in the context of a dementia consistent with the dementia with Lewy bodies phenotype and either two or more core clinical features or the presence of one core clinical feature and at least one indicative biomarker.
- In dementia with Lewy bodies, visual processing, attention, and executive functioning are typically more impaired than memory and naming.
- Individuals with a history of rapid eye movement sleep behavior disorder are 6 times more likely to have autopsy-confirmed dementia with Lewy bodies than other neurodegenerative dementias.
- Parkinson disease psychosis includes a broad range of experiences, including hallucinations in various modalities, sense of presence or passage, illusions, and delusions.
- The American Academy of Neurology Parkinson disease quality measurement set includes a measure identifying the percentage of patients with Parkinson disease who were assessed for cognitive dysfunction in the past 12 months using a recommended screening tool or neuropsychological assessment.
- The diagnosis of Parkinson disease-mild cognitive impairment should prompt clinicians to identify potentially modifiable risk factors for cognitive impairment, perform serial evaluations to monitor for changes in cognitive status, assess functional capabilities, and counsel patients and families to discuss long-term planning topics.

- In a 2016 study examining cause of death in Lewy body dementia, dementia was described as a contributor to death 71% of the time, followed by circulatory (45%) and respiratory (38%) contributors, consistent with reports that pneumonia is the most common cause of death in Parkinson disease dementia (25%).
- Treating individuals with Lewy body dementia and their families should include querying safety concerns and driving safety, assessing pain, screening for and managing behavioral and psychiatric symptoms, discussing pharmacologic and nonpharmacologic treatment approaches, encouraging advance care planning, and providing palliative care counseling and caregiver education and support.
- The first step in successfully treating an individual with Lewy body dementia is to identify medications that could contribute to symptoms or are best avoided in older adults with dementia.
- Cognitive symptoms in Lewy body dementia are treated with cholinesterase inhibitors, with use supported by multiple systematic reviews and meta-analyses.
- Pimavanserin was approved by the US Food and Drug Administration for Parkinson disease psychosis in 2016 based on a single randomized controlled trial, and it is the only approved treatment for this indication. While high-level efficacy data are lacking, quetiapine and clozapine are also commonly used to treat psychosis in the context of Parkinson disease and Lewy body dementia as these are safer than alternative antipsychotics. All antipsychotic agents have a boxed warning regarding increased risk of death in patients with dementia-related psychosis.
- Melatonin is first-line treatment for rapid eye movement sleep behavior disorder in the context of Lewy body dementia, but clonazepam is often cautiously tried if melatonin is not sufficiently helpful.
- Physical therapy, occupational therapy, and speech-language pathology assessments (addressing both speech and swallowing) are important interdisciplinary considerations for care of patients with Lewy body dementia. Therapy sessions will usually include both patients and caregivers to compensate for patients' cognitive limitations and also to teach caregiver-specific skills (eg, assistance in transfers and fall reduction).

Article 7: Vascular Cognitive Impairment

Jonathan Graff-Radford, MD. Continuum (Minneap Minn). February 2019; 25 (1 Dementia):147–164.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of vascular cognitive impairment; discusses its epidemiology, subtypes, and associations with other neurodegenerative diseases; and reviews the diagnostic evaluation and management of these disorders.

RECENT FINDINGS:

Cerebrovascular disease is a common cause of dementia and frequently coexists with neurodegenerative causes. The heterogeneity of mechanisms leading to vascular cognitive impairment makes developing unifying clinical and research criteria difficult. Recognizing the neuroimaging hallmarks of different forms of vascular cognitive impairment can allow for individualized treatment and management. In individuals with mild vascular cognitive impairment, aerobic exercise appears to be a promising treatment but requires further investigation.

SUMMARY:

Vascular cognitive impairment can be caused by several mechanisms. While treating vascular risk factors is rational to prevent worsening of cognitive impairment, well-designed studies are needed to demonstrate efficacy.

KEY POINTS

- Vascular cognitive impairment represents a spectrum of vascular disorders that cause cognitive impairment.

- No single neuropsychological pattern distinguishes vascular cognitive impairment from other etiologies of cognitive impairment; however, patients with vascular cognitive impairment tend to perform worse on tests of executive function compared to memory function.
- In the community setting, cerebrovascular disease commonly occurs with neurodegenerative diseases.
- Both clinical and so-called "silent" strokes are significant risk factors for the development of dementia.
- Neuroimaging biomarkers may allow for identification of different mechanisms leading to small vessel disease. For example, deep cerebral microbleeds are suggestive of hypertensive arteriopathy, and lobar cerebral microbleeds are suggestive of cerebral amyloid angiopathy.
- Several strategic brain regions have been associated with the development of dementia after an infarct, including the angular gyrus, thalamus, caudate and putamen, basal forebrain, posterior cerebral artery (ie, hippocampus), and anterior cerebral artery territories.
- While multi-infarct dementia was once considered synonymous with vascular dementia, it is now recognized that multi-infarct dementia represents a subset of individuals with vascular cognitive impairment.
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a genetic cerebral small vessel disease caused by mutations in the *NOTCH3* gene. Cognitive impairment is common in CADASIL, as are migraine headaches and stroke.
- T2 hyperintensity involvement of the anterior temporal lobes on MRI may suggest CADASIL as a possible diagnosis.
- Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) occurs due to mutations in the *HTRA1* gene and is associated with alopecia and spondylosis in addition to the cerebral small vessel disease.
- Microinfarcts are increasingly recognized as an important contributor to cognitive decline. Recent advances in MRI techniques have allowed a subset to be imaged in vivo.
- Treatment of vascular risk factors in midlife, aerobic exercise, and a Mediterranean diet are promising treatments to prevent and treat vascular cognitive impairment but require further investigation.

Article 8: Normal Pressure Hydrocephalus

Neill R. Graff-Radford, MBBCH, FRCP, FAAN; David T. Jones, MD. Continuum (Minneap Minn). February 2019; 25 (1 Dementia):165–186.

ABSTRACT

PURPOSE OF REVIEW:

Since it was first described in 1965, normal pressure hydrocephalus (NPH) has been a controversial subject. New studies have shed light on its epidemiology and pathogenesis and provided objective ways to measure outcome in patients with NPH. Neuroimaging has improved and allows better recognition of both NPH and the presence of overlapping diseases

RECENT FINDINGS:

Several recent epidemiologic studies confirm that NPH is a rare disease, but the presence of large ventricles is a common finding with aging. NPH may be multifactorial, including congenital causes, vascular disease, and impaired CSF absorption. MRI features of NPH include enlarged ventricular size and CSF fluid collection outside the ventricles not due to atrophy. The term *disproportionately enlarged subarachnoid space hydrocephalus* (DESH) has been used to describe prognostic MRI features in NPH, including a "tight high convexity" and enlargement of CSF spaces in the sylvian fissure. DESH has been included in the Japanese guideline for the

diagnosis and treatment of NPH. A new NPH scale has been published that provides an objective framework for evaluating patients with NPH before and after shunt placement. Programmable shunts can noninvasively manage overdrainage complications. Surgical outcome has been improving over time. Recent studies have led to improved recognition of overlapping diseases such as Alzheimer pathology, which co-occurs in about 30% of NPH cases. Fludeoxyglucose positron emission tomography (FDG-PET) is a promising imaging modality for diagnosing NPH and detecting concomitant degenerative disease.

SUMMARY:

A systematic approach to patients with possible NPH allows recognition of the subset of patients whowill respond to shunt surgery and identification of those with alternative diagnoses.

KEY POINTS

- Hydrocephalus can occur as fluid accumulation both inside and outside the ventricles.
- Factors associated with so-called idiopathic normal pressure hydrocephalus include impaired CSF absorption, vascular disease, and congenital hydrocephalus. All these factors may alter CSF dynamics in a way that can lead to increased CSF content in the cranial vault while maintaining a relatively normal average CSF pressure.
- Normal pressure hydrocephalus is an uncommon disease, but large ventricles are commonly seen in persons older than 70 years of age.
- No pathognomonic individual or combination of clinical features exists for normal pressure hydrocephalus. Comorbid diseases are common and should be evaluated.
- The triad of gait abnormality, incontinence, and cognitive impairment seen in normal pressure hydrocephalus may possibly be related to periventricular frontal cortical–basal ganglia–thalamocortical circuitry. Most often, patients with normal pressure hydrocephalus do not have the full triad of symptoms, and gait abnormality usually presents first.
- Cognitive features of normal pressure hydrocephalus include psychomotor slowing, decreased attention and concentration, impaired executive functions, and apathy. Anomia suggests the presence of a cortical dementia and is a poor prognostic factor when deciding about shunt placement.
- The differential diagnosis of gait abnormalities in the elderly is broad and should be reviewed in detail when evaluating patients for normal pressure hydrocephalus.
- A focused history and examination should be performed looking for diseases that can co-occur or mimic the symptoms of normal pressure hydrocephalus and looking for factors that may influence management.
- In the assessment of patients for NPH, establish that there is ventriculomegaly; look for congenital factors such as aqueductal stenosis or webbing; and recognize the features of disproportionately enlarged subarachnoid space hydrocephalus (DESH), not mistaking DESH for atrophy.
- The two best diagnostic tests for normal pressure hydrocephalus are evaluating the MRI for the characteristic features, and performance of a high-volume lumbar puncture, measuring gait features objectively before and within 30 minutes after the lumbar puncture.
- Overlapping chronic diseases are common in persons being considered for shunt surgery because their average age is about 74 years. At this age, 30% of cognitively normal persons have Alzheimer disease pathology. Fludeoxyglucose positron emission tomography may help reveal a concomitant degenerative disease.
- In idiopathic normal pressure hydrocephalus, most metabolic proteins are low in the CSF, so Alzheimer biomarkers (eg, amyloid-β_{1-42} and phosphorylated tau) are also low and are not helpful in distinguishing Alzheimer disease from idiopathic normal pressure hydrocephalus.
- Surgical complications following shunt surgery are common but have decreased over the decades. Adjustable shunts allow treatment of overdrainage without surgical intervention.
- Objective measurements to assess patient change with shunt placement are very helpful in management.

- Surgical outcome is improving, and patients who are seen in follow-up 3 years after shunt surgery have a good chance of remaining improved.

Article 9: Chronic Traumatic Encephalopathy

Katherine W. Turk, MD; Andrew E. Budson, MD. Continuum (Minneap Minn). February 2019; 25 (1 Dementia):187–207.

ABSTRACT

PURPOSE OF REVIEW:

This article provides a discussion on the current state of knowledge of chronic traumatic encephalopathy (CTE), with an emphasis on clinical features and emerging biomarkers of the condition.

RECENT FINDINGS:

The results of several large brain bank case series among subjects with a history of contact sports or repetitive head trauma have indicated that a high frequency of CTE may exist in this population. However, the true prevalence of CTE among individuals with a history of head trauma remains unknown, given that individuals who experienced cognitive, behavioral, and mood symptoms during life are more likely to have their brains donated for autopsy at death and epidemiologic studies of the condition are lacking. Neuropathologic consensus criteria have been published. Research-based clinical criteria have been proposed and are beginning to be applied, but the definitive diagnosis of CTE in a living patient remains impossible without effective biomarkers for the condition, which is an active area of study.

SUMMARY:

The field of CTE research is rapidly growing and parallels many of the advances seen for other neurodegenerative conditions, such as Alzheimer disease decades ago.

KEY POINTS

- Chronic traumatic encephalopathy is a pathologically defined neurodegenerative disorder associated with repetitive concussive or subconcussive head injury.
- The frequency, severity, and total exposure to head trauma and the exact pathophysiologic mechanism by which blows to the head result in chronic traumatic encephalopathy are active areas of research.
- Head injury is an important but nonsufficient risk factor in the development of chronic traumatic encephalopathy; other exposure and genetic risk factors are under investigation.
- Currently, no validated clinical diagnostic criteria for chronic traumatic encephalopathy exist, although research diagnostic criteria have been developed.
- Concussion is a clinical syndrome of impaired brain function, typically impacting memory and orientation, with or without loss of consciousness that results from head injury.
- Chronic traumatic encephalopathy is defined by neuropathology: perivascular aggregation of phosphorylated tau protein within neurons and astrocytes that begins in the depths of sulci and progresses to involve the medial temporal lobes and other parts of the brain.
- Chronic traumatic encephalopathy deficits involve progressive cognitive, behavior, and mood changes as well as possible motor deficits.
- The most common cognitive difficulties in patients with chronic traumatic encephalopathy involve memory and executive function.

- Four traumatic encephalopathy syndrome subtypes have been described: (1) a behavioral/mood variant, occurring in younger patients; (2) a cognitive variant, which occurs later in life; (3) a mixed variant; and (4) a dementia form.
- The classification of patients into the diagnostic categories probable, possible, and unlikely chronic traumatic encephalopathy relies, in part, on results of potential research-based biomarker findings, thus diagnoses are for use in research, not clinical settings.
- The evaluation for possible chronic traumatic encephalopathy should include asking about a history of repetitive head trauma, with or without concussion, including exposures during contact sports, military service, domestic abuse, assault, and motor vehicle accidents.
- The differential diagnosis for chronic traumatic encephalopathy often includes frontotemporal dementia and Alzheimer disease.
- No disease-modifying or symptomatic treatments for chronic traumatic encephalopathy are US Food and Drug Administration approved. All medication management is off-label and symptom-based, and can include acetylcholinesterase inhibitors, selective serotonin reuptake inhibitors, and memantine.
- The incidence and prevalence of chronic traumatic encephalopathy is unknown because of a lack of epidemiologic data. However, the frequency of chronic traumatic encephalopathy is potentially increased within the professional contact sports community and others exposed to head trauma.
- The age of clinical onset of traumatic encephalopathy syndrome/chronic traumatic encephalopathy symptoms is delayed by several years or decades following exposure to head injuries and is currently estimated to be between 30 and 65 years of age.
- Posttraumatic stress disorder and traumatic brain injury often co-occur in military veterans and may share a common pathophysiology.
- Posttraumatic stress disorder, postconcussive disorder, and chronic traumatic encephalopathy share many common symptoms, including difficulty with concentration, changes in mood, memory problems, irritability, and sleep disturbances.
- Chronic traumatic encephalopathy frequently involves TDP-43 pathology, but TDP-43 is not necessary for pathologic confirmation.
- Chronic traumatic encephalopathy can co-occur pathologically with other neurodegenerative conditions, including motor neuron disease, Alzheimer disease, Lewy body disease, and frontotemporal dementia.
- The main genetic risk factor investigated in association with head injury and chronic traumatic encephalopathy is the *APOE* ε4 allele.
- The *APOE* ε4 allele may lower the threshold for an individual to develop cognitive deficits following repeated head injury.
- Nongenetic potential risk factors for chronic traumatic encephalopathy include cognitive reserve, age of first exposure, and cumulative exposure to head injuries.
- Serum tau concentration elevations may indicate the existence of prior head injury but have not been found to correlate with cognitive function.

Article 10: Hippocampal Sclerosis, Argyrophilic Grain Disease, and Primary Age-Related Tauopathy

Gregory A. Jicha, MD, PhD; Peter T. Nelson, MD, PhD. Continuum (Minneap Minn). February 2019; 25 (1 Dementia):208–233.

ABSTRACT

PURPOSE OF REVIEW:

Hippocampal sclerosis, argyrophilic grain disease, and primary age-related tauopathy are common Alzheimer disease mimics that currently lack clinical diagnostic criteria. Increased understanding of these pathologic entities is important for the neurologist who may encounter patients with an unusually slowly progressive degenerative dementia that may appear to meet criteria for Alzheimer disease but who progress to develop symptoms that are unusual for classic Alzheimer disease

RECENT FINDINGS:

Hippocampal sclerosis has traditionally been associated with hypoxic/ischemic injury and poorly controlled epilepsy, but it is now recognized that hippocampal sclerosis may also be associated with a unique degenerative disease of aging or may be an associated pathologic finding in many cases of frontotemporal lobar degeneration. Argyrophilic grain disease has been recognized as an enigma in the field of pathology for over 30 years, but recent discoveries suggest that it may overlap with other tau-related disorders within the spectrum of frontotemporal lobar degeneration. Primary age-related tauopathy has long been recognized as a distinct clinical entity that lies on the Alzheimer pathologic spectrum, with the presence of neurofibrillary tangles that lack the coexistent Alzheimer plaque development; thus, it is thought to represent a distinct pathologic entity.

SUMMARY:

Despite advances in dementia diagnosis that suggest that we have identified and unlocked the mysteries of the major degenerative disease states responsible for cognitive decline and dementia in the elderly, diseases such as hippocampal sclerosis, argyrophilic grain disease, and primary age-related tauopathy demonstrate that we remain on the frontier of discovery and that our diagnostic repertoire of diseases responsible for such clinical symptoms remains in its infancy. Understanding such diagnostic confounds is important for the neurologist in assigning appropriate diagnoses and selecting appropriate therapeutic management strategies for patients with mild cognitive impairment and dementia.

KEY POINTS

- Several clinically uncharacterized neuropathologic disease states are found at high frequency in the elderly population and may contribute to the observed inaccuracy of clinical diagnostic criteria in clinicopathologic correlation studies in dementia.
- Recent and ongoing work over the past several decades has brought to light the importance and high prevalence of diseases such as hippocampal sclerosis, argyrophilic grain disease, and primary age-related tauopathy as common mimics of Alzheimer disease and other dementing disorders, largely because their own clinical phenotype has been poorly elucidated to date.
- The prevalence of diseases such as hippocampal sclerosis, argyrophilic grain disease, and primary age-related tauopathy can be as high as 20% of normal controls and higher than 50% in individuals with clinical dementia.
- It is now recognized that hippocampal sclerosis occurs not only in "pure" or isolated forms but is frequently found to be a comorbid process, coexisting with other neurodegenerative pathologies such as Alzheimer disease, dementia with Lewy bodies, progressive supranuclear palsy, and amyotrophic lateral sclerosis.
- The presence of hippocampal sclerosis should always be suspected in patients diagnosed with frontotemporal dementia who demonstrate appreciable anterograde amnestic signs and symptoms, irrespective of other associated clinical features or diagnoses.
- The extent of TDP-43 pathology seen in hippocampal sclerosis of aging can frequently extend well beyond the medial temporal lobe to include neighboring regions of the frontal and temporal cortices as well as subcortical regions, demonstrating that hippocampal sclerosis of aging is not confined to the medial temporal lobe structures but instead can be associated with more widespread pathology.

- The "coiled bodies," "ballooned" neurons, and "tufted" or "thorny" astrocytes seen in argyrophilic grain disease all involve accumulation of phosphorylated tau protein, suggesting its central role in the pathogenesis of the disease. At the time of their original description, it was understood that they were associated with an increased frequency of clinical dementia, but their presence is not an absolute determinant of clinical dementia.
- Biochemical differences stemming from discoveries in postmortem brain tissue have not yet been translated into antemortem serum or CSF biomarkers for argyrophilic grain disease. At present, argyrophilic grain disease remains a diagnosis that can only be made and confirmed at autopsy.
- In brains with primary age-related tauopathy pathology, neuritic amyloid plaques are not detected, but tau neurofibrillary tangles are observed.
- By definition, the neurofibrillary tangles of primary age-related tauopathy are not associated with underlying frontotemporal lobar degeneration or chronic traumatic encephalopathy, differentiating this entity from other degenerative disease states characterized by predominant tau-related pathology.
- Despite the near-identical molecular and structural nature and anatomic distribution of neurofibrillary tangles between primary age-related tauopathy and early Alzheimer disease, the neuroanatomic extent of neurofibrillary tangle pathology in primary age-related tauopathy appears largely restricted to the temporal lobes, unlike in Alzheimer disease, in which the distribution of neurofibrillary tangles can be more widespread cortically.
- In large autopsy series, the distribution of primary age-related tauopathy pathology has been shown to be associated with antemortem cognitive impairment, and primary age-related tauopathy is also implicated in subjective memory symptoms and mild cognitive impairment.
- Prospective testing of multimodal use of antemortem biomarkers remains to be confirmed but holds much promise for the antemortem detection of pathologic diseases such as primary age-related tauopathy.
- Hippocampal sclerosis of aging, argyrophilic grain disease, and primary age-related tauopathy all have a predilection for medial temporal lobe and hippocampal involvement, present in a common phenotype as an early amnestic syndrome, and can be associated with medial temporal lobe atrophy. These clinical characteristics make them indistinguishable from Alzheimer disease using routine clinical diagnostic tests and MRI.
- Hippocampal sclerosis of aging and argyrophilic grain disease (but not primary age-related tauopathy) have strong associations with the genetic, biochemical, neuroanatomic, and clinical presentations of frontotemporal lobar degeneration syndromes. These data suggest that frontotemporal lobar degeneration–associated features are common in the aging population.
- Data acquired over the past decade have advanced our understanding of hippocampal sclerosis of aging, argyrophilic grain disease, and primary age-related tauopathy and may begin to allow the development of clinical trials for both symptomatic therapeutics and disease-modifying agents.

Article 11: Reversible Dementias

Gregory S. Day, MD, MSc. Continuum (Minneap Minn). February 2019; 25 (1 Dementia): 234–253.

ABSTRACT

PURPOSE OF REVIEW:

This article describes the clinical features that suggest a reversible cause of dementia.

RECENT FINDINGS:

Substantial variability exists in the presenting features and clinical course of patients with common neurodegenerative causes of dementia, but the response to available therapies and

eventual outcomes are often poor. This realization has influenced the evaluation of patients with dementia, with diagnostic approaches emphasizing routine screening for a short list of potentially modifiable disorders that may exacerbate dementia symptoms or severity but rarely influence long-term outcomes. Although a standard approach to the assessment of dementia is appropriate in the vast majority of cases, neurologists involved in the assessment of patients with dementia must recognize those rare patients with reversible causes of dementia, coordinate additional investigations when required, and ensure expedited access to treatments that may reverse decline and optimize long-term outcomes.

SUMMARY:

The potential to improve the outcome of patients with reversible dementias exemplifies the need to recognize these patients in clinical practice. Dedicated efforts to screen for symptoms and signs associated with reversible causes of dementia may improve management and outcomes of these rare patients when encountered in busy clinical practices.

KEY POINTS

- Neurologists involved in the diagnosis and management of patients with dementia should recognize the symptoms and signs that suggest a reversible cause of dementia.
- Truly reversible causes of dementia account for a small proportion of cases in outpatient clinics.
- Patients with rapidly progressive dementia warrant an expedited assessment, with the goal of rapidly identifying and remedying reversible causes of and contributors to dementia.
- Younger than expected age at symptomatic onset is a well-recognized marker of secondary causes of dementia, warranting careful evaluation and screening for reversible causes.
- Autoantibody testing should be considered in all patients meeting criteria for possible autoimmune encephalitis and in patients 60 years of age or older with characteristic central nervous system syndromes, even if neuroimaging and CSF findings do not suggest an underlying autoimmune disease.
- Toxic-metabolic disturbances, medications, untreated sleep disorders (including obstructive sleep apnea), and psychiatric illnesses may all present with prominent fluctuations in cognition.
- Transient epileptic amnesia is associated with acute and transient memory disruptions lasting minutes (typically less than an hour) that are often accompanied by fluctuations in attention.
- Anticholinergic medications may be especially problematic in patients with Alzheimer disease–associated degeneration of acetylcholine-producing basal forebrain cells.
- If promptly recognized, the life-threatening effects of thiamine deficiency may be counteracted by administration of high doses of parenteral thiamine.
- The high potential for response to appropriate treatment, high cost of delayed diagnosis, and low risk of complications associated with parenteral thiamine supplementation justify expedited treatment in all patients with possible nutritional deficiency and features consistent with Wernicke encephalopathy.
- Syphilis testing should be considered in patients with dementia from endemic regions within and beyond the United States and in those with a past or present history of high-risk behaviors.
- A thorough history, including screening for past or present high-risk behaviors, is imperative when investigating patients with unusual presentations of cognitive impairment.
- The discovery of abnormal neurologic findings—whether subtle or pronounced—warrants consideration of atypical causes of dementia, including reversible causes.
- Detection of features of the triad of progressive memory loss, gait apraxia, and urinary incontinence warrants screening for causes of normal pressure hydrocephalus and high-pressure hydrocephalus.
- Performance on cognitive testing that is substantially better or worse than expected from the clinical history should trigger investigations for reversible causes of dementia.
- Sleep dysfunction, attributable to obstructive sleep apnea or other causes, is increasingly identified as a contributor to cognitive impairment.

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EPILEPSY

ARTICLE 1: EVALUATION OF FIRST SEIZURE AND NEWLY DIAGNOSED EPILEPSY

Elaine Wirrell, MD, FRCP(C), FAAN. Continuum (Minneap Minn). April 2022; 28 (2 Epilepsy):230–260.

ABSTRACT

PURPOSE OF REVIEW:

This article focuses on the evaluation of children and adults who present with new-onset seizures, with an emphasis on differential diagnosis, classification, evaluation, and management.

RECENT FINDINGS:

New-onset seizures are a common presentation in neurologic practice, affecting approximately 8% to 10% of the population. Accurate diagnosis relies on a careful history to exclude nonepileptic paroxysmal events. A new classification system was accepted in 2017 by the International League Against Epilepsy, which evaluates seizure type(s), epilepsy type, epilepsy syndrome, etiology, and comorbidities. Accurate classification informs the choice of investigations, treatment, and prognosis. Guidelines for neuroimaging and laboratory and genetic testing are summarized.

SUMMARY:

Accurate diagnosis and classification of first seizures and new-onset epilepsy are key to choosing optimal therapy to maximize seizure control and minimize comorbidities.

KEY POINTS

- Epilepsy is defined as any of the following: (1) at least two unprovoked (or reflex) seizures occurring more than 24 hours apart, (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years, or (3) diagnosis of an epilepsy syndrome.
- A careful history taken from both the patient as well as any witnesses to the event(s) is the most critical aspect in distinguishing a seizure from a nonepileptic paroxysmal event.
- It is the first convulsive seizure that typically brings the patient to medical attention. Many people presenting with a "first seizure" have a history of prior seizures, which may not have been recognized, and thus have epilepsy.

- A diagnosis of an epilepsy syndrome is possible in approximately one-quarter of epilepsy cases beginning in infancy and childhood but is less frequently found in adults. Diagnosis of a specific syndrome provides key information to assist with choosing optimal investigations and treatment and for providing accurate prognosis.
- Genetic causes of epilepsy are increasingly recognized. In some cases, such as the idiopathic generalized epilepsies, inheritance is polygenic, and pathogenic variants are typically not found on gene panels. In other cases, particularly in early-onset developmental epileptic encephalopathies, inheritance is monogenic, and pathogenic variants are identified on epilepsy gene panels or whole-exome sequencing.
- Increasingly, specific antibodies are being detected in people with autoimmune encephalitis that result in acute symptomatic seizures. These should be distinguished from immune-mediated epilepsies in which an enduring predisposition to seizures is present.
- Despite advances in neuroimaging and genetics, approximately 40% of people with new-onset epilepsy have no known etiology found.
- Cognitive and psychiatric comorbidities are common in people with epilepsy and often predate seizure onset. The causes are multifactorial, but they are critical to diagnose and treat as they often have an even greater impact than seizures on quality of life.
- An EEG is indicated in all patients with new-onset, unprovoked seizures. Care must be taken to avoid misinterpreting normal variants as epileptogenic. The EEG assists with determination of seizure and epilepsy type, choice of further investigations, and prognosis regarding the risk for seizure recurrence.
- Neuroimaging is recommended for all patients with new-onset, unprovoked seizures, except those with a well-defined, drug-responsive idiopathic generalized epilepsy or self-limited focal epilepsy of childhood. In patients who have returned to their neurologic baseline and for whom there are no concerns for an acute neurologic process, urgent CT is not needed. Rather, MRI can be obtained on an outpatient basis.
- Routine blood and urine studies are commonly obtained but of low yield in patients with new-onset, unprovoked seizures.
- A lumbar puncture should be considered if the clinical picture is suggestive of possible meningitis, encephalitis, or subarachnoid hemorrhage but is otherwise is of low yield.
- All patients with new-onset, unprovoked seizures must be counseled about lifestyle issues, seizure safety, and what to do if further seizures occur. Water safety is of utmost importance. Showers are safe; however, bathing or swimming alone is not recommended.
- Although immediate initiation of antiseizure medication after a first unprovoked seizure does reduce the risk of recurrence, it does not impact long-term epilepsy outcome or quality of life.

ARTICLE 2: EEG ESSENTIALS

William O. Tatum IV, DO, FAAN, FACNS, FAES. Continuum (Minneap Minn). April 2022; 28 (2 Epilepsy):261–305.

ABSTRACT

PURPOSE OF REVIEW:

EEG is the best study for evaluating the electrophysiologic function of the brain. The relevance of EEG is based on an accurate interpretation of the recording. Understanding the neuroscientific basis for EEG is essential. The basis for recording and interpreting EEG is both brain site–specific and technique-dependent to detect and represent a complex series of waveforms. Separating normal from abnormal EEG lies at the foundation of essential interpretative skills.

RECENT FINDINGS:

Seizures and epilepsy are the primary targets for clinical use of EEG in diagnosis, seizure classification, and management. Interictal epileptiform discharges on EEG support a clinical

diagnosis of seizures, but only when an electrographic seizure is recorded is the diagnosis confirmed. New variations of normal waveforms, benign variants, and artifacts can mimic epileptiform patterns and are potential pitfalls for misinterpretation for inexperienced interpreters. A plethora of medical conditions involve nonepileptiform and epileptiform abnormalities on EEG along the continuum of people who appear healthy to those who are critically ill. Emerging trends in long-term EEG monitoring to diagnose, classify, quantify, and characterize patients with seizures have unveiled epilepsy syndromes in patients and expanded medical and surgical options for treatment. Advances in terminology and application of continuous EEG help unify neurologists in the diagnosis of nonconvulsive seizures and status epilepticus in patients with encephalopathy and prognosticate recovery from serious neurologic injury involving the brain.

SUMMARY:

After 100 years, EEG has retained a key role in the neurologist's toolkit as a safe, widely available, versatile, portable test of neurophysiology, and it is likely to remain at the forefront for patients with neurologic diseases. Interpreting EEG is based on qualitative review, and therefore, the accuracy of reporting is based on the interpreter's training, experience, and exposure to many new and older waveforms.

KEY POINTS

- Since the first description in the 1920s, EEG has remained the most relevant testing modality to evaluate people with seizures.
- Signals detected and ultimately recorded by EEG are generated by dynamic extracellular currents produced by transmembrane ion flow.
- Most standard EEGs are obtained using standard scalp electrodes and acquired in the interictal period when patients are asymptomatic.
- A normal EEG is a common result when patients obtain a standard study. However, a normal result does not exclude the possibility that a patient has epilepsy, and EEG should not be used to make an epilepsy diagnosis independent of the clinical context of recording.
- Benign variants of uncertain significance, normal waveform variations, and artifacts may be pitfalls to overinterpreting a normal record as abnormal leading to inappropriate treatment with antiseizure medication.
- Standard EEG is the diagnostic test of choice to provide electrophysiologic information about the presence of neurophysiologic dysfunction.
- An EEG that contains spikes and sharp waves supports a clinical diagnosis of epilepsy.
- When EEG records an electrographic seizure in patients with a history of recurrent unprovoked seizures, this is diagnostic of epilepsy.
- People who experience a first seizure are at risk for recurrence when EEG demonstrates abnormal interictal epileptiform discharges.
- When history and other imaging modalities are considered in addition to an ictal EEG, epilepsy syndromes can usually be defined for the purpose of providing optimal treatment.
- Selection of antiseizure medication may be guided by EEG when the historical recount for an observed manifestation is unable to classify the seizures or an epilepsy syndrome.
- A significant minority of people are self-unaware of experiencing seizures despite impaired consciousness and overt signs that are visible to other individuals.
- Video-EEG classifies focal and diffuse cerebral dysfunction and can support an epilepsy syndromic diagnosis that aids in medical and surgical management.
- EEG is the only test in critically ill patients with altered mental status that can result in the diagnosis of nonconvulsive seizures and nonconvulsive status epilepticus.
- The goals of therapy for ongoing nonconvulsive seizures and nonconvulsive status epilepticus aim at achieving seizure suppression on continuous EEG and reducing cerebral metabolic rates by achieving a burst-suppression pattern.

ARTICLE 3: NEUROIMAGING OF EPILEPSY

Samuel Lapalme-Remis, MDCM, MA, FRCPC; Dang K. Nguyen, MD, PhD, FRCPC.
Continuum (Minneap Minn). April 2022; 28 (2 Epilepsy):306–338.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of imaging modalities, important imaging pathologies, and the role each imaging modality can play in the diagnosis, evaluation, and treatment of epilepsy, including epilepsy surgery.

RECENT FINDINGS:

The Harmonized Neuroimaging of Epilepsy Structural Sequences (HARNESS-MRI) protocol was proposed to standardize MRI imaging for all patients with seizures. The role of 7-Tesla MRI in finding previously occult epileptogenic lesions is under investigation, and the technique is increasingly used. Developing MRI postprocessing techniques can increase the sensitivity of MRI. Improvements in functional imaging techniques such as EEG–functional MRI (fMRI) and magnetic source imaging provide complementary methods of identifying seizure foci. New epileptogenic pathologies such as multinodular and vacuolating neuronal tumors (MVNT) are being discovered, and the importance of others, such as encephaloceles, is better appreciated.

SUMMARY:

Brain imaging is a critical component of the diagnosis and evaluation of patients with epilepsy. Structural imaging modalities such as MRI and CT allow for the identification of a wide variety of potentially epileptogenic lesions. For patients with drug-resistant epilepsy under consideration for resective surgery, both structural and functional neuroimaging may be needed for focus identification and surgical planning for preservation of neurologic function.

KEY POINTS

- The finding of an epileptogenic lesion on brain imaging in a patient with a single seizure may lead to the diagnosis of epilepsy if the treating neurologist estimates a risk of seizure recurrence greater than 60%.
- In adults with an unprovoked first seizure, significant brain imaging abnormalities are associated with an increased risk of seizure recurrence within 2 years.
- Brain imaging assists neurologists in estimating whether a paroxysmal event was likely a seizure, determining whether a patient has epilepsy, classifying the epilepsy type, selecting treatments, predicting the prognosis, and completing a presurgical workup.
- A first seizure associated with a cavernous malformation is strongly associated with recurrent seizures, with a 5-year risk of 94%. Only about half of patients achieve seizure freedom with antiseizure medications alone.
- In the acute setting, a CT scan of the head is often necessary to ensure that the seizure was not caused by a threatening intracranial pathology.
- The International League Against Epilepsy Neuroimaging Task Force recommends that MRI be performed for all patients presenting with a first seizure or newly diagnosed epilepsy where resources allow.
- The Harmonized Neuroimaging of Epilepsy Structural Sequences (HARNESS-MRI) protocol is recommended for all patients with seizures. It consists of three mandatory sequences and two optional sequences, optimized for 3-Tesla (T) scanners but compatible with 1.5T scanners.
- CT remains useful in the evaluation of potentially epileptogenic calcifications, vascular abnormalities, and encephaloceles.

- Malformations of cortical development are a heterogeneous group of mostly congenital and potentially epileptogenic brain lesions arising from disrupted cerebral cortex development that can be caused by genetic, infectious, vascular, or other etiologies.
- Focal cortical dysplasia is a common cause of drug-resistant focal epilepsy that may escape detection on routine MRI.
- The transmantle sign denotes a long region of T2/fluid-attenuated inversion recovery (FLAIR) hyperintense signal tapering between the affected region of cortex and the ventricular wall, usually associated with focal cortical dysplasia type IIb.
- Because focal cortical dysplasia can be masked by the maturation of myelination in childhood, it is essential to obtain high-quality MRI early in the course of epilepsy.
- Periventricular nodular heterotopias are solid masses of neurons that line lateral ventricle walls after aborted migration of neurons destined for the cortex. Seizures can emerge from one or more nodules, areas of the overlying cortex, or a complex network.
- Periventricular nodular heterotopias are conspicuous on MRI or CT as solid masses isointense/isodense to gray matter; their location in a region where pathologic lesions rarely occur makes them easy to miss.
- Cerebral cavernous malformations may have a classic "popcorn" appearance on MRI. T2* sequences such as gradient recalled echo (GRE) or susceptibility-weighted imaging (SWI) show areas of hypointensity and the epileptogenic hemosiderin rim that surrounds the structure.
- Low-grade gliomas are infiltrating tumors causing focal seizures. They are treated with surgery, radiation therapy, and chemotherapy. Their continued growth may lead to a more drug-resistant epilepsy.
- Dysembryoplastic neuroepithelial tumors (DNETs) are among the most common tumors causing focal epilepsy. MRI displays a classic "bubbly" appearance, with multiple lobulated regions of hyperintensity on T2-weighted sequences.
- Multinodular and vacuolating neuronal tumors (MVNTs) are recently described epileptogenic lesions with an MRI appearance of multiple discrete ovoid intra-axial nodules found at the junction of superficial subcortical white matter and a deep cortical ribbon, often surrounding a sulcus.
- Mesial temporal sclerosis is a surgically treatable form of drug-resistant epilepsy that can be diagnosed in the clinic.
- On MRI, mesial temporal sclerosis is characterized by hippocampal atrophy, T2/FLAIR hyperintensity, and loss of internal architecture. Supportive imaging findings include temporal lobe atrophy or asymmetry of the fornix and mammillary bodies.
- An encephalocele is a region of brain herniation through a defect of bone and dura mater. Anterior temporal encephaloceles are a surgically treatable cause of temporal lobe epilepsy, often missed during image interpretation.
- Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy is an inflammatory cause of meningoencephalitis with seizures. It has a typical imaging pattern of diffuse perivascular enhancement radiating out from the lateral ventricles on contrast-enhanced MRI.
- CT imaging may be necessary as a complement to MRI images for the imaging diagnosis of neurocysticercosis.
- In the course of a presurgical evaluation for drug-resistant epilepsy, imaging results are essential for seizure focus identification and surgical planning for the preservation of neurologic function.
- In the presurgical evaluation of a patient with focal epilepsy, the presence or absence of an epileptogenic lesion on structural imaging has a major impact on surgical planning and seizure-free outcomes.
- MRI postprocessing techniques such as volumetry of mesiotemporal lobe structures, hippocampal T2 relaxometry, and automated texture analysis may be helpful in identifying lesions that were not detectable on simple visual inspection.
- Functional imaging evaluates physiologic characteristics of epileptogenic brain regions to identify regions of abnormal function, helping to lateralize or localize the seizure focus.
- Fludeoxyglucose positron emission tomography (FDG-PET) imaging identifies regions of interictal glucose hypometabolism. In temporal lobe epilepsy, unilateral temporal hypometabolism is correlated with the side of seizure focus. FDG-PET is less sensitive in extratemporal epilepsy.

- Single-photon emission computed tomography (SPECT) uses a radiotracer to detect increased blood flow during the ictal period to identify the seizure focus. The tracer must be injected immediately on seizure onset, creating logistic challenges.
- Functional MRI (fMRI) and diffusion tensor imaging (DTI) are imaging modalities that can help identify the location of critical brain tissue and assist with the safe resection of the seizure focus.

ARTICLE 4: GENETIC EPILEPSY SYNDROMES

Kenneth A. Myers, MD, PhD, FRCPC, CSCN(EEG). Continuum (Minneap Minn). April 2022; 28 (2 Epilepsy):339–362.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the clinical features, typical EEG findings, treatment, prognosis, and underlying molecular etiologies of the more common genetic epilepsy syndromes. Genetic generalized epilepsy, self-limited focal epilepsy of childhood, self-limited neonatal and infantile epilepsy, select developmental and epileptic encephalopathies, progressive myoclonus epilepsies, sleep-related hypermotor epilepsy, photosensitive occipital lobe epilepsy, and focal epilepsy with auditory features are discussed. Also reviewed are two familial epilepsy syndromes: genetic epilepsy with febrile seizures plus and familial focal epilepsy with variable foci.

RECENT FINDINGS:

Recent years have seen considerable advances in our understanding of the genetic factors underlying genetic epilepsy syndromes. New therapies are emerging for some of these conditions; in some cases, these precision medicine approaches may dramatically improve the prognosis.

SUMMARY:

Many recognizable genetic epilepsy syndromes exist, the identification of which is a crucial skill for neurologists, particularly those who work with children. Proper diagnosis of the electroclinical syndrome allows for appropriate treatment choices and counseling regarding prognosis and possible comorbidities.

KEY POINTS

- Genetic epilepsy syndromes may follow Mendelian patterns or may exhibit complex inheritance, likely related to both polygenic and epigenetic factors.
- Overall, the genetic generalized epilepsy syndromes are characterized by normal background activity and interictal generalized epileptiform discharges on EEG; brain imaging is also almost always normal. Genetic testing is usually negative, as the vast majority of cases are thought to occur through complex inheritance.
- In childhood absence epilepsy, the defining seizure type is a typical absence seizure, involving a sudden, brief loss of awareness (usually 4 to 30 seconds) followed by an almost immediate return to baseline (ie, no significant postictal state). Patients typically stare blankly and may have subtle automatisms, most commonly oral.
- Typical absence seizures can often be provoked by hyperventilation; asking the patient to hyperventilate for at least 3 minutes provides a useful method to evaluate seizure control in the clinic. During seizures, EEG shows an abrupt onset of generalized rhythmic spike-wave discharges at approximately 3 Hz.

- Children with absence seizures starting before the age of 4 years are considered to have early-onset absence epilepsy; 10% of these patients have glucose transporter type 1 (GLUT1) deficiency due to pathogenic *SLC2A1* variants.
- Age of onset of juvenile myoclonic epilepsy is typically between 12 and 18 years. The prototypic seizure type is myoclonic jerks that are most prominent in the mornings, although patients may also experience generalized tonic-clonic or absence seizures. Seizures are often provoked by sleep deprivation, flashing lights, or alcohol intake.
- Interictal EEG of JME typically shows normal background activity with generalized 4- to 6-Hz spike-wave and polyspike-wave fragments.
- Although the majority of patients with JME have seizures controlled with medication, the rate of long-term epilepsy remission is very low.
- Sodium channel inhibitors should be avoided in patients with juvenile myoclonic epilepsy, if possible, as there is the potential to exacerbate myoclonic seizures.
- Juvenile absence epilepsy bears many similarities to JME, with one of the main differentiating factors being the lack of myoclonic seizures.
- The ictal EEG of juvenile absence epilepsy during absences shows a faster rhythmic spike-wave signature of 4 to 5 Hz.
- Roughly 50% to 80% of patients with juvenile absence epilepsy will also experience generalized tonic-clonic seizures.
- The seizure control prognosis is poor in juvenile absence epilepsy, with less than half of patients seizure free on medications after 2 years and nearly all having seizure recurrence if medication weaning is attempted.
- Epilepsy with generalized tonic-clonic seizures alone is a genetic generalized epilepsy in which generalized tonic-clonic seizures are the only seizure type.
- Epilepsy with eyelid myoclonias is a childhood-onset genetic generalized epilepsy classically involving a triad of (1) characteristic brief eye-fluttering seizures (eyelid myoclonia), (2) eye closure–induced seizures/epileptiform abnormalities on EEG, and (3) photosensitivity.
- Children with childhood epilepsy with centrotemporal spikes first present with seizures typically between 7 and 10 years of age (range, 1 to 14 years), often from sleep. The seizure symptomatology is focal aware or focal impaired awareness, involving prominent hemifacial jerking or dystonia, facial paresthesia, drooling, and mumbling, and occasionally progressing to bilateral tonic-clonic convulsions. EEG shows focal monomorphic medium-high amplitude spikes and spike-wave discharges over one or both centrotemporal regions, having a characteristic morphology and horizontal dipole.
- Decisions on whether to initiate antiseizure medication in childhood epilepsy with centrotemporal spikes should be made on a child-by-child basis, taking into consideration frequency and duration of seizures, if seizures have progressed to bilateral tonic-clonic, as well as parent/caregiver concerns.
- In Panayiotopoulos syndrome, seizure onset is usually between 3 and 6 years of age (range, 1 to 14 years). Seizures may be focal aware or focal impaired awareness, usually occurring from sleep, with the most notable feature being prominent autonomic symptoms. Vomiting, pallor, flushing, mydriasis/miosis, and temperature changes are among the autonomic signs that may be seen. Lateral head and eye deviation may occur late in seizures, and progression to bilateral tonic-clonic seizures is possible.
- Status epilepticus is common in Panayiotopoulos syndrome, with nearly half of patients having seizures lasting longer than 30 minutes.
- Interictal EEG in patients with Panayiotopoulos syndrome shows focal spikes and spike-wave discharges, which are often abundant, over one or both occipital regions.
- Patients with Gastaut syndrome have focal aware seizures, although awareness may become impaired late in events. The symptomatology mostly involves visual hallucinations usually lasting 1 to 3 minutes. These are most typically elementary visual phenomena such as multicolored circles, but about 10% of patients can have complex hallucinations, such as faces or figures. Ictal blindness lasting several minutes is also commonly reported.

- EEG in patients with Gastaut syndrome shows focal occipital spikes and spike-wave discharges as in Panayiotopoulos syndrome, and fixation-off sensitivity (the appearance of epileptiform abnormalities with removal of visual fixation, often by eye closure) often occurs.
- Children with Gastaut syndrome may be misdiagnosed with migraines or psychiatric disorders as they present with visual hallucinations, sometimes with associated headache.
- In self-limited familial neonatal epilepsy, seizures begin in the neonatal period, usually on the second or third day of life. Seizures may involve any or all of tonic posturing, apnea, vocalization, eye deviation, change in skin color, and unilateral or bilateral clonic movements. Duration is typically brief, usually less than 30 seconds.
- Affected children with self-limited neonatal epilepsy have spontaneous resolution of seizures, occurring by 6 weeks in two-thirds of cases and by 6 months in 94% of cases.
- Self-limited infantile epilepsy is usually defined as seizures occurring in otherwise healthy and typically developing children, usually between the ages of 3 and 20 months.
- Patients with self-limited infantile epilepsy have focal impaired awareness seizure, often with hemiclonic movements, head and eye deviation, or facial/limb automatisms. Seizures usually occur in clusters of up to 8 to 10 per day over 1 to 3 days.
- Dravet syndrome first presents around 6 months of age, usually with febrile seizures that are often hemiclonic and prolonged. Patients subsequently develop afebrile seizure types that most commonly include any or all of generalized tonic-clonic, focal impaired awareness, atypical absences, and myoclonic seizures.
- Early mortality risk is high in Dravet syndrome, with death most commonly occurring due to sudden unexpected death in epilepsy (SUDEP), drowning, or massive cerebral edema following prolonged seizures.
- Myoclonic-atonic epilepsy is considered a developmental and epileptic encephalopathy, although the developmental course can be quite variable.
- Epilepsy of infancy with migrating focal seizures has a very characteristic seizure symptomatology involving focal seizures with interhemispheric migration that can be diagnosed either by clinical observation or EEG or both.
- The progressive myoclonus epilepsies are a clinically and genetically heterogeneous group of disorders that share the common features of myoclonic seizures and progressive neurologic decline. Age of onset is typically in childhood or adolescence, and patients may have additional seizure types including focal, atypical absence, atonic, and generalized tonic-clonic.
- Sleep-related hypermotor epilepsy is a form of focal epilepsy involving seizures that usually occur exclusively from sleep. Seizures usually arise from the frontal lobe; however, extrafrontal onset with spread to the frontal regions can produce the same phenotype.
- The seizure symptomatology in sleep-related hypermotor epilepsy typically involves hypermotor behaviors such as violent thrashing and writhing, often with vocalization and emotional facial expression.
- In photosensitive occipital lobe epilepsy, the classic seizure symptomatology is of a colorful visual aura that may evolve into lateral head and eye version; the patient may maintain awareness throughout.
- Epilepsy with auditory features is an epilepsy syndrome characterized by focal aware seizures localized to the lateral temporal region. Patients experience seizures involving simple or complex auditory hallucinations, and 86% of patients have focal-to-bilateral tonic-clonic seizures.
- Genetic epilepsy with febrile seizures plus is a familial syndrome in which members of the same family have different phenotypes, the most common being febrile seizures and febrile seizures plus (febrile seizures outside the usual age range or bilateral tonic-clonic seizures occurring with and without fever).

ARTICLE 5: AUTOIMMUNE-ASSOCIATED SEIZURES

Lisa Gillinder, MBBS, FRACP; Jeffrey Britton, MD, FAAN. Continuum (Minneap Minn). April 2022; 28 (2 Epilepsy):363–398.

ABSTRACT

PURPOSE OF REVIEW:

This article focuses on the seizure manifestations and presentations of autoimmune-associated epilepsy and acute symptomatic seizures in autoimmune encephalitis. It discusses the specificity of the various central nervous system autoantibodies and clarifies when their presence can be considered indicative of an immune etiology. Finally, current recommendations regarding patient selection for autoimmune antibody evaluation are reviewed, and an approach to immunotherapy is provided.

RECENT FINDINGS:

Although autoimmune seizures are caused by a heterogeneous group of autoantibodies, key features reported in the literature should alert clinicians to the possible diagnosis. In particular, seizure characteristics including frequency, timing, duration, and symptomatology can provide vital clues to help differentiate autoimmune-associated seizures from other causes of epilepsy. Diagnostic certainty also requires an understanding and integration of the spectrum of clinical and paraclinical presentations, and several scoring systems have been developed that may be useful to aid the identification of autoimmune seizures.

SUMMARY:

Seizures due to autoimmune etiology are increasingly encountered in clinical practice. It is critical that clinicians recognize immune seizure etiologies early in their course given they are often responsive to immunotherapy but are usually resistant to antiseizure medications. Currently, however, it is unfortunately not uncommon for autoimmune-associated seizure disorders to remain undiagnosed, resulting in missed opportunities to administer effective therapies. Efforts to better understand autoimmune seizure manifestations and treatment strategies are ongoing.

KEY POINTS

- Immune seizure etiologies are often responsive to immunotherapy but are usually resistant to antiseizure medications.
- The term *autoimmune-associated epilepsy* is now proposed to describe a clinical presentation with an enduring predisposition to unprovoked seizures with evidence of an immune etiology, whereas *acute symptomatic seizures secondary to autoimmune encephalitis* is recommended for seizures that occur as a symptom of active autoimmune encephalitis.
- Not all neural antibodies are considered definitively pathogenic, so clinicians must have an understanding of the pathogenic significance of each antibody to ensure accurate diagnostic and treatment decisions are made.
- Seizures in adults with autoimmune encephalitis are reported to occur at a higher frequency and with shorter duration than seizures due to other etiologies.
- Anti-LGI1 encephalitis most commonly presents with focal seizures. Patients are typically between the ages of 40 and 80 years. It is somewhat more common in men than women. Hyponatremia is relatively common. Faciobrachial dystonic seizures are the most characteristic seizure type in this disorder, although they are absent in more than half of cases.

- EEG may show no ictal findings even during focal seizures in anti-LGI1 encephalitis.
- Certain seizure manifestations can provide clues about an autoimmune etiology.
- Although seizures are common in anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis, affecting approximately 70% of cases, it is less common for them to be the presenting symptom in adults. Seizures are most common in children and young men.
- EEG changes in anti–NMDA receptor encephalitis typically progress in parallel with the severity of the clinical illness, and a higher degree of abnormality on EEG can correlate with a poorer prognosis.
- A characteristic EEG finding in anti–NMDA receptor encephalitis is the "extreme delta brush" pattern, present in up to 30% of cases.
- Although anti–leucine-rich glioma inactivated protein 1 (LGI1) and anti–NMDA receptor encephalitis are most commonly associated with seizures, many other autoimmune encephalitides can also cause seizures.
- Autoimmune encephalitis can occur in the absence of detectable neural autoantibodies, and if the pretest probability is high, then the diagnosis of seronegative autoimmune limbic encephalitis should be considered.
- Examples of autoimmune-associated epilepsy include the persistence of seizures after resolution of the active phase of encephalitis; chronic unresolving encephalitis including Rasmussen encephalitis; and in patients with epilepsy with compelling evidence of a CNS autoimmune condition where no alternative etiology for the epilepsy is identified.
- Rasmussen encephalitis is a rare neuroinflammatory disorder resulting in chronic focal seizures, emanating from one hemisphere, progressive hemiparesis, other lateralized cortical deficits, and cognitive impairment.
- Immunotherapy can lead to seizure freedom when due to autoimmune etiologies; consideration of these disorders should be given in the setting of drug-resistant seizures, especially those of recent onset and intractability from inception.
- Diagnostic accuracy requires an understanding and integration of the spectrum of clinical and paraclinical presentations, and several scoring systems have been developed that may be useful in aiding the identification of autoimmune seizures.
- If used alone, antiseizure medications are rarely effective in the setting of symptomatic seizures secondary to autoimmune encephalitis. They also may not be required after resolution of the acute illness, so cessation should be considered after 6 months or a greater period of sustained seizure freedom.
- Immunotherapy is the mainstay of treatment for autoimmune seizure etiologies and should be administered early in the course of the illness. Eighty percent to 90% of patients may achieve seizure freedom depending on the specific etiology, and it may lead to improvements in cognitive and functional outcomes.

ARTICLE 6: WOMEN'S ISSUES IN EPILEPSY

Esther Bui, MD, FRCP(C). Continuum (Minneap Minn). April 2022;
28 (2 Epilepsy):399–427.

ABSTRACT

PURPOSE OF REVIEW:

Issues pertaining to women with epilepsy have advanced with a better understanding of multidirectional influences among hormones, seizures, and antiseizure medications, as well as pregnancy-related concerns around fertility, seizure destabilization, and antiseizure medication–associated teratogenicity. This article highlights important developments in this field and reviews best practices in the management of women with epilepsy.

RECENT FINDINGS:

Important external hormonal influences may impact women with epilepsy particularly in the context of gender-affirming medications, hormonal replacement therapy, and fertility therapies. Fertility for women with epilepsy is influenced by multiple variables; however, in the absence of preexisting fertility issues, epilepsy per se is not associated with significantly impaired fertility. Once women with epilepsy are pregnant, the majority have a stable course. Antiseizure medication use in pregnancy is associated with major congenital malformations 2 to 5 times that of the general population and is highest with high-dose (≥1500 mg or greater total daily) valproate. Carefully considered changes in drug choice and dose may mitigate these risks. Therapeutic drug monitoring plays an important role in pregnancy care, and under expert supervision, women with epilepsy in pregnancy have similar seizure risks as women with epilepsy who are not pregnant. As women with epilepsy age, bone health and menopause may further be impacted by seizures and antiseizure medications.

SUMMARY:

The care of women with epilepsy is a multifaceted discipline that recognizes the life-long impact of sex and gender influences on epilepsy care.

KEY POINTS

- Gender-affirming medications may interact with antiseizure medications, and antiseizure medications may have unwanted esthetic side effects and significant drug-drug interactions.
- Women with epilepsy without preexisting infertility have as good of a chance for conceiving as do women without epilepsy.
- Seizure exacerbation may occur with hormonal therapies used in assisted reproductive technology; however, women with epilepsy have a similar chance at successful assisted reproductive technology treatment as women without epilepsy irrespective of concurrent antiseizure medication use.
- The intrauterine device, either hormonal based or copper based, continues to be the top-recommended contraceptive choice for women with epilepsy taking enzyme-inducing antiseizure medications or lamotrigine.
- Up to two-thirds of women with epilepsy remain seizure free in pregnancy. The best predictor of seizure frequency during pregnancy is the 9 to 12 months of seizure frequency before conceiving.
- Under specialized epilepsy care, women with epilepsy in pregnancy have similar rates of seizures as women with epilepsy who are not pregnant, but women with epilepsy in pregnancy require higher rates of antiseizure medication dose adjustments.
- The risk of major congenital malformations is drug and dose dependent. When these factors are combined, some risks may be near comparable, for example, high-dose carbamazepine (>700 mg total daily) and low-dose valproate (≤650 mg total daily).
- Different antiseizure medications are associated with different malformation types, and fetal assessment as well as neonatal examination should be tailored to these risks.
- Data on major congenital malformation risk of newer antiseizure medications continue to be insufficient because of the limited numbers of reported exposure, with most on polytherapy.
- Polytherapy that includes either valproate or topiramate as a component infers the highest risk of major congenital malformations among different polytherapy combinations.
- The risk of major congenital malformations with antiseizure medication exposure is highest with high-dose (≥1500 mg total daily) valproate. The risks may be lowered with low-dose valproate combined with another antiseizure medication.
- Genetic factors are important additional influences for the risk of major congenital malformations. A paternal and maternal history should be acquired to fully characterize the risks.
- Decisions to withdraw or avoid valproate should be specific to the individual woman, her seizure type, and physical as well as psychosocial impact of potential seizure recurrence.

- Preconception folic acid 0.4 mg to 5 mg daily is recommended for women with epilepsy of reproductive potential, although some recent concerns have been raised about supratherapeutic (>5 mg daily) folic acid supplementation.
- Antiseizure medication clearance and metabolism are differentially impacted at specific stages in pregnancy. When these serum drug levels decrease by more than 35% of preconception levels, seizures may recur.
- Regular therapeutic drug monitoring should be considered in pregnancy, when available, especially with drugs recognized to have pregnancy-related altered pharmacokinetics such as lamotrigine, levetiracetam, oxcarbazepine, topiramate, and zonisamide.
- Maternal mortality is elevated 5 to 11 times for women with epilepsy compared with the general population, although in absolute numbers, these occurrences remain rare.
- If dose increases have been made during pregnancy, tapering antiseizure medication doses should be planned within the first few weeks postpartum, especially with lamotrigine.
- Breastfeeding is generally safe and beneficial for women with epilepsy who are taking antiseizure medications and for their babies.
- Antiseizure medications are associated with osteoporosis. Vitamin D and calcium supplementation and a baseline bone mineral density are recommended especially with chronic antiseizure medication use.
- Hormonal replacement therapy may exacerbate seizures in a dose-dependent way. If necessary, simplified estrogen with natural progesterone could be considered.

ARTICLE 7: SEIZURES AND EPILEPSY IN CHILDHOOD

Maria Gogou, MD, PhD; Judith Helen Cross, MBChB, PhD. Continuum (Minneap Minn). April 2022; 28 (2 Epilepsy):428–456.

ABSTRACT

PURPOSE OF REVIEW:

This article highlights basic concepts of seizures and epilepsy in pediatric patients, as well as basic treatment principles for this age group.

RECENT FINDINGS:

Epilepsy is the most common neurologic disorder in childhood. Accurate diagnosis is key; in older children, epileptic seizures need to be differentiated from various paroxysmal nonepileptic events, whereas in neonates, the majority of seizures are subclinical (electroencephalographic). Antiseizure medications remain the first-line treatment, but ketogenic diet and epilepsy surgery have also shown positive outcomes and can decrease drug burden. Genetic causes account for approximately 30% of cases, and the recognition of electroclinical syndromes is being replaced by the concept of genetic spectrums. Precision medicine therapies are promising, but wide application in daily practice still has a long way to go. Early access to specialist centers and optimal treatments positively affects prognosis and future neurodevelopment.

SUMMARY:

Although novel findings from all fields of research are being incorporated into everyday clinical practice, a better quality of life for children with seizures and epilepsy and their families is the ultimate priority.

KEY POINTS

- Epilepsy affects 0.5% to 1% of children, and its prevalence is highest during infancy.
- Seizures need to be differentiated from several paroxysmal nonepileptic events (eg, seizure mimics in infancy, paroxysmal nonepileptic seizures in older children). Parental mobile videos and video-EEG records are useful screening tools.
- Seizures can be classified according to their onset or their ictal symptomatology.
- Etiology has been included as an essential part of the operational definition of epilepsy. An underlying cause can be identified in two-thirds of children with epilepsy (genetic in one-third, structural in one-third).
- Neonatal seizures affect 2 to 3 per 1000 births, and they are mainly subclinical (electroencephalographic-only); hypoxic-ischemic encephalopathy is the most frequent cause.
- A diagnosis of epilepsy is clinical with a medical history and description of the event being the principal diagnostic tools.
- Although several well-known epilepsy syndromes have been associated with seizures in the setting of fever, the majority of febrile seizures (simple or complex) have a favorable and self-limiting course, but recurrences are frequent. The total risk of epilepsy after a previous simple febrile seizure is 2%.
- Although well-described electroclinical syndromes with age-related expression are known, they still represent parts of different spectrums and can also share underlying genetic mechanisms.
- The term *developmental and epileptic encephalopathy* was first introduced in 2017 and highlights the fact that the epileptic activity contributes to the neurodevelopmental compromise beyond what might be expected from the underlying pathology alone but also that the underlying cause independently impacts neurodevelopment beyond what might be expected from the epilepsy.
- Children with epilepsy (even those with self-limited types) exhibit a wide range of comorbidities, which are often more deleterious than seizures themselves.
- Several epilepsy syndromes with childhood onset have a very good prognosis, but early-life onset epilepsies usually have poor outcomes.
- Sudden unexpected death in epilepsy (SUDEP) is a significant cause of death in pediatric epilepsy; incidence is similar in children and adults.
- Treatment with antiseizure medications leads to seizure freedom in almost two-thirds of cases, and ketogenic diet and epilepsy surgery represent valid therapeutic options for children with drug-resistant epilepsy. Precision medicine treatments are also available for patients with specific genetic epilepsies.
- Beyond seizure control, clinicians need to consider the full spectrum of needs of children with epilepsy. Early referral for optimal therapeutic choices in appropriate centers is justified to enable appropriate management and optimize the natural course of the disease.

ARTICLE 8: NEUROPSYCHIATRIC AND COGNITIVE COMORBIDITIES IN EPILEPSY

Marco Mula, MD, PhD, FRCP, FEAN; Honor Coleman, MPsych, PhD; Sarah J. Wilson, PhD, FAHMS, FASSA. Continuum (Minneap Minn). April 2022; 28 (2 Epilepsy):457–482.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses psychiatric and cognitive comorbidities of epilepsy over the lifespan and illustrates opportunities to improve the quality of care of children and adults with epilepsy.

RECENT FINDINGS:

One in 3 people with epilepsy have a lifetime history of psychiatric disorders, and they represent an important prognostic marker of epilepsy. Contributors are diverse and display a complex relationship. Cognitive comorbidities are also common among those living with epilepsy and are increasingly recognized as a reflection of changes to underlying brain networks. Among the cognitive comorbidities, intellectual disability and dementia are common and can complicate the diagnostic process when cognitive and/or behavioral features resemble seizures.

SUMMARY:

Comorbidities require consideration from the first point of contact with a patient because they can determine the presentation of symptoms, responsiveness to treatment, and the patient's day-to-day functioning and quality of life. In epilepsy, psychiatric and cognitive comorbidities may prove a greater source of disability for the patient and family than the seizures themselves, and in the case of essential comorbidities, they are regarded as core to the disorder in terms of etiology, diagnosis, and treatment.

KEY POINTS

- Psychiatric disorders occur more commonly in epilepsy than in the general population and are increasingly recognized as a major source of disability in epilepsy.
- The etiology of psychiatric disorders in epilepsy is complex and can include both biological and psychosocial factors, including altered functioning of brain networks, stigma, social limitations, and distress.
- The relationship between epilepsy and psychiatric disorders is bidirectional, including depression, psychogenic nonepileptic seizures, attention deficit hyperactivity disorder, autism spectrum disorder, and schizophrenia.
- Consideration of psychiatric comorbidities is clinically relevant for neurologists because comorbid psychiatric conditions have been associated with poorer treatment outcomes, as well as increased health care utilization and increased mortality.
- Barriers to diagnosis and treatment can include a lack of training of neurologists and psychiatrists in the psychiatric aspects of neurologic disorders and a lack of clinical resource allocation to support a multidisciplinary approach, as well as broader stigma and cultural barriers to mental health support.
- Some useful tools to screen for psychiatric conditions in epilepsy include the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), Epilepsy Anxiety Survey Instrument (EASI), the brief Epilepsy Anxiety Survey Instrument, the Beck Depression Inventory II (BDI-II), Patient Health Questionnaire 9 (PHQ-9), the Hospital Anxiety and Depression Scale (HADS), and the Generalized Anxiety Disorder Scale (GAD-7).
- Diagnosis of psychiatric conditions in epilepsy involves careful consideration of the timing of symptom onset and progression to determine the presence of postictal symptoms and/or possible contribution of antiseizure medications.
- Further research is needed to examine the efficacy of treatment approaches for psychiatric disorders in epilepsy, but first-line treatment involves psychoeducation and psychological interventions.
- Choice of medication for psychiatric conditions should include consideration of metabolic, extrapyramidal cardiovascular, and hormonal side effects and interactions with antiseizure medications, including the possibility of amplifying side effects of antiseizure medications.
- Cognitive comorbidities are common among people living with epilepsy and can range from generalized cognitive impairment to relatively circumscribed deficits.
- The International Classification of Cognitive Disorders in Epilepsy seeks to advance the understanding of the essential cognitive comorbidities of epilepsy.
- Cognitive difficulties may extend beyond intellectual functions, such as attention and memory, and may include difficulties with emotional expression and regulation.
- Several specific childhood epilepsy syndromes typically involve significant developmental delay and/or intellectual disability. Many of these syndromes represent rare genetic epilepsy syndromes.

- An epileptic encephalopathy has been defined by the International League Against Epilepsy as "a condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function."
- The recognition of a bidirectional relationship between epilepsy and dementia is growing, with an increased risk of dementia among people living with epilepsy and an increased risk of seizures in dementia.
- Increased risk of seizures has been identified across several different dementia syndromes, including Alzheimer disease, frontotemporal dementia, and dementia with Lewy bodies.
- Risk factors for seizures in dementia include poor cardiovascular health, raised inflammatory markers, decreased physical fitness, and decreased social interaction.
- Subjective cognitive concerns are not always correlated with objective cognitive performance and may be influenced by mood, lack of insight, and other psychological factors.
- Different cognitive screening measures may include the Montreal Cognitive Assessment (MoCA) or the Mini-Mental State Examination (MMSE). However, cognitive comorbidity can only be properly diagnosed following a comprehensive workup that includes formal neurologic, neuropsychological, and/or neuropsychiatric assessment.
- Consideration of a patient's cognitive functioning is crucial in the workup to epilepsy surgery. This is important not only in considering the possible cognitive risks of surgery but also in how clinicians discuss the surgery with patients and their family members and obtain informed consent. Cognitive aids, such as written and/or simplified information, may be helpful for some patients.
- Consideration of psychiatric well-being is important not only for patients' general well-being but also for their subjective cognitive functioning, because the reduced physical and social activity that may be prompted by low mood can be detrimental to cognition.

ARTICLE 9: APPROACH TO THE MEDICAL TREATMENT OF EPILEPSY

Francesco Brigo, MD; Anthony Marson, MBChB, MD, FRCP. Continuum (Minneap Minn). April 2022; 28 (2 Epilepsy):483–499.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses the use of antiseizure medications in the treatment of focal and generalized epilepsies using an evidence-based approach.

RECENT FINDINGS:

In recent years, several new antiseizure medications with differing mechanisms of action have been introduced in clinical practice, and their efficacy and safety has been evaluated in randomized controlled clinical trials. Currently, all antiseizure medications can prevent seizure occurrence, but they have no proven disease-modifying or antiepileptogenic effects in humans. The choice of therapy should integrate the best available evidence of efficacy, tolerability, and effectiveness derived from clinical trials with other pharmacologic considerations, the clinical expertise of the treating physicians, and patient values and preferences. After the failure of a first antiseizure medication, inadequate evidence is available to inform policy. An alternative monotherapy (especially if the failure is because of adverse effects) or a dual therapy (especially if failure is because of inadequate seizure control) can be used.

SUMMARY:

Currently, several antiseizure medications are available for the treatment of focal or generalized epilepsies. They differ in mechanisms of action, frequency of administration, and pharmacologic properties, with a consequent risk of pharmacokinetic interactions. Major unmet needs remain in epilepsy treatment. A substantial proportion of patients with epilepsy continue to experience seizures despite two or more antiseizure medications, with a negative impact on quality of life. Therefore, more antiseizure medications that could provide higher seizure control with good tolerability and that could positively affect the underlying disease are needed.

KEY POINTS

- The practice of evidence-based medicine integrates the best available research evidence with clinical expertise and patient values and preferences in making decisions about the care of individuals.
- Evaluating and integrating data on efficacy, safety, and effectiveness is essential to obtain the best information upon which to make treatment decisions.
- Estimating the risk of seizure recurrence for an individual and the effect of antiseizure medication on that recurrence risk is crucial to inform the decision on whether to start antiseizure medication treatment.
- Antiseizure medication treatment following a first unprovoked seizure reduces the risk of a seizure recurrence with no impact on longer-term seizure remission rates.
- According to the International League Against Epilepsy classification, every attempt should be made to consider and incorporate etiology when classifying epilepsies, as it often has relevant treatment implications.
- The choice of initial antiseizure medication therapy should integrate the best available evidence from clinical trials, other pharmacologic considerations, the clinical expertise of the treating physicians, and patient values and preferences.
- Despite the increased availability of antiseizure medications, the prognosis of patients with newly diagnosed epilepsy has not significantly improved.
- After monotherapy failure because of inadequate seizure control, the main options are an alternative monotherapy or a dual therapy.
- Several antiseizure medications are available for treating focal epilepsy with seizures refractory to a first or alternative monotherapy.
- When choosing the add-on treatment, several aspects need to be considered in addition to its efficacy and tolerability, including frequency of administration; pharmacokinetic properties, including the risk of drug interactions; and patient preferences.
- The ideal rational polytherapy should have supraadditive or synergistic effects in efficacy (ie, their combined efficacy should be greater than the sum of efficacy of each antiseizure medication alone) with infraadditive toxicity (ie, their combined toxicity should be less than the sum of the toxicity of each antiseizure medication alone).

ARTICLE 10: UPDATE ON ANTISEIZURE MEDICATIONS 2022

Bassel W. Abou-Khalil, MD, FAAN. Continuum (Minneap Minn). April 2022; 28 (2 Epilepsy):500–535.

ABSTRACT

PURPOSE OF REVIEW:

This article is an update from the article on antiepileptic drug therapy (now referred to as *antiseizure medication therapy*) published in the two previous *Continuum* issues on epilepsy and

is intended to cover the vast majority of agents currently available to the neurologist in the management of patients with epilepsy.

Treatment of epilepsy starts with antiseizure medication monotherapy. Knowledge of the spectrum of efficacy, clinical pharmacology, and modes of use for individual antiseizure medications is essential for optimal treatment for epilepsy. This article addresses antiseizure medications individually, focusing on key pharmacokinetic characteristics, indications, and modes of use.

RECENT FINDINGS:

Since the most recent version of this article was published, two new antiseizure medications, cenobamate and fenfluramine, have been approved by the US Food and Drug Administration (FDA), and the indications of some approved medications have been expanded.
Older antiseizure medications are effective but have tolerability and pharmacokinetic disadvantages. Several newer antiseizure medications have undergone comparative trials demonstrating efficacy equal to and tolerability at least equal to or better than older antiseizure medications as first-line therapy for focal epilepsy. The list includes lamotrigine, oxcarbazepine, levetiracetam, topiramate, zonisamide, and lacosamide. Pregabalin was found to be less effective than lamotrigine. Lacosamide, pregabalin, and eslicarbazepine have undergone successful trials of conversion to monotherapy for focal epilepsy. Other newer antiseizure medications with a variety of mechanisms of action are suitable for adjunctive therapy.
Antiseizure medications marketed since 2016 have benefited from the FDA policy allowing a drug's efficacy as adjunctive therapy in adults to be extrapolated to efficacy in monotherapy. In addition, efficacy in adults can be extrapolated for efficacy in children 4 years of age and older. Both extrapolations require data demonstrating that an antiseizure medication has equivalent pharmacokinetics between its original approved use and its extrapolated use. Rational antiseizure medication combinations should avoid antiseizure medications with unfavorable pharmacokinetic interactions or pharmacodynamic interactions related to mechanism of action.

SUMMARY:

Knowledge of antiseizure medication pharmacokinetics, efficacy, and tolerability profiles facilitates the choice of appropriate antiseizure medication therapy for patients with epilepsy.

KEY POINTS

- Phenobarbital, primidone, phenytoin, and carbamazepine are potent inducers of liver enzymes, reducing the efficacy of drugs metabolized by the cytochrome P450 enzyme system.
- Long-term phenobarbital use is associated with decreased bone density, Dupuytren contractures, plantar fibromatosis, and frozen shoulder.
- In addition to sedation and other adverse effects of phenobarbital, primidone use may be associated with an acute toxic reaction unrelated to phenobarbital, with potentially debilitating drowsiness, dizziness, ataxia, nausea, and vomiting.
- Phenytoin has saturable nonlinear kinetics. Beyond a certain serum concentration, usually within the accepted therapeutic range, phenytoin concentration increases disproportionately with an increase in the dose. Small increments are necessary when increasing the dose at a serum concentration in the therapeutic range.
- The traditional sodium channel blockers phenytoin, carbamazepine, and oxcarbazepine may exacerbate generalized absence and myoclonic seizures and should be avoided in idiopathic generalized epilepsy. Other antiseizure medications that have similar potential are gabapentin, pregabalin, tiagabine, and vigabatrin.
- Unlike phenytoin, the phenytoin prodrug fosphenytoin may be administered intramuscularly, with reliable absorption, in the absence of IV access.
- Carbamazepine induces its own metabolism, so it has to be titrated gradually to the target dose.
- The HLA-B1502 allele is predictive of a carbamazepine-induced severe rash in individuals of Asian descent.

- Oxcarbazepine is more likely to cause hyponatremia than carbamazepine. Older individuals taking a diuretic are at particularly high risk.
- Eslicarbazepine has a long half-life in CSF, justifying once-daily oral dosing.
- Valproate has a broad spectrum of efficacy against all focal and generalized seizure types.
- Valproate has the highest rate of teratogenicity among antiseizure medications and should be avoided in female patients of childbearing potential.
- Ethosuximide is the drug of choice for typical absence seizures as the only seizure type. While valproate is equally effective, it is associated with more cognitive adverse effects.
- Tolerance may develop to the therapeutic effect of benzodiazepines; this appears less likely with clobazam than clonazepam.
- Felbamate-related aplastic anemia and liver failure are unlikely to start after 1 year of treatment.
- Gabapentin bioavailability is low and decreases with increasing doses.
- Like gabapentin, pregabalin has a narrow spectrum of efficacy against focal seizures and may exacerbate generalized myoclonic and absence seizures.
- Lamotrigine clearance is decreased by valproate and increased by estrogen and pregnancy as well as by enzyme inducers.
- Tiagabine may be associated with dose-related episodes of nonconvulsive status epilepticus or encephalopathy, even in subjects who do not have epilepsy.
- Levetiracetam is the only antiseizure medication with Class I evidence of efficacy against generalized myoclonic seizures.
- Brivaracetam may have fewer behavioral side effects than levetiracetam.
- Zonisamide's long half-life of about 60 hours may be an advantage in reducing the impact of a missed dose.
- Lacosamide may produce a dose-dependent prolongation in PR interval, which could be clinically significant in patients with known cardiac conduction problems, or if it is combined with other drugs that have a similar effect.
- Long-term vigabatrin use may be associated with irreversible visual field constriction; hence, it should only be continued if it produces a remarkable improvement in seizure control.
- Valproate reduces rufinamide clearance; as a result, rufinamide has to be started at a lower dose and titrated more slowly in the presence of valproate.
- Perampanel has a very long half-life, justifying once-daily dosing.
- Cannabidiol reduces clearance of the active metabolite of clobazam, requiring reduction in the clobazam dose.
- Cenobamate requires a very slow titration to avoid allergic skin reactions.
- Antiseizure medication combinations with different mechanisms of action may have a greater probability of success.

ARTICLE 11: SURGICAL TREATMENTS FOR EPILEPSY

George W. Culler IV, MD; Barbara C. Jobst, MD, Dr Med, FAAN. Continuum (Minneap Minn). April 2022; 28 (2 Epilepsy):536–558.

ABSTRACT

PURPOSE OF REVIEW:

More than 20 new antiseizure medications have been approved by the US Food and Drug Administration (FDA) in the past 3 decades; however, outcomes in newly diagnosed epilepsy have not improved, and epilepsy remains drug resistant in up to 40% of patients. Evidence

supports improved seizure outcomes and quality of life in those who have undergone epilepsy surgery, but epilepsy surgery remains underutilized. This article outlines indications for epilepsy surgery, describes the presurgical workup, and summarizes current available surgical approaches.

RECENT FINDINGS:

Class I evidence has demonstrated the superiority of resective surgery compared to medical therapy for seizure control and quality of life in patients with drug-resistant epilepsy. The use of minimally invasive options, such as laser interstitial thermal therapy and stereotactic radiosurgery, are alternatives to resective surgery in well-selected patients. Neuromodulation techniques, such as responsive neurostimulation, deep brain stimulation, and vagus nerve stimulation, offer a suitable alternative, especially in those where resective surgery is contraindicated or where patients prefer nonresective surgery. Although neuromodulation approaches reduce seizure frequency, they are less likely to be associated with seizure freedom than resective surgery.

SUMMARY:

Appropriate patients with drug-resistant epilepsy benefit from epilepsy surgery. If two well-chosen and tolerated medication trials do not achieve seizure control, referral to a comprehensive epilepsy center for a thorough presurgical workup and discussion of surgical options is appropriate. Mounting Class I evidence supports a significantly higher chance of stopping disabling seizures with surgery than with further medication trials.

KEY POINTS

- Drug-resistant epilepsy is diagnosed when a person continues to have seizures despite adequate trials of two appropriately chosen and well-tolerated antiseizure medications.
- One-third of patients with epilepsy have drug-resistant epilepsy. Drug-resistant epilepsy is associated with higher rates of morbidity (eg, loss of independence, depression, worse quality of life) and mortality.
- Epilepsy surgery evaluation is appropriate for anyone with focal disabling seizures that continue to occur despite treatment with two appropriately chosen antiseizure medications.
- Evaluation for surgery begins at an established comprehensive epilepsy center, where the diagnosis of epilepsy is confirmed.
- A presurgical evaluation is necessary to identify the cortical area that is generating seizures, which, when removed, will result in seizure freedom; this is known as the epileptogenic zone.
- Video-EEG monitoring confirms the diagnosis of epilepsy type by recording the patient's habitual seizures and correlates the patient's reported symptomatology to aid in localization.
- Abnormalities on initial brain MRI may be missed. Careful inspection by an expert neuroradiologist and the use of higher-resolution MRI scanners and positron emission tomography (PET) may identify subtle lesions (eg, dysplasia).
- Neuropsychological testing and functional imaging help predict postoperative deficits and localize eloquent cortex.
- Resective surgery may be possible without intracranial EEG studies if presurgical findings (eg, ictal and interictal EEG, seizure symptomatology, and MRI) are concordant to the nondominant temporal lobe.
- The goals of intracranial EEG are twofold: (1) to further localize the epileptogenic zone and prove/disprove a hypothesis and (2) to determine the location of eloquent cortex with electrical stimulation.
- Only 30% to 50% of epilepsy surgeries require intracranial EEG, which includes the use of stereotactic electrodes, subdural grid electrodes, or a combination of the two to aid in delineation of the epileptogenic zone.
- Three Class I randomized controlled trials have shown the effectiveness of resective surgery compared to continued medical treatment in adults and children with drug-resistant epilepsy.
- Different surgical options are available for drug-resistant epilepsy, including resection, laser ablation, and neurostimulation, which can be tailored to the specific patient.

- Verbal memory deficits are the most consistent adverse effect following dominant (typically left) temporal resections when compared to nondominant resection.
- Visual field deficits, most commonly a superior quadrantanopia, comprise half of all permanent neurologic deficits after temporal lobe resection and are generally well tolerated.
- Surgery for lesional epilepsy, as defined by an unequivocal MRI abnormality responsible for seizures, is associated with better postoperative seizure outcome than nonlesional epilepsy.
- The most common lesions associated with seizures include malformations of cortical development, focal cortical dysplasia, cavernous and arteriovenous malformations, and low-grade gliomas.
- Laser ablation and stereotactic radiosurgery are minimally invasive options available in some centers for patients who are candidates for resection but do not want a craniotomy.
- Three implantable neurostimulation therapies are now available for patients with drug-resistant epilepsy who undergo full surgical evaluation and are deemed poor candidates for resective surgery.
- Responsive neurostimulation should be considered as a treatment option in those with seizures that arise from eloquent cortex and/or up to two suspected seizure foci.
- Deep brain stimulation and vagus nerve stimulation are reserved as options for poorly localized epilepsy or multifocal epilepsy.
- All three available neurostimulation devices are associated with seizure reduction, which improves over time. Rates of adverse events are low and typically perioperative or related to stimulation, which can be modified.

ARTICLE 12: MANAGEMENT OF STATUS EPILEPTICUS, REFRACTORY STATUS EPILEPTICUS, AND SUPER-REFRACTORY STATUS EPILEPTICUS

Eugen Trinka, MD, MSc, FRCP; Markus Leitinger, MD, MSc. Continuum (Minneap Minn). April 2022; 28 (2 Epilepsy):559-602.

ABSTRACT

PURPOSE OF REVIEW:

Status epilepticus is a serious condition caused by disorders and diseases that affect the central nervous system. In status epilepticus, hypersynchronous epileptic activity lasts longer than the usual duration of isolated self-limited seizures (time t1), which causes neuronal damage or alteration of neuronal networks at a certain time point (time t2), depending on the type of and duration of status epilepticus. The successful management of status epilepticus includes both the early termination of seizure activity and the earliest possible identification of a causative etiology, which may require independent acute treatment. In nonconvulsive status epilepticus, patients present only with subtle clinical signs or even without any visible clinical manifestations. In these cases, EEG allows for the assessment of cerebral function and identification of patterns in need of urgent treatment.

RECENT FINDINGS:

In 2015, the International League Against Epilepsy proposed a new definition and classification of status epilepticus, encompassing four axes: symptomatology, etiology, EEG, and age. Various validation studies determined the practical usefulness of EEG criteria to identify nonconvulsive status epilepticus. The American Clinical Neurophysiology Society has incorporated these

criteria into their most recent critical care EEG terminology in 2021. Etiology, age, symptomatology, and the metabolic demand associated with an increasing duration of status epilepticus are the most important determinants of prognosis. The consequences of status epilepticus can be visualized in vivo by MRI studies.

SUMMARY:

The current knowledge about status epilepticus allows for a more reliable diagnosis, earlier treatment, and improved cerebral imaging of its consequences. Outcome prediction is a soft tool for estimating the need for intensive care resources.

KEY POINTS

- The outcome of status epilepticus depends on etiology, age, symptomatology, and duration of status epilepticus.
- At time t1, the diagnosis of status epilepticus is established and therapy is started.
- At time t2, treatment should be successful in preventing neuronal damage.
- For convulsive (bilateral tonic-clonic) status epilepticus, time t1 is 5 minutes.
- For focal status epilepticus with or without impairment of consciousness, time t1 is 10 minutes.
- Unsuccessful therapy with a benzodiazepine and one antiseizure medication defines refractory status epilepticus.
- The management of status epilepticus should be viewed as a process.
- The changing symptomatology within one episode of status epilepticus is called *evolution of symptomatology*; the status epilepticus symptomatology that comes later determines outcomes.
- The epidemiology of status epilepticus is determined by several factors.
- The etiology of status epilepticus can be divided into symptomatic (acute, remote, progressive, and electroclinical syndromes) and cryptogenic.
- Rare causes of status epilepticus include immunologically mediated disorders, mitochondrial diseases, uncommon infective disorders, genetic disorders, and drugs or toxins.
- Status epilepticus and acute stroke share many features (eg, time is brain, the onset is often not witnessed, and both need a structured diagnostic and therapeutic approach).
- Acute etiologies of status epilepticus may need a specific emergency treatment (eg, ischemic stroke).
- The main reason for unsuccessful treatment of status epilepticus is underdosing.
- The electro-paraclinical gap exists if the EEG findings cannot sufficiently be explained by imaging, laboratory, or toxicologic investigations.
- The electro-paraclinical gap is a useful tool to diagnose nonconvulsive status epilepticus and to increase specificity.
- The Salzburg diagnostic EEG criteria for nonconvulsive status epilepticus are part of the recent American Clinical Neurophysiology Society Standard Criteria for Critical Care EEG Terminology.
- The impact of the burden model integrates structural damage and metabolic derangement, the burden of status epilepticus, the success and burden of treatment, and the impact of burden.
- The amount of structural and metabolic reserves determines the optimal end point parameters in studies.
- MRI is useful to demonstrate ictal hyperperfusion by arterial spin labeling in those with status epilepticus.
- New-onset refractory status epilepticus (NORSE) is a form of a clinical presentation of refractory status epilepticus.
- Febrile infection–related epilepsy syndrome (FIRES) denotes a condition in which a febrile infection preceded NORSE.
- Data from patients with NORSE should be collected in international registries.
- A predictive score should have at least a very high positive or negative predictive value.

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HEADACHE

ARTICLE 1: DIAGNOSING SECONDARY AND PRIMARY HEADACHE DISORDERS

David W. Dodick, MD, FAAN, FAHS. Continuum (Minneap Minn). June 2021; 27 (3 Headache):572–585.

ABSTRACT

PURPOSE OF REVIEW:

This article provides a systematic diagnostic approach to the patient with headache.

RECENT FINDINGS:

The vast majority of patients presenting with headache in clinical practice have a primary headache disorder. The most common primary headache disorder in clinical practice is overwhelmingly migraine. Unfortunately, a substantial proportion of patients with migraine do not receive an accurate diagnosis. In addition, the clinical features of migraine overlap with secondary causes of headache, making a careful history and deliberative evaluation for warning symptoms or signs of a secondary headache disorder of paramount importance.

SUMMARY:

The approach to the patient with headache requires knowledge of the diagnostic criteria for primary headache disorders, recognition of the importance of a systematic evaluation for red flags associated with secondary headache disorders, and awareness of the pearls and pitfalls encountered in the diagnostic evaluation of a patient with headache.

KEY POINTS

- **The $SNOOP_4$ acronym is a useful guide to assist clinicians in systematically evaluating for warning symptoms and signs of a secondary cause of headache.**
- **Since secondary causes of headache often have features that resemble migraine, tension-type headache, or a trigeminal autonomic cephalalgia, caution must be exercised and warning signs and symptoms of secondary headache must be evaluated.**
- **A headache history is the most important aspect of the evaluation of a patient presenting with headache, and eliciting worrisome features with directed questioning is necessary. The history must be taken without assuming that key features will be volunteered by the patient.**
- **Brain MRI is the imaging procedure of choice when evaluating for intracranial or neurovascular causes of headache. Other than the detection of skull fracture or acute intracranial blood, the use of CT in the evaluation of secondary headaches should be restricted, especially in children.**

- PITS (parenchymal, intraventricular, truncal, sulci) is a useful acronym that highlights the anatomic areas where subarachnoid blood can be overlooked.
- In the setting of a thunderclap headache, MRI of the brain and intracranial and extracranial vasculature should always be obtained after subarachnoid hemorrhage is excluded.
- Knowledge of the qualitative and quantitative findings on MRI in patients suspected of having intracranial hypertension or hypotension is important and can help support a diagnosis.
- The overwhelming majority (94%) of patients presenting with recurrent nonsecondary headaches as a chief complaint in clinical practice have migraine.
- If clinicians remember any part of the *International Classification of Headache Disorders, Third Edition*, it should be the diagnostic criteria for migraine, chronic migraine, and medication-overuse headache as these are the most common primary headaches seen in clinical practice.

ARTICLE 2: PATHOPHYSIOLOGY OF MIGRAINE

Ana Recober, MD. Continuum (Minneap Minn). June 2021; 27 (3 Headache):586–596.

ABSTRACT

PURPOSE OF REVIEW:

This article summarizes the current understanding of the pathophysiology of migraine, including some controversial aspects of the underlying mechanisms of the disorder.

RECENT FINDINGS:

Recent functional neuroimaging studies focusing on the nonpainful symptoms of migraine have identified key areas of the central nervous system implicated in the early phases of a migraine attack. Clinical studies of spontaneous and provoked migraine attacks, together with preclinical studies using translational animal models, have led to a better understanding of the disease and the development of disease-specific and targeted therapies.

SUMMARY:

Our knowledge of the pathophysiology of migraine has advanced significantly in the past decades. Current evidence supports our understanding of migraine as a complex cyclical brain disorder that likely results from dysfunctional sensory processing and dysregulation of homeostatic mechanisms. This article reviews the underlying mechanisms of the clinical manifestations of each phase of the migraine cycle.

KEY POINTS

- It is widely accepted that migraine is an inherited disorder of sensory processing, but many aspects of the underlying basis of this disorder still remain unknown.
- Migraine attacks are often preceded by alterations in homeostasis, supporting the role of the hypothalamus in the prodromal phase.
- Neuroimaging studies have found hypothalamic activation and altered connectivity with other brain and brainstem regions that could explain the polyuria, yawning, food cravings, and changes in appetite reported in the prodromal phase.
- During the prodromal phase, photophobia is associated with activation of the visual cortex, and nausea is associated with activation of the rostral dorsal medulla and periaqueductal gray. Neck stiffness or discomfort is attributed to early activation of the trigeminocervical complex, the region of the brainstem and upper cervical spinal cord where pain signals from the trigeminal and cervical nerves converge.

- Taken together, the nature of the symptoms and neuroimaging findings support the current understanding of migraine as a disorder of the central nervous system and not as a vascular disorder.
- Traditionally, aura has been described as preceding the headache phase; however, the aura can overlap with headache, and it is not rare for the aura to occur in the absence of headache.
- Cortical spreading depolarization is widely accepted to be the pathophysiologic mechanism of aura.
- Cortical spreading depolarization is a bioelectrical phenomenon consisting of a wave of intense cortical neuronal activity associated with hyperemia, followed by a more prolonged period of neuronal activity suppression associated with cortical oligemia.
- Cortical spreading depolarization has been demonstrated to occur in the human brain as a result of acute injury in the setting of stroke or traumatic brain injury; however, no direct evidence of the simultaneous occurrence of cortical spreading depolarization and aura has been seen in humans.
- The aura can start in multiple sites of the visual cortex in the same individual, although certain areas show higher propensity to be the initiating focus.
- The mechanisms underlying visual aura appear to propagate in a linear fashion along gyri or sulci, rather than spreading as a concentric wave as usually depicted based on studies of cortical spreading depolarization in animal models.
- The aura may propagate silently in the cortex, without clinical manifestations.
- Migraine pain is mediated by the trigeminovascular pathway.
- Some experts maintain that nociceptive activation of the peripheral trigeminal nociceptors is necessary for the perception of head pain and implicate cortical spreading depolarization and peripheral sensitization of perivascular sensory nerve terminals. Others argue that migraine pain is the result of abnormal central processing of otherwise normal sensory input from the peripheral trigeminal sensory system.
- Some studies have challenged the presumption that the pulsating quality of pain in migraine is determined by arterial pulsations and suggest a neuronal rather than vascular "pacemaker" of the throbbing pain in migraine.
- The postdrome can last for 24 to 48 hours after resolution of the headache. Some experts have suggested that global reductions in cerebral blood flow could occur in this phase and could be mediated by activation of brainstem nuclei, resulting in widespread vasoconstriction. Alternatively, this reduction in regional cerebral blood flow has been attributed to the persistent hypoperfusion that follows cortical spreading depolarization.
- People with migraine report cognitive, autonomic, and sensory symptoms between their migraine attacks. Resting-state functional connectivity MRI studies have demonstrated altered network connectivity in multiple cortical and subcortical brain regions during the interictal phase.
- Multiple neurotransmitters, neuropeptides, and neurochemical systems play a role in migraine. The most studied include calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating polypeptide (PACAP), serotonin, and noradrenergic and dopaminergic mechanisms.

ARTICLE 3: ACUTE MIGRAINE TREATMENT

Jessica Ailani, MD, FAHS, FAAN. Continuum (Minneap Minn). June 2021; 27 (3 Headache):597–612.

ABSTRACT

PURPOSE OF REVIEW:

Migraine is a disabling disease of attacks of moderate to severe pain with associated symptoms. Every person with migraine requires treatment for acute attacks. Treatments can range from behavioral management and nonspecific medications to migraine-specific medications and

neuromodulation. For many with migraine, having a combination of tools allows for effective treatment of all types of attacks.

RECENT FINDINGS:

Over the past several years, four neuromodulation devices have been cleared by the US Food and Drug Administration (FDA) for treatment of acute migraine, and three medications with novel mechanisms of action have been FDA approved. They add to the arsenal available to people with migraine and focus on migraine-specific pathways to allow for precise care with fewer side effects.

SUMMARY:

This article discusses acute migraine therapy, focusing on best-level evidence.

KEY POINTS

- Migraine attacks are disabling and require treatment. Ineffective treatment can increase emergency department visits and place the patient at increased risk for chronic migraine.
- Acute treatment can be nonspecific or migraine specific. Opioids and barbiturates should be limited in their use for migraine.
- Triptans, acetaminophen, aspirin, ibuprofen, naproxen, and diclofenac sodium have Level A evidence for the acute treatment of migraine.
- A nonoral route for migraine medication is preferred in patients with nausea or vomiting or rapid-onset attacks.
- Stratified care is best for patients with multiple types of migraine attacks.
- Triptans are considered first-line treatment for moderate to severe migraine attacks.
- Triptans are contraindicated in people with vascular disease.
- Dihydroergotamine has shown to be effective early or late in a migraine attack. Consider dihydroergotamine in a patient who has found triptans to be ineffective.
- Lasmiditan 50 mg, 100 mg, or 200 mg can be considered in patients with cardiovascular contraindications to triptans.
- Patients who are prescribed lasmiditan must be instructed not to drive for 8 hours after taking medication.
- Ubrogepant is dosed as needed for migraine, with an additional second dose as needed in 2 to 24 hours.
- Rimegepant is dosed once a day as needed for migraine.
- Consider adding neuromodulation in patients who have side effects to current therapy, prefer nondrug therapy, or are overusing acute medications.
- The goals of acute migraine treatment are to treat attacks quickly and consistently, prevent recurrence, and restore the patient to functionality.

ARTICLE 4: PREVENTIVE MIGRAINE TREATMENT

Rebecca Burch, MD, FAHS. Continuum (Minneap Minn). June 2021;
27 (3 Headache):613-632.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of preventive interventions for migraine, including when to start and how to choose a treatment, pharmacologic options (both older oral treatments and new monoclonal antibodies to calcitonin gene-related peptide [CGRP] or its receptor),

nonpharmacologic treatment such as neuromodulation, and preventive treatment of refractory migraine.

RECENT FINDINGS:

The migraine preventive treatment landscape has been transformed by the development of monoclonal antibodies targeting CGRP or its receptor. These treatments, which are given subcutaneously or intravenously monthly or quarterly, have high efficacy and were well tolerated in clinical trials. Emerging real-world studies have found higher rates of adverse events than were seen in clinical trials. They are currently recommended for use if two traditional preventive therapies have proven inadequate. Since the commonly cited 2012 American Headache Society/American Academy of Neurology migraine prevention guidelines were released, clinical trials supporting the preventive use of lisinopril, candesartan, and memantine have been published. Neuromodulation devices, including external trigeminal nerve stimulation and single-pulse transcranial magnetic stimulation devices, have modest evidence to support preventive use. The American Headache Society/American Academy of Neurology guidelines for the preventive treatment of migraine are currently being updated. A new class of oral CGRP receptor antagonists (gepants) is being tested for migraine prevention.

SUMMARY:

Successful preventive treatment of migraine reduces disease burden and improves quality of life. Many pharmacologic and nonpharmacologic treatment options are available for the prevention of migraine, including newer therapies aimed at the CGRP pathway as well as older treatments with good evidence for efficacy. Multiple treatment trials may be required to find the best preventive for an individual patient.

KEY POINTS

- Preventive treatment reduces migraine-related disability over and above the associated reduction in attack frequency.
- A collaborative approach to choosing preventive treatment may improve adherence and patient satisfaction with treatment options.
- The goal of preventive treatment is reduction of disability and improvement in quality of life rather than complete relief from migraine attacks.
- Objective measures are helpful for tracking response to preventive treatment and may be more reliable than patient recall.
- Prevention is started when migraine attacks are frequent, disabling, or hard to treat, or if acute medications have been overused.
- Oral preventive treatments with good evidence include sodium valproate, topiramate, propranolol, metoprolol, and amitriptyline.
- Amitriptyline and venlafaxine are the antidepressant drugs with the best evidence for prevention of migraine.
- Propranolol and verapamil are the antihypertensive drugs most commonly used for migraine prevention and are generally well tolerated.
- Recent evidence suggests that lisinopril and candesartan are effective migraine preventives with a good side effect profile.
- Topiramate and sodium valproate are potent migraine preventives but have a higher side effect burden than other preventives.
- Antiepileptic drugs sometimes used for prevention include gabapentin, pregabalin, and zonisamide.
- Oral medication choice depends on effectiveness, side effect profile, contraindications, and patient preference.
- Four calcitonin gene-related peptide (CGRP) monoclonal antibodies are now US Food and Drug Administration approved for migraine prevention.
- CGRP monoclonal antibodies are given monthly or quarterly, either subcutaneously or intravenously.

- CGRP monoclonal antibodies are effective for migraine prevention, with up to 60% of patients seeing a 50% or greater reduction in headache days.
- Studies showed that CGRP monoclonal antibodies are effective for refractory migraine and sustain efficacy over several years.
- Discontinuation because of adverse events was less than 5% in clinical trials of CGRP monoclonal antibodies, but these trials may not have accurately captured the side effects seen in clinical practice.
- The long-term safety of CGRP blockade, particularly the risk of rare but serious cardiovascular events, is not completely known.
- CGRP monoclonal antibodies may have a faster onset of action than oral preventives.
- Limitations of CGRP monoclonal antibody use include cost and access issues, long duration of any side effects that may occur, and the need to avoid use during pregnancy.
- American Headache Society guidelines suggest that CGRP monoclonal antibodies may be considered if two traditional (oral or neurotoxin) preventives are not effective or not tolerated.
- OnabotulinumtoxinA, topiramate, and the CGRP monoclonal antibodies have good evidence for prevention of chronic migraine.
- Medication-overuse headache is often treated with a combination of discontinuation of the overused medication and starting preventive medication. OnabotulinumtoxinA and topiramate have the best evidence for prevention in patients with medication overuse.
- Patients with chronic migraine have a higher burden of medical and psychiatric comorbidity and benefit significantly from a multidisciplinary approach.
- Important lifestyle factors to consider in people with migraine include getting adequate and good-quality sleep, maintaining good hydration, eating well-balanced frequent meals, avoiding alcohol, keeping caffeine to a modest level and at a regular time each morning, managing stress, and participating in regular physical activity.
- The herbal and nutritional supplements with the best evidence for migraine prevention are magnesium and riboflavin. Evidence for feverfew has been conflicting.
- *Petasites* (butterbur) is no longer recommended as a preventive because of possible contamination with hepatotoxic alkaloids.
- Behavioral therapies with good evidence for migraine prevention include cognitive-behavioral therapy, relaxation training, thermal or electromyographic biofeedback, and mindfulness meditation.
- Layering behavioral and pharmacologic treatment is more effective than either approach alone, particularly for people with both migraine and mood disorders.
- Acupuncture is a popular nonpharmacologic treatment that has good evidence for use in migraine prevention and is generally well tolerated.
- The decision on whether to use devices for migraine prevention in clinical practice is often driven by cost and access concerns.
- The external trigeminal nerve stimulation device and the single-pulse transcranial magnetic stimulation device have evidence for migraine prevention.

ARTICLE 5: CLUSTER HEADACHE AND OTHER TRIGEMINAL AUTONOMIC CEPHALALGIAS

Stephanie J. Nahas, MD, MSEd, FAHS, FAAN. Continuum (Minneap Minn). June 2021; 27 (3 Headache):633-651.

ABSTRACT

PURPOSE OF REVIEW:

The trigeminal autonomic cephalalgias (TACs) are relatively rare, but they represent a distinct set of syndromes that are important to recognize. Despite their unique features, TACs often go undiagnosed or misdiagnosed for several years, leading to unnecessary pain and suffering. A significant proportion of TAC presentations may have secondary causes.

RECENT FINDINGS:

The underlying pathophysiology of TACs is likely rooted in hypothalamic dysfunction and derangements in the interplay of circuitry involving trigeminovascular, trigeminocervical, trigeminoautonomic, circadian, and nociceptive systems. Recent therapeutic advancements include a better understanding of how to use older therapies more effectively and the identification of new approaches.

SUMMARY:

TAC syndromes are rare but important to recognize because of their debilitating nature and greater likelihood for having potentially serious underlying causes. Although treatment options have remained somewhat limited, scientific inquiry is continually advancing our understanding of these syndromes and how best to manage them.

KEY POINTS

- The trigeminal autonomic cephalalgias share some similarity with migraine phenotype, pathophysiology, and therapy but represent a distinct set of syndromes requiring different management.
- The pain of trigeminal autonomic cephalalgias tends to be relatively short and intense, and, by definition, it is accompanied by symptoms reflective of autonomic dysfunction.
- The pathophysiology of trigeminal autonomic cephalalgias is likely linked to dysfunction of the hypothalamus, trigeminally mediated reflexes, and nociception.
- Trigeminal autonomic cephalalgias are distinguished clinically by temporal patterns and combinations of symptoms.
- Cluster headache attacks must be addressed with rapid-onset therapies (eg, inhaled or injected), and, since attacks can be frequent, toxicity from repeated treatments must be considered.
- Corticosteroids (administered orally, via suboccipital injection, or, less commonly, intravenously) are instrumental as transitional therapy in cluster headache.
- Episodic cluster headache should be managed with maintenance therapy only during bouts, not continuously without interruption.
- Paroxysmal hemicrania is clusterlike, with a female predominance, greater attack frequency, less periodicity, different triggers, and, above all else, exquisite response to indomethacin.
- Indomethacin is most useful for paroxysmal hemicrania and hemicrania continua, requires proper titration, and monitoring for prolonged use for its potential adverse effects.
- If indomethacin is contraindicated or intolerable for patients with paroxysmal hemicrania and hemicrania continua, alternative therapies are available.
- If a chronic primary headache diagnosis is unclear, consider an indomethacin trial, particularly if there are no contraindications, and if cranial autonomic symptoms are present.
- Short-lasting unilateral neuralgiform headache attacks are like V1 trigeminal neuralgia, with autonomic features and no refractory period to cutaneous triggering (when present); look for pituitary pathology and vascular loop compression in all cases, repeatedly in refractory cases.
- Hemicrania continua is increasingly recognized as a mimic of chronic migraine.
- In many cases, syndromic overlap exists in the presentation of trigeminal autonomic cephalalgias, and treatment should be tailored initially to the entity with the closest fit based on diagnostic criteria.

ARTICLE 6: OTHER PRIMARY HEADACHE DISORDERS

Jonathan H. Smith, MD, FAHS. Continuum (Minneap Minn). June 2021; 27 (3 Headache): 652–664.

ABSTRACT

PURPOSE:

This article provides an overview of a diverse group of primary headache disorders that are categorized in the *International Classification of Headache Disorders, 3rd Edition* (*ICHD-3*), as "other primary headache disorders." This article provides clinicians with a distilled understanding of the diagnoses and their epidemiology, pathophysiology, and management.

RECENT FINDINGS:

Cough-induced headache requires neuroimaging to exclude posterior fossa pathology and recently has been reported as a common symptom in patients with CSF-venous fistula. Clinical overlap is observed between patients with primary exercise headache and primary headache associated with sexual activity. Patients with recurrent thunderclap headache associated with sexual activity should be presumed to have reversible cerebral vasoconstriction syndrome until proven otherwise. De novo external-pressure headache is a common sequela among health care workers using personal protective equipment during the COVID-19 pandemic. New daily persistent headache is an important mimicker of chronic migraine or chronic tension-type headache and is distinguished by a daily-from-onset progression of persistent headache; a treatment-refractory course is often observed, and early involvement of a multidisciplinary team, including a psychotherapist, is advised.

SUMMARY:

Patients with primary headache disorders that are classified as "other primary headache disorders" have presentations with unique diagnostic and management considerations. The disorders are highly recognizable, and an appreciation of the diagnoses will aid clinicians in providing safe and effective care for patients presenting with headache.

KEY POINTS

- Clinical distinction must be made between headache that is triggered by a Valsalva maneuver (a red flag) and headache that is aggravated by a Valsalva maneuver (typical of migraine).
- In nearly two-thirds of patients, a history of cough-induced headache may indicate a posterior fossa lesion, most often a Chiari malformation type I.
- Although not part of the diagnostic criteria for primary cough headache, the disorder classically responds to treatment with indomethacin.
- Unlike migraine, primary exercise headache often has a short duration and generally does not have typical migraine features apart from a throbbing pain character.
- Among older adults at risk for coronary artery disease, cardiac angina may present with an exertional headache (termed *cardiac cephalalgia*).
- Primary exercise headache exists as a self-limited disorder in the majority of patients.
- Recurrent thunderclap headaches associated with sexual activity should be presumed to be reversible cerebral vasoconstriction syndrome until proven otherwise. A patient with an initial presentation of headache associated with sexual activity should be evaluated for the possibility of subarachnoid hemorrhage.

- External-pressure headache should be considered in occupational groups in which helmets or personal protective equipment are commonly worn.
- Routine neuroimaging for suspected primary stabbing headache is not recommended in the absence of additional red flags.
- Patients with recurrent thunderclap headache should be initially presumed to have a clinical diagnosis of reversible cerebral vasoconstriction syndrome. Patients with a new presentation of thunderclap headache should first be evaluated for subarachnoid hemorrhage.
- To help distinguish hypnic headache from cluster headache, the diagnostic criteria specify that hypnic headache is not associated with cranial autonomic symptoms or restlessness.
- Hypnic headache appears to occur more often in adults older than 50 years.
- Polysomnography has not shown a consistent association with sleep stage and hypnic headache onset.
- Hypnic headache is unique relative to other headache disorders because frequent caffeine use is advocated as therapy.
- The scalp area affected by the nummular headache should be examined for alopecia or a visible skin lesion, which may indicate a dermatologic condition.
- Migrainous features are not typical of nummular headache, although comorbid migraine is common.
- The temporal progression should be ascertained for all patients presenting for evaluation of a refractory chronic daily headache because the hallmark of new daily persistent headache is a daily-from-onset progression of chronic headache.
- In specialty headache practices, disorders of intracranial pressure, including idiopathic intracranial pressure with or without papilledema and spontaneous CSF leak, are relatively common; these disorders should be considered when evaluating patients for new daily persistent headache.
- New daily persistent headache is characteristically refractory to standard therapies, and empiric treatment guided by the underlying phenotype (eg, chronic migraine) is recommended.
- Early acknowledgment of a refractory course allows for early involvement of a multidisciplinary team to help bolster self-efficacy and self-management strategies in patients with new daily persistent headache.

ARTICLE 7: CRANIAL NEURALGIAS

Carrie Robertson, MD, FAHS. Continuum (Minneap Minn). June 2021;
27 (3 Headache):665-685.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses the differential diagnosis, evaluation, and management of trigeminal neuralgia and reviews other neuralgias of the head and neck, including those that contribute to neuralgic ear pain.

RECENT FINDINGS:

Most cases of trigeminal neuralgia are related to vascular compression, a demyelinating plaque, or a compressive mass affecting the trigeminal nerve. However, recent studies have shown that up to 11% of patients have a family history of trigeminal neuralgia, suggesting that some patients may have a genetic predisposition to demyelination or nerve hyperexcitability. In these patients, trigeminal neuralgia may occur at a younger age, on both sides of the face, or in combination with other neuralgias.

SUMMARY:

When a patient presents with neuralgic pain, the diagnosis is made by careful history and neurologic examination, with attention to the dermatome involved, the triggers, and the

presence of any associated sensory deficit. All patients with new neuralgia or neuropathic facial pain warrant a careful evaluation for a secondary cause. The presence of sensory deficit on bedside examination is particularly concerning for an underlying secondary etiology.

KEY POINTS

- *Neuralgia* describes sharp, stabbing, shocklike pain that is often triggered by touching within the sensory dermatome of the affected nerve, whereas *neuropathy* describes sensory deficit within the nerve distribution, sometimes with persistent neuropathic pain, such as burning, tingling, or prickling.
- Classical trigeminal neuralgia is trigeminal neuralgia related to neurovascular compression; nerve atrophy or displacement is required on imaging (not just vascular contact). Secondary trigeminal neuralgia is trigeminal neuralgia related to another cause, such as demyelinating plaque or local mass. Idiopathic trigeminal neuralgia is trigeminal neuralgia without a known cause.
- Most patients with trigeminal neuralgia are pain free between attacks, but a subset can develop near-continuous background pain.
- Mild sensory changes may be present in trigeminal neuralgia, but true loss of sensation should alert the clinician to look for secondary causes.
- Approximately 99% of patients with trigeminal neuralgia report triggers.
- Some patients with trigeminal neuralgia may describe a refractory period after severe attacks, during which additional attacks are diminished.
- Bilateral trigeminal neuralgia can occur but is uncommon and should raise suspicion for secondary trigeminal neuralgia, such as from multiple sclerosis.
- Trigeminal neuralgia associated with pronounced autonomic symptoms should raise clinical suspicion for a trigeminal autonomic cephalalgia.
- Unexplained numbness isolated to the chin is a red flag for potential malignancy.
- Neurovascular contact of the trigeminal nerve is common even in people without symptoms. Therefore, the severity of compression on imaging may be more relevant, including nerve displacement or atrophy.
- A family history of trigeminal neuralgia may be present in up to 11% of patients. Familial cases may have an earlier onset and may be associated with additional neuralgias, such as glossopharyngeal neuralgia or hemifacial spasm.
- Patients with multiple sclerosis may have both a demyelinating plaque and neurovascular compression near the trigeminal nerve root entry zone, causing neuralgia through a "double crush" mechanism.
- Postherpetic neuralgia should be considered in patients presenting with trigeminal neuralgia who have a history of erythema or rash in the affected area at the onset of pain.
- Because of overlap from cervical cutaneous branches over the jawline, the most reliable area to test the mandibular (V3) division is over the chin.
- If the patient's pain is predominantly in V2 and V3 and without cutaneous triggers, a dental evaluation should be considered.
- Carbamazepine is considered first-line treatment for trigeminal neuralgia.
- For urgent treatment of refractory trigeminal neuralgia, IV fosphenytoin, IV lidocaine, or peripheral blocks can be considered.
- A patient with trigeminal neuralgia that is refractory to medical therapy should be referred to a neurosurgeon. If neurovascular compression is present on imaging, microvascular decompression is typically considered first. If not, a neuroablative procedure (with injury to the nerve) is typically considered first.
- Recurrence of trigeminal neuralgia after microvascular decompression may be because of a new or previously missed vessel, compression with the synthetic material used in decompression, or arachnoid adhesions.
- Repeat microvascular decompression has a lower chance of pain relief and higher risk of complications.
- The best dosing and location of radiosurgery (where to aim along the trigeminal root) for trigeminal neuralgia is still being studied.

- Pain relief from radiosurgery may start 2 weeks to 2 months after treatment, whereas decreased sensation may start an average of 6 to 36 months after treatment.
- Trigeminal neuropathy following a neuroablative procedure for trigeminal neuralgia is called *painful posttraumatic trigeminal neuropathy*.
- By convention, the term *postherpetic neuralgia* is used for either neuralgic or neuropathic facial pain starting in an area with active herpes zoster rash and persisting for more than 3 months.
- Brain MRI is not adequate for numb chin syndrome as it may not visualize the mandible and may miss a malignancy located there.
- Stabbing ear pain may be referred along six nerves with overlapping dermatomes: the auriculotemporal nerve, lesser occipital nerve, great auricular nerve, nervus intermedius, glossopharyngeal nerve, and vagus nerve.
- Brain MRI is not adequate for unexplained ear pain, as it cannot visualize many structures that radiate pain to the ear, such as the throat, cervical vessels, and thyroid.
- Glossopharyngeal neuralgia is provoked by swallowing, yawning, or coughing.
- Patients with lightheadedness, palpitations, or syncope with their glossopharyngeal neuralgia pain may require ambulatory ECG monitoring to look for an associated bradyarrhythmia.
- Similar to trigeminal neuralgia, glossopharyngeal neuralgia may be related to neurovascular compression or other lesions along the nerve path.
- Either microvascular decompression or sectioning of the glossopharyngeal nerve (and sometimes vagus nerve rootlets) is considered a reasonable first-line treatment for medically refractory glossopharyngeal neuralgia.
- Nervus intermedius neuralgia may present with stabbing pain deep in the ear triggered by cold wind or using a cotton swab in the ear canal.
- Nervus intermedius neuralgia may develop in the setting of classic Bell's palsy or Ramsay Hunt syndrome (herpes zoster affecting the ear and facial nerve).
- Occipital neuralgia is typically described as shooting or stabbing pain that starts at the posterior skull base and radiates either to the vertex (greater occipital nerve) or over the ear toward the temple (lesser occipital nerve).
- If loss of sensation is present with occipital neuralgia, a secondary cause of pain should be considered.

ARTICLE 8: HEADACHE IN WOMEN

Jelena M. Pavlović, MD, PhD. Continuum (Minneap Minn). June 2021;
27 (3 Headache):686–702.

ABSTRACT

PURPOSE OF REVIEW:

Women are greatly overrepresented among patients seeking treatment for symptoms of headache pain in general and migraine in particular. Understanding the presentation of headache in women in relation to hormonal changes both during the menstrual cycle and throughout the life span is essential for appropriate diagnosis and treatment.

RECENT FINDINGS:

Although perimenstrual migraine attacks are generally without aura, the diagnosis of migraine with aura has been added to the headache classification for menstrual migraine to account for women with the diagnosis of migraine with aura who experience menstrual migraine attacks. Emerging knowledge regarding the differences between menstrual and nonmenstrual attacks, the variability of attack triggering within and between women, and the response of women with

menstrually related migraine to new migraine drug classes is contributing to better understanding and more effective treatment of these particularly burdensome and refractory attacks. Given the burden of migraine, almost one-fourth of women with migraine avoid or delay pregnancy. Women who experience migraine during pregnancy are more likely to have a hypertensive disorder and stroke during pregnancy and/or delivery and the postpartum period. Treatment of headache in general and migraine in particular in pregnancy is challenging because of fetal and maternal risks; however, a 2021 systematic review suggests that triptans and low-dose aspirin may not be associated with fetal/child adverse effects and could be more strongly considered for headache treatment in pregnancy.

SUMMARY:

Headache in general and migraine in particular are extraordinarily common in women of reproductive age and fluctuate with hormonal changes and phases of life. Improved knowledge of the epidemiology, pathophysiology, and response to treatment of perimenstrual attacks is essential for more effective response to this most burdensome headache type. Treatment of headache in pregnancy remains challenging.

KEY POINTS

- Migraine is predominantly a disorder of women that is affected by fluctuations in ovarian hormones, affecting women throughout their lifetime by varying in frequency and burden with hormonal changes.
- Perimenstrual migraine attacks are thought to be due to estrogen withdrawal before menstruation.
- Although generally neuroexcitatory, estrogen appears to have a protective role in migraine, with migraine occurrence being related to low estrogen levels.
- Perimenstrual migraine attacks are more intense, more burdensome, and more refractory to treatment than nonmenstrual attacks, requiring a proactive approach. The predictive nature of perimenstrual attacks provides an opportunity for treatment.
- Perimenstrual migraine attacks are commonly migraine without aura, even in women who otherwise have attacks with aura.
- Clinicians and patients must recognize that menstruation can affect migraine in women in many different ways. To get a better sense of how menstruation and migraine are related in a given woman, a diary should be kept for a longer period of time than the currently recommended 3 months.
- Perimenstrual migraine can be treated with routine acute migraine treatment agents or with mini-prevention approaches in which triptans or nonsteroidal anti-inflammatory drugs are taken 2 times a day for about 5 days starting at the onset of perimenstrual migraine, typically 2 days before onset of menstruation.
- Perimenopause and the menopausal transition are marked by hormonal fluctuations and present an often-eventful time for women with migraine, who may experience an increase in both attack frequency and symptoms of perimenopause.
- Migraine is the most common primary headache disorder for which women seek help during pregnancy.
- Migraine frequency and symptomatology typically improve as pregnancy progresses, yet many women delay pregnancy for fear of migraine worsening or potential complications to themselves or the fetus. Education of women on the natural course of migraine in pregnancy is essential.
- New migraine phenomena during pregnancy are more likely to be migraine with aura than migraine without aura. Isolated auras can also occur. This is likely due to a high estrogen to progesterone ratio, which decreases the threshold for cortical spreading depression.
- Sleep deprivation and other stressors of early motherhood and infant care should be addressed and patients educated on biobehavioral approaches to this challenging time of a woman's life.
- Migraine is associated with higher rates of both medical and obstetric events; pregnant women with a history of migraine, particularly those with frequent attacks, should be considered at higher risk of adverse outcomes and should be monitored with a heightened index of suspicion.

- The prothrombotic state of pregnancy adds additional risk to pregnant women with migraine who may already be prone to often-undiagnosed hypercoagulabilities. Women with migraine with aura should be followed by their obstetricians with extra caution.
- Triptans, which are the mainstay of acute headache treatment in nonpregnant and nonlactating women, have recent reassuring safety data, and select medications in this category may be considered in these populations.
- The majority of drugs currently used as first-line acute migraine treatment have not been associated with deleterious effects to the fetus during pregnancy exposure. As most women with migraine experience improvement in their headache during pregnancy, preventive treatments are generally not needed.
- Secondary headaches likely to present in pregnancy are generally due to a prothrombotic state (stroke and thrombosis) and states of elevated blood pressure (preeclampsia).

ARTICLE 9: HEADACHE IN CHILDREN AND ADOLESCENTS

Christina Szperka, MD, MSCE, FAHS. Continuum (Minneap Minn). June 2021; 27 (3 Headache):703–731.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the approach to a child or adolescent with headache, the criteria for common diagnoses, and the evidence base for treatments.

RECENT FINDINGS:

The guidelines for acute and preventive treatment of migraine were updated in 2019. These guidelines summarize the available evidence and outline the questions that should be addressed in future research. The US Food and Drug Administration (FDA) approval of several new classes of drugs and devices to treat adult migraine in the past few years has resulted in ongoing or planned pediatric trials.

SUMMARY:

Headache is a common symptom in children, and it is important to take a detailed history and perform a thorough physical examination to make the diagnosis. Nearly 1 in 10 children experience recurrent headaches due to migraine, which cause significant impairment in school performance and quality of life. The acute and preventive treatments that are currently available will help at least two-thirds of children with migraine, and several trials of new therapies offer hope for the future.

KEY POINTS

- Headaches are a very common and disabling problem for children and adolescents. Globally, nearly 60% of children and adolescents experience significant headache, and 7.7% to 9.1% have migraine.
- Children with migraine miss more school than their peers and have impaired school performance and impaired quality of life, similar to that of children with rheumatoid arthritis or cancer. This disability is complicated by the fact that migraine is a silent disease; no outward findings are visible, so the child's report of pain may be doubted, leading to shame and frustration.
- Migraine is the leading cause of disability worldwide for older adolescents and young adults.
- Children may not volunteer other symptoms that come with headache, so they should be explicitly and concretely asked.

- Studies have demonstrated that adverse experiences in childhood (financial stress; physical, emotional, or sexual abuse; parental divorce; death; mental illness; or addiction) predispose to headache in childhood as well as later in life.
- It is important to know what the child does not have as well as what the child does have. Life-threatening causes such as brain tumors occur in approximately 2% to 3% of children who present to the emergency department for headache and in about 1% of children with headache seen in primary care.
- Several studies support that neuroimaging is unnecessary for children with stable frequency of headaches, the absence of concerning features, and a normal neurologic examination.
- Migraine is a primary headache disorder characterized by recurrent (at least five) episodes of moderate to severe pulsating head pain lasting hours and accompanied by nausea/vomiting and sensitivity to light and sound.
- Migraine prevalence and features vary from childhood to adolescence and from boys to girls. Migraine affects approximately 5% of boys and girls by the age of 10, 7% of girls and 5% of boys up to age 15, and 10% of girls and 6% of boys by the age of 20.
- Tension-type headache occurs in 10% to 24% of children and adolescents but does not usually bring the child to medical attention because the attacks are mild and cause little disability.
- In population-based self-report studies, at least 1.5% of children report headaches several times per week or daily.
- All children with migraine should receive an acute treatment plan to be used at the start of an episode that includes a school note permitting the child to be excused from class at symptom onset to hydrate, take an acute medication, and rest before returning to class.
- Menstrual migraine can be particularly disabling and difficult to treat, with the added difficulty of irregular menstrual cycles making prediction more difficult for adolescents.
- Consistent lifestyle habits may help to minimize migraine triggers and should be discussed with all patients.
- Factors outside the child's control may preclude the development of healthy lifestyle habits, including school start time, homework, and work schedules of parent(s)/guardian(s). Even when children intend to follow the advice, adherence is difficult. Furthermore, little evidence is available to guide which specific changes actually impact headache frequency.
- Preventive treatment should be considered in all children who have frequent headaches or significant headache-related disability, or both.
- High placebo response in trials limits the ability to demonstrate efficacy of a medication. However, in clinical practice, placebo response can be beneficial, as the goal is patient improvement without harm. The guidelines recommend consideration of topiramate, propranolol, and amitriptyline combined with cognitive-behavioral therapy, which was demonstrated to be superior to amitriptyline plus headache education.
- Nutraceuticals were not reviewed in the current guidelines for pediatric migraine prevention, but some have evidence of benefit and safety and are commonly used by patients even before they are recommended by clinicians.
- Children with recurrent headaches have approximately double the likelihood of recurrent headaches in adulthood and also have increased likelihood of having other physical symptoms and psychiatric comorbidities.
- Children with migraine who seek care, receive a diagnosis, and take appropriate treatments have at least a two-thirds chance of significant and sustained improvement.
- Recurrent headaches are common in children and adolescents. The most common cause, migraine, is underdiagnosed and undertreated. Many unanswered questions about the "correct" approach to migraine treatment for children and adolescents remain.

ARTICLE 10: CLINIC-BASED PROCEDURES FOR HEADACHE

Matthew S. Robbins, MD, FAAN, FAHS. Continuum (Minneap Minn). June 2021; 27 (3 Headache):732-745.

ABSTRACT

PURPOSE OF REVIEW:

Headache disorders are common and disabling, and many therapies that are effective and safe are procedural.

RECENT FINDINGS:

After pivotal clinical trials, onabotulinumtoxinA has become an established preventive therapy for chronic migraine; it is better tolerated than many other treatments and may be useful for other headache disorders. Peripheral nerve blocks, especially greater occipital nerve blocks, have amassed evidence from randomized trials in the acute and short-term preventive treatment of migraine and cluster headache. Trigger point injections and sphenopalatine ganglion blocks have recent trials suggesting efficacy and safety in properly selected patients. Medical education initiatives are needed to train neurologists in these procedures to help manage the large population of patients with headache disorders who need them.

SUMMARY:

Evidence exists for the efficacy and safety of procedural therapies to be incorporated into neurology practice for the management of patients with migraine, cluster headache, and other headache disorders.

KEY POINTS

- In the periphery, the inhibitory effect of onabotulinumtoxinA may prevent the release of inflammatory substances important in migraine and pain, such as calcitonin gene-related peptide.
- One of the major benefits of onabotulinumtoxinA relative to other preventive therapies, particularly oral drugs, is its tolerability, which has been verified in comparative studies versus oral preventive agents.
- Although not specifically approved for these disorders, onabotulinumtoxinA has rationally been used in the same protocol for chronic headache disorders that are otherwise treated like chronic migraine if they feature the same headache phenotype, including chronic posttraumatic headache and new daily persistent headache.
- Peripheral nerve blocks for headache consist of injections of local anesthetic and, at times, steroids in accessible nerve branches on the head, including the greater occipital nerve, lesser occipital nerve, auriculotemporal nerve, supratrochlear nerve, and supraorbital nerve.
- Clinical data suggest that the improvement that patients receive from peripheral nerve blocks is not directly correlated to a simple local anesthetic effect, as the duration of analgesia generally far exceeds the duration of anesthesia.
- A steroid should be administered in addition to local anesthetics when greater occipital nerve injections are used for cluster headache (typically methylprednisolone, dexamethasone, or triamcinolone) based on the available evidence and guidelines. However, for migraine, the few studies performing direct comparisons of anesthetics alone versus anesthetics with steroids do not show added benefit.
- Although peripheral nerve blocks may be an excellent treatment option in pregnant women with migraine, ideally lidocaine or ropivacaine should be used as bupivacaine has more unpredictable pharmacokinetics and has been associated with maternal cardiac conduction abnormalities.

- Trigger point injections involve the administration of anesthetics into myofascial structures that may serve as mechanical sites that evoke or perpetuate an underlying headache disorder, most commonly tension-type headache or migraine.
- The evidence for trigger point injections includes randomized controlled trials for tension-type headache and migraine, with the strongest evidence for frequent tension-type headache.
- The sphenopalatine ganglion is a reasonable target for blocks and neuromodulation as it is the key peripheral structure involved in the expression of cranial autonomic symptoms and plays an important role in the trigeminoautonomic reflex in trigeminal autonomic cephalalgias and migraine and in regulation of cerebral blood flow.

ARTICLE 11: SPONTANEOUS INTRACRANIAL HYPOTENSION

Shuu-Jiun Wang, MD. Continuum (Minneap Minn). June 2021; 27 (3 Headache):746–766.

ABSTRACT

PURPOSE OF REVIEW:

Spontaneous intracranial hypotension is a disorder caused by spinal CSF leakage. This article reviews the clinical presentation, diagnosis, and treatment of spontaneous intracranial hypotension.

RECENT FINDINGS:

The hallmark symptom of spontaneous intracranial hypotension is acute orthostatic headache; however, clinical presentations can be heterogeneous. New evidence shows that lumbar puncture is not always necessary or sufficient to establish the diagnosis. Some patients may have normal opening pressure, which suggests that insufficiency of CSF volume (hypovolemia) rather than CSF pressure might be the underlying mechanism. Several neuroimaging modalities can aid in diagnosis and localization of the CSF leakage, including brain MRI, spinal MRI, CT myelography, digital subtraction myelography, and radionuclide cisternography. Complications, such as subdural hematoma, can lead to a change in the headache pattern and potentially life-threatening consequences. Conservative treatments, such as fluid supplementation, can provide temporary relief; however, epidural blood patches, especially targeted ones, are more effective and definitive. For patients with refractory spontaneous intracranial hypotension, surgical repair of spinal CSF leakages should be considered.

SUMMARY:

Brain and spinal MRIs are important for the diagnosis and treatment of patients with spontaneous intracranial hypotension. Early treatment with epidural blood patches may be considered to shorten the disease duration and minimize the potential risk of complications.

KEY POINTS

- Spontaneous intracranial hypotension is a disorder related to spinal CSF leakage. Acute orthostatic headache is the most common clinical presentation, but some patients may present with nonheadache symptoms.
- The female to male ratio of spontaneous intracranial hypotension is about 2:1, and it typically occurs in patients in their midthirties to midfifties.
- Diagnostic investigations for spontaneous intracranial hypotension include postcontrast brain MRI and spinal neuroimaging, such as spinal MRI, CT myelography, digital subtraction myelography, and radionuclide cisternography. Lumbar puncture is not always necessary or sufficient for diagnosis.

- Spinal CSF leaks can be classified as dural tear, meningeal diverticulum, or CSF-venous fistula. CSF-venous fistula is a direct communication between the spinal subarachnoid space and epidural venous plexus. The identification of CSF-venous fistulas requires dynamic CT myelography or digital subtraction myelography; spinal MRI is not capable of identifying them.
- Normal CSF pressure (>60 mm CSF) does not exclude the diagnosis of spontaneous intracranial hypotension. Insufficiency of intracranial CSF volume (ie, hypovolemia) may be more important in the pathophysiology of spontaneous intracranial hypotension.
- Brain neuroimaging findings in patients with spontaneous intracranial hypotension include cerebral venous-related signs and brain descent–related signs.
- The Monro-Kellie doctrine states that the sum of the volumes of brain tissue, vessels, and CSF within the skull is constant. The decrement of CSF volume during CSF leakage is compensated by the dilation of intracranial venous structures. Cerebral venous-related signs of spontaneous intracranial hypotension include diffuse pachymeningeal enhancement, the venous distension sign, and pituitary hyperemia (or pituitary enlargement).
- Brain descent–related signs reflect the downward displacement of brain structures or brain structural deformities in patients with spontaneous intracranial hypotension. Among these signs, closure of the midbrain-pons angle is associated with a poorer response to the first epidural blood patch. These neuroimaging findings are helpful not only for diagnosis but also for prediction of treatment response.
- Localization of spinal CSF leaks by spinal neuroimaging can provide clues for diagnosis and guide therapeutic interventions.
- Heavily T2-weighted magnetic resonance myelography can be used to visualize spinal CSF leaks; it was demonstrated to be comparable to the gold standard CT myelography. It is a noninvasive imaging technique and does not require IV or intrathecal contrast administration.
- Subdural hematoma is the most common complication of spontaneous intracranial hypotension, especially in patients who develop a change in their headache pattern.
- Purely conservative treatments for spontaneous intracranial hypotension (eg, fluid supplementation) are usually temporizing measures, and definitive treatment (eg, targeted epidural blood patches) is more effective. For patients with refractory spontaneous intracranial hypotension, surgical repair of the spinal leaks should be considered.

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Movement Disorders

Article 1: Parkinson Disease

Theresa A. Zesiewicz, MD, FAAN. Continuum (Minneap Minn). 2019; 25 (4 Movement Disorders):896–918.

ABSTRACT

PURPOSE OF REVIEW:

Parkinson disease is a common neurodegenerative disorder that affects millions of people worldwide. Important advances in the treatment, etiology, and the pathogenesis of Parkinson disease have been made in the past 50 years. This article provides a review of thecurrent understanding of Parkinson disease, including the epidemiology, phenomenology, and treatment options.

RECENT FINDINGS:

Parkinson disease is nowrecognized to be a heterogeneouscondition marked by both motor and nonmotor symptoms. It is composed of preclinical, prodromal, and clinical phases. New medications with improved ease of administration have been approved for its treatment. Innovative surgical therapies for Parkinson disease may be used when motor symptoms persist despite optimal medical management.

SUMMARY:

Parkinson disease is a complex, heterogeneous neurodegenerativedisorder. Considerable progress has been made in its treatment modalities, both pharmacologic and surgical. While its cure remains elusive, exciting new research advances are on the horizon.

KEY POINTS

- A renaissance of therapeutic options for Parkinson disease have occurred in the last 50 years. Levodopa remains the gold standard for treatment of Parkinson disease, but dopamine agonists, monoamine oxidase type B inhibitors, catechol-*O*-methyltransferase inhibitors, and surgical procedures have greatly expanded the therapeuticoptions.
- Parkinson disease affects millions of people worldwide, and its prevalence increasesgreatly with advancing age.
- Clinical features of Parkinson disease include tremor, rigidity, akinesia (or bradykinesia), and posturalinstability. Nonmotor symptoms are commonly experienced by patients and often negatively impact quality of life. Premotor symptoms include constipation, anosmia, rapid eye movement sleep disorder, and depression.
- The diagnosis of Parkinson disease is made clinically. Red flags for atypical parkinsonism include severe dysautonomia, early-onset hallucinations and dementia, freezing, postural instability, and lack of response

to levodopa. Red flags for atypical parkinsonism also include early speech difficulties and imbalance, poor response to levodopa, and symmetrical symptoms.

- Parkinson disease may be divided into preclinical, prodromal, and clinical phases. Patients generally experience good response to levodopa for several years following their diagnosis.
- Parkinson disease is characterized by the loss of dopaminergic neurons and the presence of Lewy bodies containing the misfolded protein α-synuclein.
- Parkinson disease remains a clinical diagnosis. Neuroimaging techniques such as dopamine transporter single-photon emission computed tomography are helpful in differentiating between essential tremor and tremor from parkinsoniansyndromes.
- Clinical rating scales and patient diaries are helpful inmonitoring disease progression and are useful tools in clinical research trials.
- While levodopa is the gold standard in the treatment of Parkinson disease, it is nowavailable in several formulations that may provide ease of administration and improved efficacy. Other available medications are dopamineagonists, catechol-*O*-methyltransferase inhibitors, monoamine oxidase type B inhibitors, an *N*-methyl-D-aspartate antagonist, and anticholinergic medications.
- Patients with Parkinson disease should be offered dopaminergic treatment when their symptoms are bothersome. Patients with Parkinson disease should be encouraged to exercise, as long as it is performed safely.
- The aim of Parkinson disease treatment is to optimize on time and reduce off time while minimizing troublesome levodopainduced dyskinesia. Treatment of levodopa induced dyskinesia requires identifying its occurrence in relation to levodopa dosing.
- Surgical treatment of Parkinson disease was developed for patients who, despite medication optimization, experience motor symptoms that cannot be satisfactorily ameliorated by medication.

Article 2: Progressive Supranuclear Palsy, Corticobasal Degeneration, and Multiple System Atrophy

Paul Greene, MD. Continuum (Minneap Minn). August 2019; 25 (4 Movement Disorders):919–935.

ABSTRACT

PURPOSE OF REVIEW:

Patients who have parkinsonian features, especially without tremor, that are not responsive to levodopa, usually have one of these three major neurodegenerative disorders rather than Parkinson disease: progressive supranuclear palsy (PSP), multiple system atrophy (MSA), or corticobasal degeneration (CBD). Each of these disorders eventually develops signs and symptoms that distinguish it from idiopathic Parkinson disease, but these may not be present at disease onset. Although these conditions are not generally treatable, it is still important to correctly diagnose the condition as soon as possible.

RECENT FINDINGS:

In recent years, it has been increasingly recognized that thesymptoms of these diseases do not accurately predict the pathology, and the pathology does not accurately predict the clinical syndrome. Despite this, interest has grown in treating these diseases by targetingmisfolded tau (in thecase of PSP and CBD) and misfolded α-synuclein (in the case of MSA).

SUMMARY:

Knowledge of the characteristic signs and symptoms of PSP, MSA, and CBD are essential in diagnosing and managing patients who have atypical parkinsonian syndromes.

KEY POINTS

- Patients with parkinsonian features who do not improve with levodopa usually do not have idiopathic Parkinsondisease and often have either progressive supranuclear palsy, multiple system atrophy, or corticobasal degeneration.
- Progressive supranuclear palsy is a likely diagnosis in patients with parkinsonian features and earlydevelopment of a supranuclear palsy.
- Some patients with progressive supranuclear palsy do not develop a supranuclear palsy until later in the course of the disease. Early features that suggest progressive supranuclear palsy are an angry or puzzled look, growling speech, early development of dysphagia, and a broad-based gait with abducted arms.
- A minority of patients with the pathology of progressive supranuclear palsy may have signs and symptoms suggesting a variety of conditions, including corticobasal degeneration and, rarely, idiopathic Parkinson disease, primary progressive aphasia, cerebellar ataxia, frontotemporal dementia, and primary lateral sclerosis.
- Other pathologies may produce signs and symptoms suggestive of progressive supranuclear palsy, including Alzheimer disease, some frontotemporal dementias, Whipple disease, Niemann-Pick disease type C, and Gaucher disease.
- The pathology of progressive supranuclear palsy is characterized by deposits of 4-repeat tau in astrocytes and oligodendroglia in multiple regions of the basal ganglia and cortex of the brain.
- Preliminary studies of agents that interfere with the formation or spread of misfolded tau are being conducted with the hope of stopping or slowing the progression of progressive supranuclear palsy.
- The clinical hallmarks of classic corticobasal degeneration are parkinsonism combined with unilateral dystonia, myoclonus, and cortical deficits such as apraxia, cortical sensory loss, and alien limb phenomenon.
- As in progressive supranuclear palsy, the pathology of corticobasal degeneration also involves widespread deposition of 4-repeat tau but also includes asymmetric cortical atrophy and neuronal, oligodendroglial, and astrocytic deposits distinct from the deposits in progressive supranuclear palsy.
- As with progressive supranuclear palsy, multiple pathologies may mimic the signs and symptoms of corticobasal degeneration, including progressive supranuclear palsy, Alzheimer disease, Pick disease, and Creutzfeldt-Jakob disease. When this happens, it is known as corticobasal syndrome. Similarly, the pathology of corticobasal degeneration may present as progressive supranuclear palsy, primary nonfluent aphasia, Alzheimer disease, and other conditions.
- Middle-aged patients presenting with parkinsonism, autonomic insufficiency, and ataxia usually have multiple system atrophy. However, many patients with multiple system atrophy may initially only have symptoms in one or two of these categories, making the correct diagnosis more difficult. The development of laryngeal stridor is a strong clue that the diagnosis is multiple system atrophy.
- Unlike progressive supranuclear palsy and corticobasal degeneration, multiple system atrophy is a synucleinopathy, not a tauopathy. This may have implications for future treatments.
- Like progressive supranuclear palsy and corticobasal degeneration, there are widespread pathologic abnormalities in multiple systematrophy, but the characteristic inclusions contain α-synuclein, not tau. The first identified abnormality was a glial cytoplasmic inclusion containing α-synuclein, but neuronal inclusions havealso been identified. Rarely, Lewy bodies are found in multiple system atrophy.
- There has been an intensive search for genetic risk factors for these conditions. Some candidate genes have been identified, but this has not currently led to any therapeutic innovations. Some genes have been identified thatoccasionally produce one of these syndromes, but those, so far, have been responsible for only a small percentage of known cases.

- The typical features of progressive supranuclear palsy (supranuclear palsy), corticobasal degeneration (cortical myoclonus and other focal cortical deficits), and multiple system atrophy (autonomic failure and ataxia) suggest the correct diagnosis but do not achieve both sensitivity and specificity.
- Some symptoms of progressive supranuclear palsy, corticobasal degeneration, and multiple system atrophycan be treated, such as constipation; blepharospasm and other dystonias (with botulinum toxin injections); orthostasis; depression; pain; pseudobulbar affect; and other symptoms.

Article 3: Tics and Tourette Syndrome

Harvey S. Singer, MD, FAAN. Continuum (Minneap Minn). August 2019; 25 (4 Movement Disorders):936–958.

ABSTRACT

PURPOSE OF REVIEW:

The purpose of this article is to present current information on the phenomenology, epidemiology, comorbidities, and pathophysiology of tic disorders and discuss therapy options. It is hoped that a greater understanding of each of these components will provide physicians and caregivers with the necessary information to deliverthoughtful and optimal care to affected individuals.

RECENT FINDINGS:

Recent advances include the finding that Tourette syndrome is likely due to a combination of several different genes, both low-effect and larger-effect variants, plus environmental factors. Pathophysiologically, increasing evidence supports involvement of the cortical–basal ganglia–thalamocortical circuit; however, the primary location and neurotransmitter remain controversial. Behavioral therapy is first-line treatment, and pharmacotherapy is based on tic severity. Several newer therapeutic agents are under investigation (eg, valbenazine, deutetrabenazine, cannabinoids), and deep brain stimulation is apromising therapy.

SUMMARY:

Tics, defined as sudden, rapid, recurrent, nonrhythmic motormovements or vocalizations, are essential components of Tourette syndrome. Although some tics may be mild, others can cause significant psychosocial, physical, and functional difficulties that affect daily activities. In addition to tics, most affected individuals have coexisting neuropsychological difficulties (attention deficit hyperactivity disorder, obsessive compulsive disorder, anxiety, mood disorder, disruptive behaviors, schizotypal traits, suicidal behavior, personality disorder, antisocial activities, and sleep disorders) that can further impact social and academic activities or employment.

KEY POINTS

- Tics have several characteristics that are useful in identifying their presence, including precipitating factors, a waxing and waning pattern, admixture of new and old tics, a premonitory urge thatresolveswhen the tic is done, reduction when engrossed, and variable severity.
- Tics can be highly variable and fluctuate, and an individual's tic repertoire evolves over time.
- The diagnosis of a tic disorder is based on historical features and observation of the tics; no definitivediagnostic laboratory test has yet been established.
- Simple tics are relatively common in childhood, with reports of prevalence (the number of cases in thepopulation at a given time) being 6% to 12% (range of 4% to 24%).

- Most individuals with Tourette syndrome have at least one comorbid/coexisting neuropsychological problem.
- Coexisting neuropsychological issues add a significant additional burden to patients with Tourette syndrome or chronic motor or vocal tic disorder.
- Tourette syndrome is currently classified as a polygenic inherited disorder, suggesting that a combination of a variety of genes (some common, some with a loweffect or rare, and others having a larger effect) and environmental factors are all involved in its transmission.
- The existence of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and its proposed therapy are extremely controversial.
- A series of parallel cortical–basal ganglia–thalamocortical circuits provide a framework for understanding the pathophysiology of tics and associated behaviors.
- Identification of the true primary site of anatomic abnormality in Tourette syndrome remains an area of active discussion.
- It is important to recognize that within a multitransmitter interconnected system, a successful pharmacotherapy does not necessarily indicate that the primary neurotransmitter abnormality is being targeted.
- The establishment of an effective therapeutic plan for Tourette syndrome and tics requires careful initialassessment of tics, determining the presence of co-occurring issues, and clarifying the resulting impairment of each issue.
- The first step in treatment of Tourette syndrome is education of the patient, his/her family, and the school or workplace about the diagnosis, its potential coexisting issues, and indications for therapy.
- Specific criteria for initiating behavioral or pharmacologic ticsuppressing therapy include the presence of psychosocial problems, tic-induced musculoskeletal/physical difficulties, and disruption of classroom/work settings.
- Various practice guidelines have suggested that habit reversal training, more specifically Comprehensive Behavioral Intervention for Tics (CBIT) should be the first-line intervention for tics.
- In general, a two-tiered approach to the use of pharmacotherapy is recommended for treating tics, with use of tier 1 medications for milder tics and use of tier 2medications reserved for more difficult to control symptoms.
- Deep brain stimulation is a stereotactic treatment that has significant potential for the treatment of tics.

Article 4: Tremor

Elan D. Louis, MD, MS, FAAN. Continuum (Minneap Minn). August 2019; 25 (4 Movement Disorders):959–975.

ABSTRACT

PURPOSE OF REVIEW:

Tremor may be defined as an involuntary movement that is rhythmic (ie, regularly recurrent) and oscillatory (ie, rotating around a central plane) and may manifest in a variety of ways; accordingly, tremor has a rich clinical phenomenology. Consequently, the diagnosis of tremor disorders can be challenging, and misdiagnoses are common. The goal of this article is to provide the reader with straightforward approaches to the diagnosis and treatment of tremors.

RECENT FINDINGS:

Focused ultrasound thalamotomy of the ventral intermediate nucleus of the thalamus is an emerging and promising therapy for the treatment of essential tremor.

SUMMARY:

The evaluation should start with a detailed tremor history followed by a focused neurologic examination, which should attend to the many subtleties of tremor phenomenology. Among

other things, the history and examination are used to establish whether the primary tremor is an action tremor (ie, postural, kinetic, or intention tremor) or a resting tremor. The clinician should then formulate two sets of diagnoses: disorders in which action tremor is the predominant tremor versus those in which resting tremor is the predominant tremor. Among the most common of the former type are essential tremor, enhanced physiologic tremor, drug-induced tremor, dystonic tremor, primary writing tremor, orthostatic tremor, and cerebellar tremor. Parkinson disease is the most commondisorder of resting tremor. This article details the clinical features of each of these disorders, as well as those of additional tremor disorders. Thediagnosis of tremor disorders is challenging. The approach to evaluating apatientwith a tremor involves a history and a neurologic examination that is focused on the nuances of tremor phenomenology, which are numerous.

KEY POINTS

- Tremors are involuntary movements that are both rhythmic and oscillatory.
- An initial step in evaluating patients with tremor is to determine whether the tremor is primarily present at rest or with activity.
- The key feature of essential tremor is kinetic tremor.
- The kinetic tremor of essential tremor is typically slightly asymmetric.
- Approximately one-half of patients with essential tremor exhibit intention tremor during the fingernose-finger maneuver.
- The postural tremor in essential tremor is generally out of phase; this can create a seesaw effect when thepatients' arms are held in the wing-beat position.
- Resting tremor may occur in patients with severe or long-standing essential tremor, but it is restricted to the arms.
- Neck tremor is several times more common in women with essential tremor than in men with essential tremor.
- Neck tremor is always pathologic. It is not a feature of enhanced physiologic tremor.
- Although limb tremor may be present, head tremor should not be a feature of drug-induced action tremor.
- The tremor in dystonia may be neither rhythmic nor oscillatory.
- Dystonic head tremor often persists after the patient lies on his or her back; this is generally not true of essential tremor.
- Primary writing tremor is a tremor that occurs mainly while writing but not during other tasks that involve the hands.
- In some cases, orthostatic tremor may be heard when a stethoscope is placed over the affected leg; the tremormakes a sound like a distant helicopter.
- The clinical phenomenology of tremor of cerebellar origin is heterogeneous, and it extends beyond that ofintention tremor to include postural tremor, kinetic tremor, resting tremor, and orthostatic tremor.
- Rubral tremor is strikingly asymmetric, and it has resting, postural, and kinetic components.
- Psychogenic tremors often have an abrupt onset.
- Wing-beat tremor is considered a classic tremor in Wilson disease, but it is not the most common type of tremor in that disease.
- Although intention tremor is common in patients with fragile X tremor-ataxia syndrome, kinetic, postural, and resting tremorsmay also occur.
- The resting tremor in Parkinson disease is generally asymmetric.
- In contrast to essential tremor, the jaw tremor of Parkinson disease is more often noted when the patient's mouth is closed and relaxed rather than while the patient is speaking.

Article 5: The Dystonias

H. A. Jinnah, MD, PhD. Continuum (Minneap Minn). August 2019; 25 (4 Movement Disorders):976–1000.

ABSTRACT

PURPOSE OF REVIEW:

This article provides a summary of the state of the art in the diagnosis, classification, etiologies, and treatment of dystonia.

RECENT FINDINGS:

Although many different clinicalmanifestations of dystoniahave been recognized for decades, it is only in the past 5 years that a broadly accepted approach has emerged for classifying them into specific subgroups. The new classification system aids clinical recognition and diagnosis by focusing on key clinical features that help distinguish the many subtypes. In the past few years, major advances have been made inthe discovery of new genes as well advances in our understanding of the biological processes involved. These advances have led to major changes in strategies for diagnosis of the inherited dystonias. An emerging trend is to move away from heavy reliance on the phenotype to target diagnostic testing toward a broader approach that involves large gene panels or whole exome sequencing.

SUMMARY:

The dystonias are a large family of phenotypically andetiologically diverse disorders. The diagnosis of these disorders depends on clinical recognition of characteristic clinical features. Symptomatic treatments are useful for all forms of dystonia and include oral medications, botulinum toxins, and surgical procedures. Determination of etiology is becoming increasingly important because the number ofdisorders is growing and more specific and sometimes disease-modifying therapies now exist.

KEY POINTS

- Dystonic movements are not always slow; they can be rapid or jerky, or resemble tremor.
- Dystonic movements tend to be patterned, not random.
- Dystonic movements are often triggered or worsened by voluntary muscle activity.
- Identification of a geste antagoniste (sensory trick) can be a very helpful clue because it is unique to dystonia and is important to ask patients about.
- The history and examination of patients with dystonia should focus on four areas: body region affected, age at onset, temporal features, and ancillary neurologic problems.
- For the most common focal dystonias that emerge after 40 years of age, laboratory investigations are usually not needed.
- For any dystonia that emerges in a child or young adult, laboratory investigations are guided by the history and examination.
- For almost all classic inherited dystonic disorders in children, late-onset cases or less severe cases are known to occur in adults.
- Elucidating etiology is important because specific treatments are available for several types of dystonia.
- Isolated dystonia may be the initial manifestation for neurologic disorders typically associated with more complex syndromes.
- More than 100 known causes for dystonia exist.
- Genetic forms of dystonia should be referred to by the name of the gene, not the DYT locus name.

- Dystonia results from dysfunction of a motor network that includes the basal ganglia, cerebellum, and sensorimotor cortex.
- All children and young adults with unexplained dystonia must have a trial of levodopa to rule outdopa-responsive dystonia.
- Carbamazepine and related anticonvulsant medications may be remarkably effective at very low doses in patients with paroxysmal kinesigenic dyskinesia.
- When treating dystonia, it is important to customize both the dose and the interval between doses for optimal benefits with botulinum toxin.
- Botulinum toxins are the treatment of first choice for focal and segmental dystonias and sometimes the most discomforting aspects in generalized dystonias.
- Deep brain stimulation is the most commonly offered surgical treatment for dystonia although ablative procedures may be appropriate in some cases.
- Selection of patients with dystonia for surgical intervention should be done by experienced multidisciplinary teams.
- Focused ultrasound is becoming more popular for ablative surgery in patients with dystonia although experience is still limited.

Article 6: Chorea

Pichet Termsarasab, MD. Continuum (Minneap Minn). August 2019; 25 (4 Movement Disorders):1001–1035.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of the approach to chorea in clinical practice, beginning with a discussion of the phenomenologic features of chorea and how to differentiate it from other movement disorders. The diagnostic approach, clinical features of important acquired and genetic choreas, and therapeutic principles are also discussed. Practical clinical points and caveats are included.

RECENT FINDINGS:

C9orf72 disease is the most common Huntington disease phenocopy, according to studies in the European population. Anti-IgLON5 disease can present with chorea. The role of immunotherapies in Sydenhamchorea has increased, and further clinical studiesmay be useful. Benign hereditary chorea is a syndrome or phenotype due to mutations in several genes, including *NKX2-1, ADCY5, GNAO1, PDE10A*. New-generation presynaptic dopamine-depleting agents provide more options for symptomatic treatment of chorea with fewer adverse effects. Deep brain stimulation has been performed in several choreic disorders, but features other than chorea and the neurodegenerative nature should be taken intoconsideration. Studies on genetic interventions for Huntington disease are ongoing.

SUMMARY:

Clinical features remain crucial in guiding the differentialdiagnosis and appropriate investigations in chorea. Given the complexity of most choreic disorders, treating only the chorea is not sufficient. A comprehensive and multidisciplinary approach is required.

KEY POINTS

- Randomness is the key phenomenologic feature of chorea.
- Chorea with quick velocities may look jerky, resembling myoclonic jerks.

- Chorea in one of three body distributions (hemichorea, orobuccolingual involvement, and forehead chorea) can serve as a clue to narrow down the differential diagnoses.
- Structural lesions and systemic disorders (such as nonketotic hyperglycemia and polycythemia vera) can cause hemichorea.
- Sydenham chorea can present with hemichorea or very asymmetric involvement.
- The time course can help classify chorea into acquired and genetic etiologies.
- Age group and known prevalence are very important diagnostic clues in chorea.
- The most common acquired chorea in children is Sydenham chorea.
- The most common genetic chorea in adults is Huntington disease, followed by C9orf72 disease and spinocerebellar ataxia type 17.
- The most common genetic chorea in children is benign hereditary chorea.
- A negative family history does not exclude genetic causes of chorea.
- Huntington disease–like 2 is almost exclusively seen in patients with African ancestry.
- Autoimmune chorea should be included in the differential diagnoses of chorea with a subacute temporal profile.
- Neuropsychiatric features such as irritability, attention deficit hyperactivity disorder, and obsessivecompulsive behavior can be seen in Sydenham chorea.
- It is important to search for an underlying etiology in hormonal-related chorea, including chorea gravidarum and estrogen-induced chorea.
- Nonmotor features in Huntington disease are often more debilitating than chorea itself.
- Chorea is gradually replaced by parkinsonian features in later stages of Huntington disease; thus,the treatment regimen requires revision periodically.
- Delayed initiation of saccades is a hallmark eye movement abnormality in Huntington disease.
- Senile chorea should not be used as a diagnosis, and an underlying etiology should be sought.
- Children with Huntington disease typically do not present with chorea but rather parkinsonism, dystonia, and seizures.
- Age at onset in Huntington disease is determined by the number of CAG repeats, genetic modifiers, and environmental factors.
- Genetic counseling should be considered before ordering genetic testing for Huntington disease.
- Autosomal recessive ataxia syndromes can present with a variety of hyperkinetic movement disorders, including chorea.
- In addition to chorea-acanthocytosis and McLeod syndrome, acanthocytes can also be seen in 10% of Huntington disease–like 2 and pantothenate kinase–associated neurodegeneration as well as abetalipoproteinemia and aceruloplasminemia.
- Patients with McLeod syndrome can benefit from cardiac surveillance and autologous blood transfusion.
- Caudate atrophy is not specific to Huntington disease and can also be seen in other disorders, such aschorea-acanthocytosis and Huntington disease–like 2.
- Benign hereditary chorea syndromes can be due to multiple mutations; the classic benign hereditary chorea is due to *NKX2-1* (*TITF*) mutations. Some patients with *NKX2-1*–related benign hereditary chorea can paradoxically respond to levodopa.
- Patients with choreic disorders can benefit from a multidisciplinary approach. Associated features and comorbidities, such as cognitive and neuropsychiatric features, should be taken into consideration when treating chorea. Mild and nonbothersome chorea does not require treatment. Immunotherapies are treatment options in Sydenham chorea.
- The main pharmacologic targets of chorea are dopaminergic synapses, either at presynaptic orpostsynaptic sites.

Article 7: Ataxia

Sheng-Han Kuo, MD. Continuum (Minneap Minn). August 2019; 25 (4 Movement Disorders):1036–1054.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the symptoms, laboratory and neuroimaging diagnostic tests, genetics, and management of cerebellarataxia.

RECENT FINDINGS:

Recent advances in genetics have led to the identificationof novel genetic causes for ataxia and a more comprehensive understanding of the biological pathways critical for normal cerebellar function.When these molecular pathways become dysfunctional, patients develop cerebellar ataxia. In addition, several ongoing clinical trials for Friedreich ataxia and spinocerebellar ataxia will likely result in novel symptomatic and disease-modifying therapies for ataxia. Antisense oligonucleotides for spinocerebellar ataxias associated with CAG repeat expansions might be a promising therapeutic strategy.

SUMMARY:

Cerebellar ataxias include heterogeneous disorders affecting cerebellar function, leading to ataxic symptoms. Step-by-step diagnosticworkups with genetic investigations are likely to reveal the underlying causes of ataxia. Some disease-specific therapies for ataxia exist, such as vitamin E for ataxia with vitamin E deficiency and thiamine for Wernicke encephalopathy, highlighting the importance of recognizing these forms of ataxia. Finally, genetic diagnosis for patients with ataxia will accelerate clinical trials for disease-modifying therapy and will have prognostic value and implications for family planning for these patients.

KEY POINTS

- **Determining the etiology of cerebellar ataxia iscomplex; however, step-by-step approaches can streamline the diagnostic workflow.**
- **Key questions regarding difficulty running, trouble walking in high heels or barefoot on the beach, andveering toward one side can be helpful in identifying the subtle gait abnormality associated with ataxia.**
- **Patients with ataxia can have a variety of eye movement abnormalities, including nystagmus, hypermetric or hypometric saccades, and ophthalmoplegia.**
- **The gait abnormality associated with cerebellar ataxia can change over the course of the disease.**
- **After establishing the signs of cerebellar ataxia, look for other neurologic signs (eg, tremor, dystonia, parkinsonism, motor neuron signs) as clues to the cause of ataxia.**
- **Laboratory evaluation can be helpful in identifying nutritional and immunologic causes of cerebellar ataxia.**
- **Aside from cerebellar atrophy, specific changes on MRI associated with different forms of cerebellar ataxia can provide important diagnostic clues.**

- The spinocerebellar ataxia nomenclature relates to the autosomal dominant causes of ataxia.
- Autosomal recessive ataxia can be divided into three categories: (1) cerebellar ataxia with predominant sensory neuronopathy, (2) cerebellar ataxia with sensorimotor axonal neuropathy, and (3) cerebellar ataxia without sensory neuropathy.
- Fragile X tremor-ataxia syndrome is the most common cause of X-linked ataxia.
- The first approach to the genetics of ataxia is to investigate for repeat expansions, which are the common causes of autosomal dominant, recessive, and X-linked ataxia.
- Patients with multiple system atrophy can have cerebellar ataxia, parkinsonism, autonomic dysfunction, and pyramidal signs.

Article 8: Myoclonus

John N. Caviness, MD, FAAN. Continuum (Minneap Minn). August 2019; 25 (4 Movement Disorders):1055–1080.

ABSTRACT

PURPOSE OF REVIEW:

This article offers clinicians a strategic approach for making sense of a symptom complex that contains myoclonus. The article presents an evaluation strategy that highly leverages the two major classification schemes of myoclonus. The goal of this article is to link evaluation strategy with diagnosis and treatment of myoclonus.

RECENT FINDINGS:

The growth of medical literature has helped better define myoclonus etiologies. Physiologic study of myoclonus types and etiologies with electrophysiologic testing has provided greater clarity to the pathophysiology of the myoclonus in various diseases. Although studies have been limited, the role of newer treatment agents and methods has made progress.

SUMMARY:

Myoclonus has hundreds of different etiologies. Classification is necessary to evaluate myoclonus efficiently and pragmatically. The classification of myoclonus etiology, which is grouped by different clinical presentations, helps determine the etiology and treatment of the myoclonus. The classification of myoclonus physiology using electrophysiologic test results helps determine the pathophysiology of the myoclonus and can be used to strategize symptomatic treatment approaches. Both basic ancillary testing (including EEG and imaging) and more comprehensive testing may be necessary. Treatment of the underlying etiology is the ideal approach. However, if such treatment is not possible or is delayed, symptomatic treatment guided by the myoclonus physiology should be considered. More controlled study of myoclonus treatment is needed. Further research on myoclonus generation mechanisms should shed light on future treatment possibilities.

KEY POINTS

- The brief, lightninglike muscle contraction defines it as myoclonus.
- Myoclonus is a symptom or sign, not a diagnosis. It occurs in multiple diseases and conditions.
- Evaluation for myoclonus begins with a comprehensive history and neurologic examination that allows the clinical presentation classification into a physiologic, essential, epileptic, or symptomatic category.
- EEG should be the initial electrophysiologic testing for myoclonus without a determined etiology.

- Cortical myoclonus physiology is best defined by brief (<50 ms) EMG discharges and a focal EEG correlating with the myoclonus. Enlarged cortical somatosensory evoked potential wave, abnormal long-latency EMG reflex, and increased corticomuscular coherence are supportive but not confirmatory.
- Cortical-subcortical myoclonus physiology is best defined by generalized epileptiform discharges that occur with the myoclonus. It most commonly takes the form of EEG generalized spike-and-wave discharges.
- Subcortical-nonsegmental myoclonus physiology is defined by one of two patterns: (1) initiation from the brainstem or spinal cord followed by simultaneous rostral and caudal EMG recruitment or (2) multifocal myoclonus EMG discharges. Both patterns show EMG discharges of more than 100 ms.
- Segmental myoclonus physiology is defined by low-frequency rhythmic myoclonus EMG discharges that persist almost continuously, with more than 100 ms duration EMG discharges confined to a few contiguous muscle segments.
- Peripheral myoclonus physiology is defined by a highly variable myoclonus EMG discharge duration confined to a specific root, plexus, or peripheral nerve.
- Physiologic myoclonus is a normal phenomenon. Education and reassurance are usually the best treatments.
- Essential myoclonus is pathologic but chronic with little or no disability. It is not common.
- Epileptic myoclonus etiologies are chronic seizure disorders that have myoclonus as a prominent phenomenon.
- Symptomatic myoclonus is secondary to another disorder, neurologic or non-neurologic. Multiple other symptoms and signs are usually present or tied to definable pathology.
- A determined etiology for themyoclonus will allow the clinician to determine whether the underlying myoclonus cause is treatable or curable.
- If treatment of the etiology of myoclonus is not possible or is delayed, then symptomatic treatment should be considered if overall improvement is possible when weighing potential side effects.
- Symptomatic treatment best aligns with the myoclonus physiology classification. An agent that suppresses a specific myoclonus physiology can potentially do that for all myoclonus cases with that common physiology.
- Cortical myoclonus treatments are also antiseizure agents and are able to reduce the hyperexcitability of the cortex resulting in suppression of cortical myoclonus.
- Subcortical myoclonus agents operate at the subcortical movement areas such as the basal ganglia and brainstem.
- Deep brain stimulation has been used successfully for the myoclonus-dystonia syndrome.
- Botulinum toxin injections have been used for segmental and peripheral myoclonus.

Article 9: Tardive Syndromes

Joseph H. Friedman, MD, FAAN, FANA. Continuum (Minneap Minn). August 2019; 25 (4 Movement Disorders):1081–1098.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the history, nosology, clinical features, epidemiology, and treatment of tardive syndromes.

RECENT FINDINGS:

The major advance in the field of tardive syndromes has been the development and US Food and Drug Administration (FDA) approval of two vesicular monoamine transporter type 2 inhibitors, valbenazine and deutetrabenazine, for treating tardive syndromes. These medications are derivatives of tetrabenazine and reduce dyskinetic movements by reducing dopamine stimulation. Treatment is not curative, and the medications reduce, or "mask," symptoms but presumablywithout adding to the long-term risk of increased involuntary movements believed to

accrue from suppressive treatment with dopamine receptor–blocking drugs. A confounding advance has been the accumulation of data finding that second-generation antipsychotics, also known as atypical antipsychotics, may not be safer than first-generation antipsychotics in causing tardive syndromes. The public health risk of tardive syndromes may actually have increased as some second-generation antipsychotics, widely promoted to both doctors and patients, are increasingly used asantidepressants.

SUMMARY:

Tardive syndromes remain a public health risk. Second-generationantipsychotics have not been proven to have less risk than first-generation drugs in causing tardive syndromes and are nevertheless being used more widely to treat depression, bipolar disease, and insomnia. Symptomatic treatment for tardive syndromes is available, although expensive.

KEY POINTS

- The relationship between tardive dyskinesia and antipsychotics took several years to establish and was initially thought to be rare.
- All definitions of tardive dyskinesia or tardive syndromes require at least several weeks exposure to a drug preceding the development of a new movement disorder that persists for several weeks while on the drug, or off the drug, and is not better explained by an alternative etiology.
- There are several different tardive syndromes. Dyskinesia and stereotypies are very similar, while akathisia and dystonia are very different. The others are rare. Patients may have more than one syndrome. It is important to note that patients often have more than one tardive syndrome.
- While widely believed to represent dopamine supersensitivity, the pathophysiology of tardive syndromes remains unknown, and no explanation explains the variety of tardive syndromes.
- Tardive syndromes remain a major problem for patients treated with dopamine receptor–blocking drugs. While there are data to suggest that second-generation antipsychotics are less likely to cause a tardive syndrome than first-generation antipsychotics, these data are not convincing, and the largest study performed to answer this question did not find a difference.
- Deutetrabenazine and valbenazine are approved treatments for tardive syndromes, and probably work best for nondystonic disorders. Replacing the neuroleptic with clozapine at a dose to treat the psychosis may be very helpful, especially for dystonic syndromes.
- Botulinumtoxin is likely to be helpful for all focal dystonias, including tardive dystonias. Deep brain stimulation, with globus pallidus interna as the target, may be helpful for dystonic or choreoathetoid tardive disorders.

Article 10: Movement Disorders in Children

Toni S. Pearson, MBBS; Roser Pons, MD. Continuum (Minneap Minn). August 2019; 25 (4 Movement Disorders):1099–1120.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of the clinical features and disorders associated with movement disorders in childhood. This article discusses movement disorder phenomena and their clinical presentation in infants and children and presents a diagnostic approach to suspected genetic disorders with a focus on treatable conditions.

RECENT FINDINGS:

Technologic advances inmolecular genetic testing over thepast decade continue to lead to the discovery of new diseases. This article discusses the clinical presentation and early experience with treatment for several recently described genetic forms of infantile-onset and childhood-onset dystonia and chorea.

SUMMARY:

The clinical spectrum of pediatric movement disorders is broad and heterogeneous, ranging from acute or transient self-limited conditions to conditions that cause profound lifelong motor disability. Most movement disorders in childhood are chronic, and the large number of rare, genetic conditions associated with pediatricmovement disorders can pose a significant diagnostic challenge. Recognition of distinctive diagnostic clues in the history and examination can facilitate the diagnosis of potentially treatable disorders.

KEY POINTS

- Many causes of childhood ataxia exist that may be broadly divided into acute, intermittent, and chronic categories.
- Myoclonus can be physiologic (hypnic myoclonus), or it can be the manifestation of a broad range of systemic disorders and metabolic derangements.
- Parkinsonism in children differs from parkinsonism in adults, often manifesting as bradykinesia/hypokinesia, dystonia, and axial hypotonia; tremor is often absent.
- Neonates, infants, and toddlers may manifest with a number of benign and transient movement disorders such as myoclonus, dystonia, or tremor; development is normal, and treatment is not required.
- The most common etiologies underlying acute movement disorders in a previously healthy child are autoimmune, drug-induced, and psychogenic.
- In a child with a dyskinetic cerebral palsy phenotype, absent risk factors for perinatal brain injury, and normal brain MRI, investigation for an underlying genetic disorder should be considered. Some genetic disorders have disease-specific treatment that improves symptoms and developmental outcome.
- The primary monoamine neurotransmitter disorders comprise defects of enzymes, cofactors, and transporters involved in the metabolism and homeostasis of the catecholamines and serotonin.
- In biogenic amine disorders, neuroimaging is usually normal, and diagnosis is confirmed with the analysis of monoamine neurotransmitter metabolites and pterins in CSF and with molecular analysis.
- The epileptic-dyskinetic encephalopathies are a heterogeneous group of disorders that are associated with a spectrum of movement disorders, most frequently chorea, but also dystonia and stereotypies.
- Huntington disease in childhood often presents with an akinetic-rigid syndrome rather than chorea.
- Myoclonus-dystonia is a rare genetic movement disorder characterized by a combination of nonepileptic myoclonic jerks and dystonia.
- Myoclonus-dystonia is compatible with an active and normal life span; however, some patients have a progressive course leading to considerable disability. Treatment is usually disappointing.
- Progressive myoclonic epilepsy is characterized by action myoclonus, epileptic seizures, and progressive neurologic decline. The majority of genes involved in progressive myoclonic epilepsy encode lysosomal proteins and are inherited in an autosomal recessive pattern. The largest group of progressive myoclonic epilepsies are the neuronal ceroid lipofuscinosis.
- Juvenile parkinsonism refers to hereditary conditions with onset before the age of 21 years that clinically resemble Parkinson disease but with different histopathologic characteristics.
- In juvenile parkinsonism disease, progression is slower than in idiopathic Parkinson disease. Patients have a marked response to levodopa, although dyskinesias and motor fluctuations occur early.
- The classic genetic paroxysmal dyskinesias may be clinically distinguished from one another by the episode triggers, episode duration, and the presence or absence of interictal neurologic features.

Article 11: Psychogenic (Functional) Movement Disorders

Mary Ann Thenganatt, MD; Joseph Jankovic, MD, FAAN. Continuum (Minneap Minn). August 2019; 25 (4 Movement Disorders):1121–1140.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews a practical approach to psychogenic movement disorders to help neurologists identify and manage this complex group of disorders.

RECENT FINDINGS:

Psychogenic movement disorders, also referred to as functional movement disorders, describe a group of disorders that includes tremor, dystonia, myoclonus, parkinsonism, speech and gait disturbances, and other movement disorders that are incongruent with patterns of pathophysiologic (organic) disease. The diagnosis is based on positive clinical features that include variability, inconsistency, suggestibility, distractibility, suppressibility, and other supporting information. While psychogenic movement disorders are often associated with psychological and physical stressors, the underlying pathophysiology is not fully understood. Although insight-oriented behavioral and pharmacologic therapies are helpful, a multidisciplinary approach led by a neurologist, but also including psychiatrists and physical, occupational, and speech therapists, is needed for optimal outcomes.

SUMMARY:

The diagnosis of psychogenic movement disorders is based on clinical features identified on neurologic examination, and neurophysiologic and imaging studies can provide supporting information.

KEY POINTS

- Early diagnosis of a psychogenic movement disorder is important as longer duration of symptoms is associated with poor outcome.
- Diagnosis of a psychogenic movement disorder is based on positive signs and symptoms and isnot a diagnosis of exclusion.
- Psychogenic movement disorders are typically sudden in onset and rapidly progress to severe disability.
- In patients with psychogenic tremor, variability of tremor frequency and direction is common, as well as suggestibility, distractibility, and entrainability.
- Total body tremor is a typical manifestation of psychogenic tremor, including a bobbing of the head and trunk.
- A rapid-onset fixed dystonia is the typical phenotype of psychogenic dystonia.
- A clinical diagnosis of propriospinal myoclonus is unreliable, and more than 50% of cases are psychogenic.
- Psychogenic gait often presents as slowness and buckling at the knees, dramatic compensatory measures, and improvement with minimal support.
- Psychogenic parkinsonism often coexists with organic parkinsonism.
- Psychogenic facial spasms are typically tonic contractions of the lower face with ipsilateral platysma contraction and downward deviation of the lip.
- Psychogenic tics typically lack a premonitory urge, suppressibility, and often lack a family or childhood history of tics.

- Psychogenic paroxysmal dyskinesias have variable duration and phenomenology and often have atypical triggers.
- The neurologist's role involves explaining the diagnosis, providing educational information, coordinating treatment and providing neurologic follow-up to patients diagnosed with psychogenic movement disorders.
- Patients with psychogenic movement disorders may benefit from psychotherapy and psychotropic medications to treat depression and anxiety.
- Specialized physical therapy focusing on motor retraining can be helpful for patients with psychogenic movement disorders.
- Functional MRI studies have demonstrated impaired self-agency and dysfunctional emotional processing in patients with psychogenic movement disorders.

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Multiple Sclerosis and Other CNS Inflammatory Diseases

Article 1: Multiple Sclerosis Risk Factors and Pathogenesis

Bardia Nourbakhsh, MD, MAS; Ellen M. Mowry, MD, MCR, FAAN, FANA. Continuum (Minneap Minn). June 2019; 25 (3 Multiple Sclerosis and Other CNS Inflammatory Diseases):596–610.

ABSTRACT

PURPOSE OF REVIEW:

This article summarizes recent advances in the identification of genetic and environmental factors that affect the risk of developing multiple sclerosis (MS) and the pathogenic processes involved in acute relapses and relapse-independent disability progression.

RECENT FINDINGS:

The number of single-nucleotide polymorphisms associated with increased risk of MS has increased to more than 200 variants. The evidence for the association of Epstein-Barr virus infection, vitamin D deficiency, obesity, and smoking with increased risk of MS has further accumulated, and, in cases of obesity and vitamin D deficiency, the evidence for causal association has strengthened. Interactions between genetic and environmental factors have been studied more extensively. Dietary factors and changes in the gut microbiota are emerging as possible modulators of the disease risk. Several processes important to MS pathogenesis have been newly investigated or investigated more comprehensively, including the role of B cells, innate immune cells, meningeal inflammation, cortical and gray matter demyelination, and early axonal and neuronal loss.

SUMMARY:

MS is a complex disease in which the interaction between genetic and environmental factors causes a cascade of events, including activation of the adaptive and innate immune system, blood-brain barrier breakdown, central nervous system demyelination, and axonal and neuronal damage with variable degrees of repair. These events manifest as potentially reversible focal neurologic symptoms or progressive nonremitting physical and cognitive disability, or both. Advances in the understanding of the risk factors and pathogenic mechanisms of MS have resulted in improved therapeutic strategies. The results of ongoing or future studies are needed to successfully and fully translate these advances into clinical practice.

KEY POINTS

- Unlike several other common neurologic diseases (such as Alzheimer disease, Parkinson disease, and amyotrophic lateral sclerosis), no mendelian form of multiple sclerosis has thus far been reported.
- No single autoantigen, autoantibody, or infectious agent has thus far been unequivocally associated with multiple sclerosis.
- Autoreactive lymphocytes that gain access to the central nervous system start a pathogenic cascade that culminates in demyelination, neuroaxonal degeneration, synaptic loss, dying-back oligodendrogliopathy, and, eventually, tissue loss and astrogliosis.
- Demyelination in multiple sclerosis is not confined to the white matter, and cortical and deep gray matter demyelination can be detected pathologically and is present even in early stages of the disease.
- Both T lymphocytes and B lymphocytes, as well as innate immune mechanisms, participate in multiple sclerosis pathogenesis.
- Although demyelination in the central nervous system is the hallmark of multiple sclerosis, axonal injury is present from the earliest stages of the disease and is a major contributor to physical and cognitive disability.
- More than 200 genetic variants have been discovered to be associated with modifying the risk of multiple sclerosis.
- Low sunlight exposure, vitamin D deficiency, obesity, and smoking are factors with strong evidence for association with multiple sclerosis risk.
- Many infectious agents have been reported to be associated with multiple sclerosis risk; however, only Epstein-Barr virus infection has been consistently shown to be a risk factor.
- Exposure to several risk factors for developing multiple sclerosis (including Epstein-Barr virus infection and obesity) during adolescence appears to be more detrimental than exposure in adulthood.
- Statistical interactions between risk factors and mendelian randomization studies have provided evidence for the causal association of several environmental factors and the risk of multiple sclerosis.
- Lung irritation from inhalation of cigarette smoke is likely the mediator of association between smoking and multiple sclerosis risk.

Article 2: Diagnosis, Differential Diagnosis, and Misdiagnosis of Multiple Sclerosis

Andrew J. Solomon, MD. Continuum (Minneap Minn). June 2019; 25 (3 Multiple Sclerosis and Other CNS Inflammatory Diseases):611–635.

ABSTRACT

PURPOSE OF REVIEW:

The diagnosis of multiple sclerosis (MS) is often challenging. This article discusses approaches to the clinical assessment for MS that may improve diagnostic accuracy.

RECENT FINDINGS:

Contemporary diagnostic criteria for MS continue to evolve, while knowledge about diseases that form the differential diagnosis of MS continues to expand. Recent data concerning causes of MS misdiagnosis (the incorrect assignment of a diagnosis of MS) have further informed approaches to syndromes that may mimic MS and the accurate diagnosis of MS.

SUMMARY:

This article provides a practical update on MS diagnosis through a discussion of recently revised MS diagnostic criteria, a renewed consideration of MS differential diagnosis, and contemporary data concerning MS misdiagnosis.

KEY POINTS

- Diagnosis of relapsing-remitting multiple sclerosis begins with confirmation of objective evidence of a syndrome typical for multiple sclerosis.
- Knowledge of the recent revisions to the 2017 McDonald criteria is essential for the proper use of paraclinical (ie, visual evoked potentials, CSF examination) and radiographic data to substitute for a second clinical attack for the demonstration of dissemination in space and dissemination in time for the diagnosis of multiple sclerosis.
- Objective evidence of a demyelinating syndrome typical for multiple sclerosis demonstrating both dissemination in space and dissemination in time must be accompanied by a search for "no better explanation" to confirm a diagnosis of multiple sclerosis.
- A syndrome typical for multiple sclerosis may also exhibit characteristics atypical for multiple sclerosis, suggesting a specific alternative diagnosis.
- The demographic profile of patients presenting with syndromes typical for multiple sclerosis may provide an important red flag prompting evaluation for alternative diagnoses.
- Noninflammatory conditions may also be mistaken for a typical presentation of multiple sclerosis. Knowledge of broad red flags suggesting a structural, functional, metabolic, infectious, neoplastic, or other disease may lead to a specific alternative diagnosis.
- The McDonald criteria have not been evaluated in patients presenting with atypical syndromes or typical syndromes with red flags, and additional clinical, paraclinical, or radiographic evaluation and monitoring is necessary to confirm a diagnosis of multiple sclerosis.
- In patients presenting to establish care with a preexisting diagnosis of multiple sclerosis, reassessment of the accuracy of multiple sclerosis diagnosis is prudent.
- The diagnosis of primary progressive multiple sclerosis and its mimics differs from that of relapsing-remitting multiple sclerosis and requires a thorough understanding of the assessment of clinical progression.
- Misdiagnosis of multiple sclerosis is often caused by misapplication of the McDonald criteria in patients with atypical syndromes, overreliance on or misunderstanding of MRI dissemination in space, or consideration of historical episodes of symptoms without objective evidence of a central nervous system lesion for demonstration of dissemination in time.

Article 3: Phases and Phenotypes of Multiple Sclerosis

Orhun H. Kantarci, MD. Continuum (Minneap Minn). June 2019; 25 (3 Multiple Sclerosis and Other CNS Inflammatory Diseases):636–654.

ABSTRACT

PURPOSE OF REVIEW:

This article describes the dynamic evolution of multiple sclerosis (MS) through its phases and the impact of this understanding on treatment decisions.

RECENT FINDINGS:

MS consists of three phases: (1) the high-risk phase, (2) the relapsing-remitting phase, and (3) the progressive phase. Increasingly, subclinical disease activity is becoming an integral part of our definition of disease course in MS. In many patients, the relapsing-remitting phase starts as subclinical activity, likely long before they present with a clinically isolated syndrome. Differentiating progressive MS subgroups is also becoming less relevant. This is illustrated by comparing progressive MS that evolves from an asymptomatic state in individuals with

radiologically isolated syndrome (primary progressive MS) and symptomatic individuals with relapsing-remitting MS (secondary progressive MS). In each case, the background disease activity and pathology can be indistinguishable. These phases evolve on a continuum and largely follow the aging process with little influence by the preceding clinical activity level. Recently, it also became evident that one or a few poorly recovered relapses at the beginning of clinical manifestations of MS predict much earlier progressive MS onset.

SUMMARY:

These findings suggest that interventions to prevent progressive MS, when they become available for clinical practice, may need to be considered as early as when the asymptomatic radiologically isolated syndrome is detected. This early treatment approach is being evaluated with ongoing trials with available disease-modifying therapies. In contrast, continuing the use of disease-modifying therapy beyond a certain age may have little benefit. However, being in the progressive phase of MS is not, in itself, an argument against disease-modifying therapy use in active disease in younger patients.

KEY POINTS

- Current disease course classification in multiple sclerosis consists of three phases: the multiple sclerosis high-risk phase, the relapsing-remitting phase, and the progressive phase.
- Progression is the insidious and irreversible worsening of neurologic function due to multiple sclerosis over years.
- *Active disease* in multiple sclerosis is defined as new symptomatic relapses or asymptomatic MRI activity (contrast-enhancing T1-hyperintense lesions, new T2-hyperintense lesions, or enlarging T2-hyperintense lesions).
- Worsening disability can be due to the stepwise accumulation of neurologic deficit from partially recovered relapses, the insidious accumulation of neurologic deficit from a progressive disease course, a combination of both, or other multiple sclerosis or non–multiple sclerosis-related factors.
- The relapsing-remitting multiple sclerosis diagnosis that most clinicians are familiar with requires the presence of multiple clinically distinct events affecting different parts of the central nervous system separated in time (arbitrarily defined as at least 1 month apart). This operational diagnostic rule, core to understanding the diagnosis of multiple sclerosis, is referred to as *dissemination in time and space*.
- When a patient presents with symptoms not typical of multiple sclerosis (MS) and an MRI is obtained that fulfills the diagnostic imaging criteria, a diagnosis of radiologically isolated syndrome is given. When these patients develop their first MS symptom, they fulfill the criteria for single-attack MS (30% in 5-year follow-up). This evolution is significantly faster in pediatric radiologically isolated syndrome (60% in 1-year follow-up).
- Onset of the progressive phase of multiple sclerosis seemingly is age dependent but agnostic for disease duration and preprogressive phase.
- Several clinically useful predictors of evolution to progressive multiple sclerosis (other than age) are having spinal cord lesions, being male, consuming tobacco, being obese, and having a low serum 25-hydroxyvitamin D_3 level. Even in the absence of specific medications targeting progression alone in multiple sclerosis, some of these factors are modifiable and, together with an active lifestyle and physical therapy, can potentially help build nervous system reserve and resistance to injury.
- Disease-modifying therapies are efficacious early in multiple sclerosis, but the utility of continuing them in patients older than age 60 should be considered on an individual basis.
- Seemingly a pathologic hallmark of progressive multiple sclerosis, smoldering plaques peak in frequency at around the fifth decade, a time when the dominant plaque type also switches from active to inactive plaques, mirroring the independent epidemiologic observation of established mean age of progressive multiple sclerosis onset of 45 years.

Article 4: Management of Multiple Sclerosis Relapses

Pavle Repovic, MD, PhD. Continuum (Minneap Minn). June 2019; 25 (3 Multiple Sclerosis and Other CNS Inflammatory Diseases):655–669.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of the clinical and pathologic features of multiple sclerosis (MS) relapses and reviews evidence-based approaches to their treatment.

RECENT FINDINGS:

Despite the increasing number and potency of MS treatments, relapses remain one of the more unpredictable and disconcerting disease aspects for many patients with MS, making their accurate recognition and treatment an essential component of good clinical care. The expanding range of relapse treatments now includes oral corticosteroids, comparable in efficacy to IV methylprednisolone at a fraction of the cost. While this development improves access to prompt treatment, it also underscores the importance of recognizing mimics of MS relapses to reduce corticosteroid overuse and its attendant risks.

SUMMARY:

Like MS itself, MS relapse remains primarily a clinical diagnosis. The treatment options for MS relapse include corticosteroids, adrenocorticotropic hormone (ACTH), plasma exchange, and rehabilitation, used singly or sequentially, with the goal of limiting the duration and impact of associated disability. Even when treated promptly and effectively, clinical or subclinical sequelae of MS relapses frequently remain.

KEY POINTS

- Typical manifestations of multiple sclerosis relapses include optic neuritis, spinal cord syndromes, and brainstem syndromes.
- The shared pathologic substrate of multiple sclerosis relapses is impaired axonal conduction resulting from the combined effects of demyelination, inflammation, and variable degree of neuronal loss.
- Viral and bacterial infections increase the risk of multiple sclerosis relapse.
- Resolution of the inflammatory phase of a multiple sclerosis relapse is followed by a reparative phase.
- Even when symptoms are unequivocally multiple sclerosis–related, a distinction needs to be made between a bona fide multiple sclerosis relapse and a pseudorelapse.
- Fluctuation of symptoms in patients with multiple sclerosis is attributed to variable efficiency of repair following a relapse.
- *Uhthoff phenomenon* refers to reoccurrence of a neurologic deficit from an earlier relapse in the setting of increased core body temperature, classically observed with exercise.
- Several clinical trials and two meta-analyses provide evidence that high-dose corticosteroids hasten neurologic recovery after multiple sclerosis relapse.
- Oral steroids are less expensive, somewhat more convenient, and no less effective than IV steroids for the treatment of multiple sclerosis relapses.
- Given the considerable frequency of steroid side effects, a proactive approach to minimize their impact on patients is recommended.
- Compared to corticosteroids, adrenocorticotropic hormone use in multiple sclerosis relapses is not well defined.

- Second-line treatment options for multiple sclerosis relapse include repetition of corticosteroid treatment (sometimes using a different dose, route, or type of steroid), adrenocorticotropic hormone, and plasma exchange.
- In one study, plasma exchange led to significant improvement in 42% of patients who remained severely impaired after relapses treated with high-dose corticosteroids, compared to only 5% with sham treatment.
- The decision whether to treat or monitor a multiple sclerosis relapse should be made jointly between a patient and a clinician, considering the impact of both the relapse and the proposed treatment on a patient.

Article 5: Clinically Isolated Syndrome and Early Relapsing Multiple Sclerosis

Luanne M. Metz, MD, FRCPC. Continuum (Minneap Minn). June 2019; 25 (3 Multiple Sclerosis and Other CNS Inflammatory Diseases):670–688.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews management of clinically isolated syndrome and early relapsing-remitting multiple sclerosis (MS). It provides a general approach to patient management and determination of prognosis, reviews first-line disease-modifying therapies, and provides an approach to treatment selection.

RECENT FINDINGS:

Revision of the MS diagnostic criteria allows an earlier MS diagnosis, which reduces diagnostic uncertainty and often allows additional treatment options. Identification of factors that influence disease activity and progression highlights the importance of counseling patients about behavior modifications that, along with disease-modifying therapy, may improve long-term outcomes. Recommended lifestyle modifications include smoking cessation, vitamin D supplementation, a healthy diet, maintaining a healthy weight, remaining active, and management of cardiovascular risk factors. Identifying individuals at high risk for future disability allows them to make informed decisions about the use of highly effective, higher-risk disease-modifying therapies.

SUMMARY:

Patients with clinically isolated syndrome, even those with only dissemination in space but not dissemination in time, and patients with relapsing-remitting MS and disease activity within the prior 2 years, are at high risk of disease activity within the next 2 years. Lifestyle modification suggestions and disease-modifying therapy should be considered. Treatment decisions should be made in collaboration with patients using the shared decision-making approach.

KEY POINTS

- A serious diagnosis such as multiple sclerosis may motivate people toward a healthy lifestyle. Diagnosis provides the opportunity to inform patients of health behaviors that are associated with worse multiple sclerosis outcomes.
- Education and supported self-management are the mainstays of chronic disease management.
- Patients at low risk of disease activity over the short term are less likely to benefit from disease-modifying therapy but may still benefit from disease monitoring because risk assessment is not precise.
- In clinically isolated syndrome, the chance of new clinical or MRI activity is 60% to 70% within 6 months and 80% to 90% within 2 years.

- Factors associated with greater risk of long-term disability may identify those most likely to benefit from initiation of highly effective therapy or additional vigilance in monitoring disease-modifying therapy effectiveness.
- The main advantage of the injectable therapies interferon beta and glatiramer acetate is their long-term safety profile. The main disadvantages are modest efficacy and limited tolerance and convenience because they are injectable.
- The first-line oral therapies dimethyl fumarate and teriflunomide are convenient, but they are relatively new and cause immune suppression long term. Safety, including a long-term risk of malignancy, is a concern. Teriflunomide must be used with caution in women of childbearing age because of the risk of fetal malformation.
- A shared decision-making process should be used to select a preferred disease-modifying therapy option.
- Delays in disease-modifying therapy should be avoided. The risk of reaching an Expanded Disability Status Scale score of 4.0 is increased by 7.4% for every year of delay in treatment initiation after multiple sclerosis onset.

Article 6: Highly Aggressive Multiple Sclerosis

James D. Bowen, MD. Continuum (Minneap Minn). June 2019; 25 (3 Multiple Sclerosis and Other CNS Inflammatory Diseases):689–714.

ABSTRACT

PURPOSE OF REVIEW:

Newly introduced disease-modifying therapies offer greater efficacy than previous therapies but also have serious side effects. This article reviews factors useful in identifying those at risk of developing aggressive relapsing multiple sclerosis (MS) and therapies available for treatment.

RECENT FINDINGS:

Several factors predict aggressive MS, including demographic factors, relapses, symptom characteristics, MRI activity, and other biomarkers. These can be used to select patients for more aggressive therapies, including natalizumab, alemtuzumab, fingolimod, and ocrelizumab. Additional off-label treatments are available for patients with severe disease. The benefits and side effects of these treatments must be considered when making therapeutic decisions.

SUMMARY:

Selecting patients who are most appropriate for aggressive therapy involves considering risk factors for poor outcomes, early recognition of treatment failure, balancing treatment efficacy and side effects, and sharing the decision with patients to assist them in making optimal treatment choices. Vigilance for signs of treatment failure and early switching to more aggressive therapy are important components in optimal care.

KEY POINTS

- Demographic factors that suggest a more aggressive multiple sclerosis course include male sex, onset after 40 years of age, nonwhite race, and smoking.
- Clinical characteristics that predict the risk of aggressive multiple sclerosis include frequent relapses; shorter interattack intervals; incomplete recovery from attacks; pyramidal, cerebellar, sphincter, or cognitive symptoms; and multifocal onset.
- Rapidly worsening disability and multiple sclerosis that is progressive from onset predict an aggressive course.

- MRI characteristics that predict more aggressive course include the number and volume of T2 lesions; the presence of gadolinium-enhancing lesions; the volume of T1-hypointense lesions; and the presence of atrophy, infratentorial lesions, or spinal cord lesions.
- Oligoclonal bands are associated with several markers for aggressive multiple sclerosis.
- The most serious side effect of natalizumab is progressive multifocal leukoencephalopathy. The risk of progressive multifocal leukoencephalopathy is estimated by the duration of natalizumab therapy, prior immunosuppressive use, and JC virus antibody index.
- Rebound can occur between 3 and 6 months after stopping natalizumab. Other disease-modifying therapies should be started before this time to minimize rebound risk.
- The side effects of alemtuzumab include immediate infusion reactions, autoimmune diseases, infections, and malignancies.
- The side effects of fingolimod include first-dose bradycardia. Fingolimod and siponimod may cause macular edema and opportunistic infections, including *Cryptococcus* and progressive multifocal leukoencephalopathy. Risk for infection cannot be assessed using absolute lymphocyte counts.
- The side effects of ocrelizumab include infusion reactions, infections (especially herpes infections), and possible malignancy; progressive multifocal leukoencephalopathy and reactivation of hepatitis B are theoretical risks, but thus far no cases have been seen.
- Cladribine is an oral immunosuppressant that was recently approved by the US Food and Drug Administration. Side effects include infections and malignancies.
- Mitoxantrone's use has been limited by cardiotoxicity and acute myelogenous leukemia.
- Cyclophosphamide is widely available and has some evidence to support its use, but definitive trials have not been performed.
- Rituximab's mechanism of action and side effects are similar to those of ocrelizumab. Rituximab is not US Food and Drug Administration approved for multiple sclerosis, but many have used it off-label because it is less expensive than ocrelizumab.
- High-dose immunosuppressive therapy with stem cell transplantation is the most aggressive therapy available for multiple sclerosis today. Outcomes are possibly double the rate of "no evidence of disease activity" of other therapies. Thus far, only phase 2 studies have been completed.

Article 7: Monitoring, Switching, and Stopping Multiple Sclerosis Disease-Modifying Therapies

Robert H. Gross, MD; John R. Corboy, MD, FAAN. Continuum (Minneap Minn). June 2019; 25 (3 Multiple Sclerosis and Other CNS Inflammatory Diseases):715–735.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews appropriate monitoring of the various multiple sclerosis (MS) disease-modifying therapies, summarizes the reasons patients switch or stop treatment, and provides a framework for making these management decisions.

RECENT FINDINGS:

With the increasing number of highly effective immunotherapies available for MS, the possibility of better control of the disease has increased, but with it, the potential for side effects has rendered treatment decisions more complicated. Starting treatment early with more effective

and better-tolerated disease-modifying therapies reduces the likelihood of switching because of breakthrough disease or lack of compliance. Clinical and radiographic surveillance, and often blood and other paraclinical tests, should be performed periodically, depending on the disease-modifying therapy. Helping patients navigate the uncertainty around switching or stopping treatment, either temporarily or permanently, is one of the most important things we do as providers of MS care.

SUMMARY:

Ongoing monitoring of drug therapy is a crucial component of long-term MS care. Switching treatments may be necessary for a variety of reasons. Permanent discontinuation of treatment may be appropriate for some patients with MS, although more study is needed in this area.

KEY POINTS

- Studies of factors related to multiple sclerosis disease-modifying therapies highlight that adherence is extremely variable and that switching or discontinuing disease-modifying therapies is very common in both the long and short term.
- Discontinuation of disease-modifying therapy may be temporary because of insurance interruption; a desire to become pregnant, becoming pregnant, or lactating; lack of adherence (for many reasons); or deliberate installation of a washout period between medications when switching disease-modifying therapies to limit overlapping risks with two medications used in sequence.
- Requiring patients to use less effective and less tolerable disease-modifying therapies first simply subjects patients to greater disability and discomfort over time.
- Ultimately, best practice likely reinforces that individual aspects should dictate the optimal approach for any one patient.
- Decisions made at the beginning of the disease course have potential long-term implications for use of other disease-modifying therapies.
- One source of ambiguity when considering switching disease-modifying therapy is that no standard definition of treatment "failure" exists, nor is there a universally accepted standard as to the appropriate time to switch disease-modifying therapies in multiple sclerosis.
- With the recognition of "no evidence of disease activity" as a treatment goal and ever-higher rates of no evidence of disease activity emerging from clinical trials of multiple sclerosis disease-modifying therapies, disease activity that previously would have been tolerated is now frequently no longer deemed acceptable.
- Practices vary regarding the use and length of washout periods, and evidence from randomized controlled trials to guide management is limited.
- An overly lengthy washout risks disease reactivation, especially with disease-modifying therapies that impair lymphocyte migration or trafficking and the cessation of which can be associated with rebound activity (fingolimod, natalizumab).
- In the natural history of multiple sclerosis, the risk of what are considered new episodes of inflammation, relapses, and gadolinium-enhancing lesions on MRI scans is highest after clinical onset and generally diminishes significantly with age, so that by age 50 the annual risk of any of the three is below 10%.
- As all presently available disease-modifying therapies alter, modulate, or suppress the immune system, with minimal documented effects on potential repair or regeneration of the nervous system, the benefits have been shown to be greatest in those with active inflammatory disease (ie, younger patients).
- Stopping disease-modifying therapies may have potential benefits, including fewer side effects, long-term risks, costs, and reminders that the patient has MS.
- Young age, a recent MS diagnosis, and recent disease activity (relapses or MRI changes) are characteristic of those most likely to benefit from MS immunotherapy.

Article 8: Progressive Multiple Sclerosis

Daniel Ontaneda, MD. Continuum (Minneap Minn). June 2019; 25 (3 Multiple Sclerosis and Other CNS Inflammatory Diseases):736–752.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an update on progressive forms of multiple sclerosis (MS), with a focus on pathogenic mechanisms, clinical features, imaging features, and recent therapeutic advances.

RECENT FINDINGS:

Progressive forms of MS are identified by a history of progressive accrual of disability independent of relapse, but they share many biological, clinical, and MRI features with relapsing MS. Both relapses and new lesions can occur in the context of progressive MS, and establishing when the transition from relapsing to progressive MS occurs is often difficult. Several pathogenic mechanisms coexist in progressive MS. Targeting inflammation in both primary and secondary progressive MS appears to reduce the accumulation of disability.

SUMMARY:

Progressive MS remains a diagnostic challenge, and the pathogenesis underlying progression is complex. Significant overlap in the biology and clinical and imaging features of progressive MS exists with relapsing forms of the disease. The use of disease-modifying and symptomatic treatments may improve the quality of life for patients with progressive MS.

KEY POINTS

- Progressive multiple sclerosis was previously considered an untreatable from of the disease, but current and future disease-modifying agents will change our approach to this form of the disease.
- Several mechanisms are present in both relapsing and progressive multiple sclerosis, and differences between relapsing and progressive multiple sclerosis are more relative than absolute.
- Inflammation plays a significant role in the pathogenesis of progressive multiple sclerosis.
- Because of the insidious onset of symptoms, the diagnosis of progressive multiple sclerosis is typically delayed, both as the initial presentation in primary progressive multiple sclerosis and when reclassifying a patient with relapsing-remitting multiple sclerosis as having secondary progressive multiple sclerosis.
- The 2017 McDonald diagnostic criteria for multiple sclerosis include specific criteria for primary progressive multiple sclerosis, including 1 year of disability progression (retrospectively or prospectively determined) independent of relapses plus at least two of the following: one or more T2 lesions in characteristic regions on brain MRI, two or more spinal cord MRI lesions, or the presence of CSF oligoclonal bands.
- Progressive and relapsing multiple sclerosis should be considered to occur on a spectrum rather than as different diseases, and the understanding that these two forms share several common features in biology, clinical evolution, and imaging findings is growing.
- Measurement of progressive accrual of disability is inherently difficult and remains a significant obstacle in progressive multiple sclerosis.
- Brain lesions in progressive multiple sclerosis are indistinguishable from those seen in relapsing multiple sclerosis; however, on average, patients with primary progressive multiple sclerosis tend to have fewer brain T2 lesions and fewer lesions with gadolinium enhancement.
- Conventional and advanced spinal cord MRI measures hold promise as potential biomarkers for progressive multiple sclerosis.
- Siponimod was studied in a phase 3 trial in secondary progressive multiple sclerosis and is now approved by the US Food and Drug Administration for the treatment of active secondary progressive multiple sclerosis.

- Ocrelizumab is now an approved medication for primary progressive multiple sclerosis and will be helpful in treating the inflammatory components in patients with the disease, especially in younger patients with inflammatory disease on MRI.

Article 9: Management of Multiple Sclerosis Symptoms and Comorbidities

W. Oliver Tobin, MBBCh, BAO, PhD. Continuum (Minneap Minn). June 2019; 25 (3 Multiple Sclerosis and Other CNS Inflammatory Diseases):753–772.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses the prevalence, identification, and management of multiple sclerosis (MS)–related symptoms and associated comorbidities, including complications that can present at all stages of the disease course.

RECENT FINDINGS:

The impact of comorbidities on the outcome of MS is increasingly recognized. This presents an opportunity to impact the course and outcome of MS by identifying and treating associated comorbidities that may be more amenable to treatment than the underlying inflammatory and neurodegenerative disease. The identification of MS-related symptoms and comorbidities is facilitated by brief screening tools, ideally completed by the patient and automatically entered into the patient record, with therapeutic suggestions for the provider. The development of free, open-source screening tools that can be integrated with electronic health records provides opportunities to identify and treat MS-related symptoms and comorbidities at an early stage.

SUMMARY:

Identification and management of MS-related symptoms and comorbidities can lead to improved outcomes, improved quality of life, and reduced disease activity. The use of brief patient-reported screening tools at or before the point of care can facilitate identification of symptoms and comorbidities that may be amenable to intervention.

KEY POINTS

- Fatigue is the most common symptom in patients with multiple sclerosis, present in almost half of patients with clinically isolated syndrome and over 80% of patients over the course of the disease.
- Restless legs syndrome has been reported in 13% to 65% of patients with multiple sclerosis and appears to be related to spinal cord disease.
- Limited evidence exists for commonly used but unapproved medications, such as amantadine, modafinil, armodafinil, methylphenidate, and amphetamine compounds for management of fatigue in multiple sclerosis.
- It is recommended that all patients with multiple sclerosis be screened for depression at annual visits.
- Screening for depression and anxiety can be completely automated, with the patient responding electronically to brief screening questionnaires and the responses automatically recorded in the patient's electronic health record.
- Patients may develop cognitive dysfunction in the absence of a significant burden of white matter disease and in the absence of accumulating T2-hyperintense brain lesions.
- Interpretation of a cognitive assessment at a single point in time may not provide an adequate assessment of an individual's overall performance.

- Paroxysmal symptoms in multiple sclerosis are typically sensory with variable motor involvement. They usually last between 1 and 90 seconds and are exquisitely sensitive to sodium channel blockade.
- Commonly used aural thermometers are often inaccurate in the setting of hypothermia, and identification of hypothermia requires the use of a low-reading rectal thermometer.
- Initial treatment of spasticity should primarily focus on stretching exercises. Stretches should be held for 30 to 60 seconds, and patients should be counseled to stretch twice daily.
- For patients who are nonambulatory with severe spasticity that is not responsive to or intolerant of other treatment strategies, intrathecal baclofen is a useful strategy, particularly for facilitating toileting and cleaning.
- In contrast to other neurologic disorders affecting the spinal cord, such as spina bifida, upper urinary tract disorders in multiple sclerosis are rare, possibly because of the slowly progressive nature of the disease.
- In patients with multiple sclerosis presenting with urinary symptoms, a urinalysis and postvoid residual ultrasound of the bladder should be performed.
- Indwelling catheters are associated with a greater risk of urinary tract infections, genital erosions, and bladder stone formation than intermittent catheterization.
- Percutaneous and transcutaneous tibial nerve stimulation have been shown to have short-term benefits on urinary symptoms for patients with overactive bladder secondary to multiple sclerosis and may also have a positive effect on fecal incontinence.
- Sexual dysfunction affects up to 90% of patients with multiple sclerosis during the course of the disease.

Article 10: Pregnancy and Family Planning in Multiple Sclerosis

Annette M. Langer-Gould, MD, PhD. Continuum (Minneap Minn). June 2019; 25 (3 Multiple Sclerosis and Other CNS Inflammatory Diseases):773–792.

ABSTRACT

PURPOSE OF REVIEW:

This article provides practical guidance on successful management of women with multiple sclerosis (MS) through pregnancy and the postpartum period.

RECENT FINDINGS:

Recent studies indicate that most women diagnosed with MS today can have children, breast-feed, and resume beta interferons or glatiramer acetate per their preferences without incurring an increased risk of relapses during the postpartum period. More than 40% of women with mild MS do not require any treatment before conception or in the postpartum period. Women with highly active MS can now become well-controlled before, throughout, and after pregnancy via highly effective treatments. Unfortunately, pregnancy does not protect against relapses following the cessation of fingolimod or natalizumab, and some women experience severe rebound relapses during pregnancy. Accidental first-trimester exposure to teriflunomide or fingolimod increases the risk of fetal harm.

SUMMARY:

Most women with MS can have normal pregnancies and breast-feed without incurring harm. Clinicians should avoid prescribing medications with known teratogenic potential (teriflunomide, fingolimod), known risk of severe rebound relapses (fingolimod, natalizumab), or unclear but plausible risks (dimethyl fumarate, alemtuzumab) to women of childbearing age who desire pregnancy or are not on reliable birth control. If a treatment needs to be resumed

during breast-feeding, clinicians should opt for glatiramer acetate, interferon beta, natalizumab, or rituximab/ocrelizumab, as biologically plausible risks to the infant are exceedingly low.

KEY POINTS

- Multiple sclerosis does not increase the risk of infertility, adverse pregnancy outcomes, or adverse neonatal outcomes, but some multiple sclerosis treatments may increase these risks.
- Potential risks not captured by US Food and Drug Administration pregnancy categories include neonatal immunosuppression, impaired early-life neurocognitive development, delayed toxicities in the child (eg, cancer), and risks incurred from severe rebound relapses in pregnancy.
- It is important to assess whether the patient's disease activity is adequately controlled before counseling about pregnancy. First decide whether patients with multiple sclerosis need to be on highly effective or modestly effective disease-modifying therapy to control their disease activity, then consider the possibility of pregnancy when choosing a disease-modifying therapy.
- It is important to ask patients with multiple sclerosis about pregnancy plans and contraception regularly.
- Many patients with multiple sclerosis have adequately controlled disease without any treatment or only modestly effective disease-modifying therapies. If these patients start trying to conceive, discontinuing treatment, if any, is prudent.
- Glatiramer acetate and interferon beta are the preferred modestly effective disease-modifying therapies for women who are not on reliable birth control.
- Consider a B-cell–depleting drug if a highly effective disease-modifying therapy is needed for a woman who is trying to get pregnant or not on reliable birth control. Assess for pregnancy before each infusion and do not infuse the medication if the patient is currently pregnant.
- Pregnancy does not protect against the risk of return of disease activity or rebound relapses after cessation of fingolimod or natalizumab.
- To prevent return of disease activity or rebound relapses during pregnancy after cessation of fingolimod or natalizumab, consider switching women to a B-cell–depleting therapy before conception.
- Fingolimod and natalizumab rebound relapses are treatable, even if they occur during pregnancy.
- Encourage and support breast-feeding for optimal infant and maternal health.
- Glatiramer acetate and interferon beta pose exceedingly low risk to infants via breast milk exposure and can be resumed when desired.
- Natalizumab and rituximab have very low theoretical risks to infants with breast milk exposure only and may be resumed during lactation if necessary.

Article 11: Pediatric Central Nervous System Demyelinating Diseases

Tanuja Chitnis, MD, FAAN. Continuum (Minneap Minn). June 2019; 25 (3 Multiple Sclerosis and Other CNS Inflammatory Diseases):793–814.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an up-to-date summary of the categories, diagnosis, and management of pediatric demyelinating disorders.

RECENT FINDINGS:

Understanding of the diverse spectrum of pediatric demyelinating disorders, including monophasic and multiphasic forms, has improved. Pediatric multiple sclerosis (MS) is the most common demyelinating disorder in children, and recent genetic and environmental risk research

has clarified that pediatric MS is on the same continuum of disease as adult MS. Recent advances in the treatment of pediatric MS include clinical trials leading to regulatory agency–approved treatments. The identification of myelin oligodendrocyte glycoprotein and aquaporin-4 antibodies in children has been a major advance, allowing for appropriate treatment and management of these syndromes.

SUMMARY:

Antibody testing is now helping to define subtypes of pediatric demyelinating disorders, including myelin oligodendrocyte glycoprotein–seropositive and aquaporin-4–seropositive cases that are distinct from pediatric MS. Treatments for pediatric MS are being evaluated in clinical trials.

KEY POINTS

- Major advances in pediatric demyelinating disease in the past 5 years include improved diagnostic criteria, antibody-based biomarkers, predictors of a multiphasic course, and treatment advances for these disorders. Recent work on the genetic and environmental risk factors for pediatric multiple sclerosis points to similarities with adult disease.
- An important advance in pediatric demyelinating disorders is the recognition that an acute demyelinating syndrome can represent the first attack of not only multiple sclerosis but also neuromyelitis optica spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein (MOG) antibody–associated demyelinating disease, and other multiphasic disorders in children.
- Several studies have identified risk factors for multiple sclerosis in children, including CSF profiles with pleocytosis, Epstein-Barr virus–positive serostatus, obesity, low vitamin D levels, and the presence of T2 lesions on brain MRI. Age older than 11 and postpubertal status at the time of a clinically isolated syndrome also increase the risk for multiple sclerosis.
- Puberty is an important transition period for the clinical onset of pediatric multiple sclerosis, with 80% to 85% of children being peripubertal or postpubertal at the time of first symptoms in a large US cohort.
- In general, children with multiple sclerosis experience 2 to 3 times as many relapses as adult patients with multiple sclerosis, reflecting a continuum in the inverse relationship of age and relapse rate.
- Types of relapses or attacks in pediatric multiple sclerosis include optic neuritis, transverse myelitis, brainstem attacks, and cerebral attacks.
- Between one-third and two-thirds of pediatric patients with multiple sclerosis may have significant cognitive deficits, including issues with information processing and processing speed, memory deficits, executive dysfunction, and lowered IQs, as well as deficits in social cognition.
- In 2018, fingolimod was approved by the US Food and Drug Administration for use as first-line treatment in children with multiple sclerosis aged 10 to 17; it has received preliminary approval by the European Medicines Agency as second-line treatment based on the results of the PARADIGMS clinical trial.
- Adherence to disease-modifying therapy may be challenging, particularly in adolescents, in the setting of miseducation about the expectations for disease-modifying therapies, unaddressed side effects, busy family schedules, and travel/college.
- Up to 3% to 5% of cases of NMOSD have pediatric onset. The overall incidence of NMOSD in children and adults ranges from 0.05 to 4 per 100,000 per year, and prevalence ranges from 0.52 to 4.4 per 100,000. In Japan, the incidence of pediatric NMOSD was reported as 0.06 per 100,000 children.
- Approximately 65% of pediatric patients with NMOSD are aquaporin-4 antibody seropositive; however, seropositivity may not occur at the time of the initial attack but up to 4 years later. Therefore, serial testing is recommended for highly suspicious cases.
- Since cell-based assays became available, anti– MOG antibodies have been reported in the serum of 18% to 35% of children with an acute demyelinating syndrome.
- MOG antibody testing has now been optimized, offering increased sensitivity and specificity compared to other methods. The MOG antibody is most often detected in the serum and rarely in the CSF. The current consensus is that serum testing has the highest yield.

Article 12: Neuromyelitis Optica Spectrum Disorder and Other Non–Multiple Sclerosis Central Nervous System Inflammatory Diseases

Eoin P. Flanagan, MBBCh. Continuum (Minneap Minn). June 2019; 25 (3 Multiple Sclerosis and Other CNS Inflammatory Diseases):815–844.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the clinical features, diagnostic approach, treatment, and prognosis of central nervous system inflammatory diseases that mimic multiple sclerosis (MS), including those defined by recently discovered autoantibody biomarkers.

RECENT FINDINGS:

The discovery of autoantibody biomarkers of inflammatory demyelinating diseases of the central nervous system (aquaporin-4 IgG and myelin oligodendrocyte glycoprotein IgG) and the recognition that, despite some overlap, their clinical phenotypes are distinct from MS have revolutionized this field of neurology. These autoantibody biomarkers assist in diagnosis and have improved our understanding of the underlying disease pathogenesis. This has allowed targeted treatments to be translated into clinical trials, three of which are now under way in aquaporin-4 IgG–seropositive neuromyelitis optica (NMO) spectrum disorder.

SUMMARY:

Knowledge of the clinical attributes, MRI findings, CSF parameters, and accompanying autoantibody biomarkers can help neurologists distinguish MS from its inflammatory mimics. These antibody biomarkers provide critical diagnostic and prognostic information and guide treatment decisions. Better recognition of the clinical, radiologic, and laboratory features of other inflammatory MS mimics that lack autoantibody biomarkers has allowed us to diagnose these disorders faster and initiate disease-specific treatments more expeditiously.

KEY POINTS

- **Distinguishing multiple sclerosis from its central nervous system inflammatory disease mimics has important therapeutic and prognostic implications.**
- **In 2004, the discovery of aquaporin-4 (AQP4)–IgG as a specific biomarker of neuromyelitis optica (NMO) allowed its distinction from multiple sclerosis.**
- **The discovery of AQP4-IgG as a biomarker of NMO led to a recognition that patients can have more limited forms of the disease (eg, recurrent transverse myelitis without optic neuritis) or symptoms beyond the optic nerve and spinal cord (eg, area postrema syndrome), resulting in the current nosology of NMO spectrum disorders (NMOSDs).**
- **It is important to recognize that in regions where multiple sclerosis prevalence is lower (eg, Asia and regions closer to the equator), NMOSD represents a larger proportion of central nervous system demyelinating diseases and thus should be particularly considered in the differential in those regions.**
- **NMOSD has three cardinal manifestations: transverse myelitis, optic neuritis, and area postrema syndrome.**
- **Systemic autoimmune disorders or their autoantibody biomarkers frequently coexist with NMOSD, including systemic lupus erythematosus, Sjögren syndrome, and antiphospholipid antibody syndrome.**

- In NMOSD, optic nerve involvement is often bilateral and typically involves the posterior optic pathway, including the optic chiasm, with enhancement usually extending more than half the length of the nerve.
- Typical brain involvement in NMOSD occurs around circumventricular organs where AQP4 expression is highest, with lesions adjacent to the third and fourth ventricles (dorsal medulla/area postrema) most typical.
- Longitudinally extensive transverse myelitis, with a T2-hyperintense lesion spanning three or more contiguous vertebral segments on MRI, is characteristic of NMOSD and found in approximately 85% in patients.
- Assay techniques for AQP4-IgG have improved over time, and cell-based assays are now recommended (using fluorescence-activated cell sorting or direct immunofluorescence); they yield a sensitivity of 75% to 80% and specificity of greater than 99%.
- Approximately 20% to 25% of patients with NMOSD are AQP4-IgG seronegative.
- AQP4-IgG binds to AQP4, which is located on the end-feet of astrocytes, initiating a cascade of immune-mediated inflammation resulting in secondary demyelination.
- The use of plasma exchange for five to seven exchanges for severe, corticosteroid-refractory central nervous system inflammatory demyelinating attacks is supported by data from a prospective randomized sham-controlled crossover trial.
- Despite the lack of completed randomized controlled trials in NMOSD, preventive treatment is strongly recommended in all patients.
- With the use of cell-based assays transfected with myelin oligodendrocyte glycoprotein (MOG) in its conformational form, the antibody has been shown to be a specific biomarker of a spectrum of central nervous system inflammatory demyelinating disease distinct from multiple sclerosis and AQP4-IgG–seropositive NMOSD.
- The major clinical manifestations of MOG-IgG disease include optic neuritis, acute disseminated encephalomyelitis, NMOSD (seronegative for AQP4-IgG), transverse myelitis, and brainstem demyelinating episodes.
- Some patients with MOG-IgG disease have a monophasic course, while others go on to develop relapsing disease.
- Radiologic findings in MOG-IgG disease include enhancement that involves more than half of the length of the optic nerve in 80% of patients and may involve the optic nerve sheath or extend into the orbital fat.
- Multifocal white matter T2 hyperintensities with involvement of the deep gray matter are typical in MOG-IgG disease, particularly with acute disseminated encephalomyelitis–like presentations.
- Positive oligoclonal bands are found in less than 15% of patients with MOG-IgG.
- A 2018 consensus article outlined patients in whom MOG-IgG should be tested and recommended against testing MOG-IgG in all patients with multiple sclerosis, given the risk of false positives when testing in low-probability situations. In general, testing for MOG-IgG should be reserved for those with one of the classic phenotypes that lacks characteristic features of multiple sclerosis.
- A major area of study in MOG-IgG disease is determining which patients may have a monophasic disorder and not require treatment.
- For patients with relapsing MOG-IgG disease, the treatment approach is almost identical to that of acute and maintenance therapy for NMOSD, although IV immunoglobulin appears to be useful in children acutely and as a maintenance treatment.
- In 2016, an antibody to glial fibrillary acidic protein (GFAP) was reported that, when detected in CSF, appeared to be specific for an inflammatory meningoencephalomyelitis, termed *autoimmune GFAP astrocytopathy*.
- In autoimmune GFAP astrocyopathy, brain MRI may reveal a characteristic radial perivascular enhancement perpendicular to the ventricles, although a similar pattern can be seen with intravascular lymphoma, neurosarcoidosis, and central nervous system vasculitis.
- Susac syndrome is an inflammatory endotheliopathy that is characterized by a triad of branched retinal artery occlusions, hearing loss, and dementia/encephalopathy.

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Muscle and Neuromuscular Junction Disorders

Article 1: Approach to Muscle and Neuromuscular Junction Disorders

Mamatha Pasnoor, MD, FAAN; Mazen M. Dimachkie, MD, FAAN, FANA. Continuum (Minneap Minn). December 2019; 25 (6 Muscle and Neuromuscular Junction Disorders):1536–1563.

ABSTRACT

PURPOSE OF REVIEW:

Muscle and neuromuscular junction disorders are a diverse group of disorders that can be difficult to diagnose. This article provides a diagnostic approach based on clinical history and neurologic examination leading to a narrow set of diagnostic tests.

RECENT FINDINGS:

Numerous discoveries in recent years have facilitated clinician access to more advanced laboratory and genetic testing to pinpoint the exact diagnosis in patients with muscle or neuromuscular junction disorders. Large-scale genetic testing has become much less expensive, and free testing has become available for many of the rare conditions because of increased research and the availability of effective therapies for these rare disorders.

SUMMARY:

The approach to muscle and neuromuscular junction disorders depends on the clinical pattern of muscle weakness. By classifying patients into one of 10 muscle patterns, diagnostic testing can be targeted and gene testing yield will be optimized. With the increased accessibility and reduced cost of genetic testing (eg, gene panels, whole-exome sequencing, whole-genome sequencing, and chromosomal microarray), this clinical approach to muscle weakness and targeted gene testing will ensure a cost-effective investigational plan. This clinical approach should also assist clinicians in making a timely and accurate diagnosis.

KEY POINTS

- **Thorough history of onset and progression is fundamentally important for the diagnosis of myopathies and neuromuscular junction disorders.**
- **The main features that distinguish neuromuscular junction defects from myopathies are fluctuation in symptoms and signs, as well as ocular manifestations.**

- Identification of triggering factors for weakness or stiffness is useful for diagnosis of muscle and neuromuscular junction disorders.
- The 10 patterns of muscle involvement are an extremely valuable starting point to formulate the initial diagnoses and guide ordering of confirmatory tests.
- Family history and pattern of inheritance provide information for the efficient diagnosis of genetic conditions.
- Examination of children can be challenging in comparison with that of adults with neuromuscular disease. Examination of the parent may provide a valuable clue to the diagnosis (eg, grip myotonia in a mother of a hypotonic infant).
- Assessment for other organ involvement is important for diagnosis and prognosis of muscle and neuromuscular junction disorders.
- Muscle biopsies are mostly useful for acquired myopathies and hereditary myopathies with negative genetic testing or with variants of unknown significance.
- Needle EMG or MRI can be used to identify the most useful muscle site to biopsy.
- Commercial genetic testing has significantly improved in recent years with increased efficiency and reduced cost.
- Despite genetic testing becoming more readily available and affordable, the resolution of variants of uncertain significance requires the implementation of a careful and thoughtful pattern approach, support from electrophysiology, and muscle biopsy.

Article 2: Immune-Mediated Myopathies

Namita A. Goyal, MD, FAAN. Continuum (Minneap Minn). December 2019; 25 (6 Muscle and Neuromuscular Junction Disorders):1564–1585.

ABSTRACT

PURPOSE OF REVIEW:

This article summarizes the clinical features, diagnostic evaluation, and management of the common immune-mediated myopathies: dermatomyositis, antisynthetase syndrome, immune-mediated necrotizing myopathy, and overlap myositis.

RECENT FINDINGS:

The identification of myositis-specific autoantibodies has improved the characterization of the subtypes of myositis and associated clinical phenotypes, as the severity of muscle involvement, extramuscular manifestations, and risk of malignancy may vary among the subtypes of autoimmune myopathies.

SUMMARY:

The understanding and diagnostic accuracy of the subtypes of autoimmune myopathies have been enhanced with careful attention to the key clinical features, the emergence of myositis-specific autoantibodies, the characterization of histopathologic hallmark features, and the aid of muscle imaging. Several immunotherapeutic options now exist that can be selected to target a specific subtype, often with a favorable prognosis, especially when treatment starts early in the disease course.

KEY POINTS

- Muscle weakness in patients with dermatomyositis, antisynthetase syndrome, immune-mediated necrotizing myopathy, overlap myositis, and polymyositis is symmetric and proximal, often involving the proximal shoulder and hip girdle limb muscles; with progression, it may also affect the truncal muscles.

- Dermatomyositis presents in children and adults with a subacute onset of proximal muscle weakness that is accompanied or preceded by a distinct skin rash, a cardinal feature of dermatomyositis.
- A pathognomonic heliotrope (violaceous discoloration) rash often involves the upper eyelids with or without periorbital edema.
- Aside from the cutaneous involvement, other extramuscular manifestations in dermatomyositis include involvement of cardiac, pulmonary, gastrointestinal, and joint systems, as well as malignancy.
- In dermatomyositis, creatine kinase levels are often increased; however, they may range from normal to up to thousands of international units per liter.
- Patients with dermatomyositis with a positive anti–Mi-2 antibody are noted to have more classical cutaneous features of dermatomyositis, confer a good prognosis with a favorable response to steroids, and have a relatively low malignancy risk.
- The anti–TIF-1γ antibody in dermatomyositis is highly associated with malignancy (in adult dermatomyositis but not in juvenile dermatomyositis) and severe skin manifestations, including diffuse photoerythema and "dusky red face" and unique characteristic cutaneous lesions of hypopigmented and telangiectatic ("red on white") patches.
- Anti–nuclear matrix protein 2 antibodies are found in up to 25% of patients with juvenile dermatomyositis but are also detected in up to 40% of patients with adult dermatomyositis.
- Perifascicular muscle fiber atrophy is a specific and pathologic hallmark feature of dermatomyositis.
- In dermatomyositis, short tau inversion recovery MRI sequences commonly demonstrate hyperintensity or edema in a patchy distribution in the muscle, along with edema of the subcutaneous tissues and fascia (an uncommon finding in other inflammatory myopathies), and may mirror the distribution of skin involvement.
- Patients with antisynthetase syndrome may present with a constellation of all or some of the following clinical features: inflammatory myopathy, interstitial lung disease, arthritis, Raynaud syndrome, fever, and mechanic's hands.
- Of the antisynthetase antibodies, anti–Jo-1 (the first to be discovered and most frequent antisynthetase autoantibody) is associated with the greatest risk of developing a myositis.
- Up to 90% of patients with Jo-1 antibodies have a myositis; however, the risk of developing interstitial lung disease has been reported in up to 50% of patients with anti–PL-12 antibodies, but they have no muscle involvement.
- Serum creatine kinase levels in immune-mediated necrotizing myopathy are typically markedly elevated, up to several thousands of international units per liter, with the median peak reported at 4700 U/L.
- The 2017 European Neuromuscular Centre criteria for immune-mediated necrotizing myopathy describe three subtypes: anti–SRP myopathy, anti–3-hydroxy-3-methylglutaryl coenzyme A reductase myopathy, and antibody-negative immune-mediated necrotizing myopathy.
- The anti–3-hydroxy-3-methylglutaryl coenzyme A reductase antibody associated immune-mediated necrotizing myopathy was first described in patients with a history of statin exposure with weakness that continued to progress despite stopping use of the statin mediation; however, up to one-third may be statin naïve and may have a more resistant treatment response.
- The muscle histopathology in immune-mediated necrotizing myopathy is characterized by the presence of necrosis of muscle fibers or regeneration with a paucity of (if any) lymphocytic infiltrates.
- The most common myositis-associated antibodies are anti-Ro52 antibodies, which are nonspecific and have been detected in approximately 25% of patients with all types of myositis.
- Immunosuppressive therapy is widely accepted as the mainstay of treatment for autoimmune myopathies.
- Corticosteroids, commonly prednisone, are the first-line therapy in the treatment of inflammatory myopathies, typically prescribed at a dose of 0.5 mg/kg/d to 1 mg/kg/d, with a maximum dose of 60 mg/d to 80 mg/d.
- Recent evidence has suggested that particular subtypes of autoimmune myopathies (based on autoantibodies) may have a robust response to particular immunotherapies.
- Several biologic agents are under investigation for the treatment of refractory cases of autoimmune inflammatory myopathies.

- Although treatment for inflammatory myopathies remains challenging because several therapeutic options are available without consensus guidelines, patients with myositis tend to respond favorably to conventional immunotherapy when started early in the course of the disease.
- Because the majority of malignancies are identified in the first 3 years of myositis onset, a comprehensive evaluation in search of an underlying malignancy with chest, abdomen, and pelvis CT, as well as age-appropriate cancer screening should be performed, especially in myositis autoantibody subtypes with an increased risk of malignancy.

Article 3: Sporadic Inclusion Body Myositis and Other Rimmed Vacuolar Myopathies

Conrad C. Weihl, MD, PhD. Continuum (Minneap Minn). December 2019; 25 (6 Muscle and Neuromuscular Junction Disorders):1586–1598.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the clinical, laboratory, and histopathologic features of sporadic inclusion body myositis (IBM) and explores its pathogenic overlap with inherited myopathies that have IBM-like pathology.

RECENT FINDINGS:

Sporadic IBM is the most common acquired muscle disease in patients older than 50 years of age and is becoming more prevalent because of the increasing age of the population, the emerging development of more inclusive diagnostic criteria, and the advent of a diagnostic autoantibody. No effective therapy is known, and the pathogenic mechanism remains unclear. Some pathogenic insight can be gleaned from other myopathies with pathologic similarities or hereditary inclusion body myopathies. Although clinically distinct from sporadic IBM, preclinical models of hereditary inclusion body myopathy have offered an opportunity to move some therapies toward clinical development.

SUMMARY:

Patients with sporadic IBM experience significant morbidity, and the disease is associated with a large unmet medical need. As therapies are developed, improved diagnosis will be essential. Early diagnosis relies on awareness, clinical history, physical examination, laboratory features, and appropriate muscle biopsy processing. Future research is needed to understand the natural history, identify genetic risk factors, and validate biomarkers to track disease progression. These steps are essential as we move toward therapeutic interventions.

KEY POINTS

- The estimated prevalence of sporadic inclusion body myositis varies from 5 per million to 71 per million but is still likely an underestimate. Diagnostic uncertainty or ambiguity, delays in sporadic inclusion body myositis diagnosis, and the aging population support a higher prevalence.
- Patients with sporadic inclusion body myositis have a slowly progressing preferential pattern of muscle involvement that includes quadriceps, finger flexor, and ankle dorsiflexion weakness.
- An atypical pattern of weakness, rapid progression, or onset younger than 40 years age should prompt the clinician to consider an alternate diagnosis.

- Patients with sporadic inclusion body myositis have modestly elevated creatine kinase levels (≤1500 U/L) and electrodiagnostic studies that may be challenging to interpret because they suggest a mixed myopathic/neuropathic process.
- MRI of the lower extremities can reveal a differential pattern of muscle involvement that selectively affects the anterior thigh muscle. The value of MRI as a diagnostic or prognostic tool in sporadic inclusion body myositis has not been established.
- At present, muscle histology demonstrating endomysial inflammation, a feature that should be captured when a clinically affected muscle is biopsied, is required for a definitive diagnosis of sporadic inclusion body myositis.
- Overreliance on skeletal muscle histopathology and rare but specific biopsy features such as rimmed vacuoles or electron microscopic identification of proteinaceous inclusions may lead to an underdiagnosis of patients with sporadic inclusion body myositis.
- The most sensitive and specific diagnostic features for sporadic inclusion body myositis are the clinical presentation and physical examination findings.
- Diagnostic criteria that emphasize clinical measures of strength have higher sensitivity and specificity. Specifically, the presence of finger flexor weakness and knee extension strength less than or equal to hip flexion strength has a higher sensitivity for sporadic inclusion body myositis as compared with some pathologic features on muscle biopsy.
- Anti–5'-nucleotidase, cytosolic IA (NT5C1A) seropositivity is present in approximately 40% to 60% of patients with sporadic inclusion body myositis. A negative anti-NT5C1A antibody test should not be used to rule out sporadic inclusion body myositis. Moreover, anti-NT5C1A seropositivity can occur in other inflammatory myopathies and should be interpreted with caution. It remains to be determined where anti-NT5C1A seropositivity fits within current diagnostic algorithms.
- Anti–5'-nucleotidase, cytosolic IA seropositivity may predict a more severe sporadic inclusion body myositis phenotype with higher mortality and bulbar symptoms.
- Although not systematically studied, exercise may correlate with a higher functional status in patients with sporadic inclusion body myositis.
- Sporadic inclusion body myositis is a slowly progressive chronic muscle disease. Patients decline at an average rate of 4% per year in affected muscle groups. Most patients with sporadic inclusion body myositis lose ambulation after 10 to 20 years of the disease.
- Of patients with sporadic inclusion body myositis, 98% report falling within the last year. Prevention of falls by patient education is an essential aspect of care of patients with sporadic inclusion body myositis.
- Although defined as a sporadic disease, patients with sporadic inclusion body myositis may carry genetic risk factors that are associated with autoimmunity and muscle degeneration such as a human leukocyte antigen DRB1*03:01 allele or *FYCO1* missense variants.
- No treatment has been demonstrated to be clinically effective at reversing or slowing weakness in patients with sporadic inclusion body myositis.
- Patients with hereditary myopathies can be mistaken for sporadic inclusion body myositis because of clinical and biopsy features that overlap.
- Future therapies aimed at correcting muscle degeneration rather than immune dysfunction may be effective in treating patients with sporadic inclusion body myositis.

Article 4: The Limb-Girdle Muscular Dystrophies

Matthew P. Wicklund, MD, FAAN. Continuum (Minneap Minn). December 2019; 25 (6 Muscle and Neuromuscular Junction Disorders):1599–1618.

ABSTRACT

PURPOSE OF REVIEW:

As a group, the limb-girdle muscular dystrophies (LGMDs) are the fourth most prevalent genetic muscle disease, yet they are still not well known or understood. This article defines and describes LGMDs, delineates a diagnostic strategy, and discusses treatment of the LGMDs.

RECENT FINDINGS:

In 2018, the definition of the LGMDs was further refined, and a new nomenclature was proposed. Diagnosis of the LGMDs was long guided by the distinctive clinical characteristics of each particular subtype but now integrates use of genetics—with next-generation sequencing panels, exomes, and full genome analysis—early in the diagnostic assessment. Appreciation of the phenotypic diversity of each LGMD subtype continues to expand. This emphasizes the need for precision genetic diagnostics to better understand each subtype and formulate appropriate management for individual patients. Of significant relevance, the explosion of research into therapeutic options accentuates the need for accurate diagnosis, comprehensive disease characterization, and description of the natural histories of the LGMDs to move the field forward and to mitigate disease impact on patients with LGMD.

SUMMARY:

The LGMDs are genetic muscle diseases that superficially appear similar to one another but have important differences in rates of progression and concomitant comorbidities. Definitive diagnoses are crucial to guide management and treatment now and in the future. As targeted treatments emerge, it will be important for clinicians to understand the nomenclature, diagnosis, clinical manifestations, and treatments of the LGMDs.

KEY POINTS

- Hundreds of genes can lead to proximal muscle weakness including disorders of the motor neuron (spinal muscular atrophy), neuromuscular junction (congenital myasthenic syndromes), and muscle (genetic myopathies inclusive of limb-girdle muscular dystrophies).
- Limb-girdle muscular dystrophy is defined as a genetically inherited condition primarily affecting skeletal muscle that leads to progressive, predominantly proximal muscle weakness in individuals who have achieved independent walking and who have elevated creatine kinase levels. Degenerative changes are demonstrated on muscle imaging, and dystrophic changes are demonstrated on muscle histology in the most affected muscles.
- In 2018, the European Neuromuscular Centre set forth a new nomenclature to better delineate the limb-girdle muscular dystrophies from other genetic muscle diseases.
- The diagnostic process for the limb-girdle muscular dystrophies has changed, as now broad genetic testing should be performed once a clinical suspicion is present for a genetic muscle disease.
- Patients previously followed for the diagnosis of myositis, especially if poorly responsive to immunomodulatory therapy, should undergo limb-girdle muscular dystrophy genetic testing. Patients with limb-girdle muscular dystrophy with negative panel, exome or genome genetic analysis should be tested for autoantibodies recognizing 3-hydroxy-3-methylglutaryl coenzyme A reductase (even without exposure to statin drugs and even in children).
- Calpainopathies are the most common limb-girdle muscular dystrophy subtype, except in some Northern European countries and perhaps in Asia.
- If someone with limb-girdle muscular dystrophy cannot stand on his or her toes in the first few years after onset of disease, strong consideration should be given to limb-girdle muscular dystrophy type 2B (and type 2L).
- In the sarcoglycanopathies (limb-girdle muscular dystrophy types 2C through 2F), in leg MRIs, one often finds a predictable proximal to distal gradient of fatty and fibrous replacement in the anterior thigh, with relative sparing of the distal vasti muscles.

- Exercise-induced muscle pain affects two-thirds and myoglobinuria affects one-third of patients with limb-girdle muscular dystrophy type 2I.
- Similar to dysferlinopathies (limb-girdle muscular dystrophy type 2B), anecdotal evidence exists for athletic prowess prior to onset of symptoms in anoctaminopathies (limb-girdle muscular dystrophy type 2L).
- A significant proportion of undiagnosed patients with a limb-girdle muscular dystrophy phenotype harbor *RYR1* pathogenic variants.
- In patients with limb-girdle muscular dystrophy type 1B, early cardiology consultation and proactive intervention with cardiac pacemakers, defibrillators, and transplantation mitigate complications related to malignant arrhythmias and heart failure.
- Treatment recommendations for patients with limb-girdle muscular dystrophy include (1) medical management through multidisciplinary neuromuscular clinics; (2) access to cardiology, pulmonary, and orthopedic evaluation and treatment; (3) involvement of physical, occupational, and speech therapy along with access to orthotic and durable medical equipment services; (4) availability of genetic testing, interpretation, and counseling; and (5) encouragement for patients to remain active and lead fulfilling lives.

Article 5: The Dystrophinopathies

Mathula Thangarajh, MD, PhD, FAAN. Continuum (Minneap Minn). December 2019; 25 (6 Muscle and Neuromuscular Junction Disorders):1619–1639.

ABSTRACT

PURPOSE OF REVIEW:

The dystrophinopathies are among the most common neuromuscular conditions, and they include Duchenne and Becker muscular dystrophies. This article reviews the epidemiology, clinical manifestations, genetic cause, management, and new and emerging therapies for this condition.

RECENT FINDINGS:

New studies have highlighted how oral corticosteroids have changed the natural history of the disease, prolonging ambulation in boys with Duchenne muscular dystrophy and reducing the risk of developing scoliosis and subsequent surgical correction, improving cardiac health, and increasing long-term survival. Additionally, recent publications have provided insights into how newer and emerging treatment options are becoming more common for this condition. With gene therapy being approved in the United States for the severe form, the dystrophinopathies represent model diseases to understand the personalization of genetic treatment.

SUMMARY:

Improvement in the standardization of care and the use of oral corticosteroids have increased the life expectancy of patients with dystrophinopathy and changed the natural history of the disease. This article presents a summary of clinical features, diagnostic testing, and new and emerging treatment strategies for the dystrophinopathies.

KEY POINTS

- Clinical outcomes in dystrophinopathy have improved, and many individuals with the severe phenotype (Duchenne muscular dystrophy) are surviving into adulthood. Thus, adult neurologists are increasingly providing care for these individuals.
- Young boys presenting with developmental delay and delayed motor milestones should be tested for dystrophinopathy. Serum creatine kinase is the first diagnostic testing that can help.

- Genetic testing is readily available and should be actively pursued to establish a diagnosis of dystrophinopathy and guide therapy as more mutation-specific therapies are becoming available.
- Cardiomyopathy is a frequent complication of dystrophinopathy, especially in those with the milder but variable phenotype (Becker muscular dystrophy) and in female carriers of dystrophinopathy.
- Corticosteroids begun between the ages 4 and 7 years change the natural history of Duchenne muscular dystrophy.
- At least two drugs have been approved for treatment in Duchenne muscular dystrophy, and new therapeutic agents are increasingly being tested.
- A cohesive, interdisciplinary team is integral for the provision of high-quality medical care for individuals with dystrophinopathy.

Article 6: Congenital Muscular Dystrophy and Congenital Myopathy

Russell J. Butterfield, MD, PhD, FAAN. Continuum (Minneap Minn). December 2019; 25 (6 Muscle and Neuromuscular Junction Disorders):1640–1661.

ABSTRACT

PURPOSE OF REVIEW:

Congenital muscular dystrophies and congenital myopathies are a heterogeneous group of disorders resulting in hypotonia, muscle weakness, and dystrophic or myopathic features on muscle biopsy. This article summarizes the clinical and genetic aspects of these disorders.

RECENT FINDINGS:

Historically, diagnoses of congenital muscular dystrophy and congenital myopathy have been made by clinical features and histopathology; however, recent advances in genetics have changed diagnostic practice by relying more heavily on genetic findings. This article reviews the clinical and genetic features of the most common congenital muscular dystrophies including laminin subunit alpha 2 (LAMA2)–related (merosin deficient), collagen VI–related, and α-dystroglycan–related congenital muscular dystrophies and reviews the most common congenital myopathies including nemaline rod, core, and centronuclear myopathies. With the increasing accessibility of genetic testing, the number of genes found to be associated with these disorders has increased dramatically. A wide spectrum of severity and onset (from birth to adulthood) exist across all subtypes. Progression and other features are variable depending on the subtype and severity of the specific genetic mutation.

SUMMARY:

Congenital muscular dystrophy and congenital myopathy are increasingly recognized disorders. A growing appreciation for the breadth of phenotypic variability and overlap between established subtypes has challenged long-standing phenotypic and histopathologic classifications of these disorders but has driven a greater understanding of pathogenesis and opened the door to the development of novel treatments.

KEY POINTS

- Congenital muscular dystrophies are most often distinguished genetically by involvement of proteins important for stabilization of the cytoskeletal matrix to the sarcolemmal membrane and the extracellular matrix.

- Congenital myopathies most often involve proteins important in the contractile matrix or excitation-contraction coupling.
- Classic definitions of clinical and histopathologic phenotypes are being challenged by genetic classifications, which have revealed significant overlap between syndromes and the breadth of severity in patients with mutations in most congenital muscular dystrophy and congenital myopathy genes.
- Creatine kinase is often elevated in patients with congenital muscular dystrophy due to destabilization of the sarcolemmal membrane but is normal in patients with congenital myopathy, where stability of the sarcolemmal membrane is maintained.
- Genetic testing is rapidly emerging as the first diagnostic test in most patients with suspected congenital muscular dystrophy and congenital myopathy.
- Treatment for congenital muscular dystrophies and congenital myopathies requires a multidisciplinary team including orthopedic, pulmonary, nutrition, and cardiac surveillance.
- Juxtaposition of distal joint hyperlaxity and proximal contracture with weakness and skin changes make collagen VI–related muscular dystrophy a recognizable clinical phenotype.
- Patients with LAMA2-related muscular dystrophies have severe white matter changes on MRI resembling a leukodystrophy but lack upper motor neuron signs and have normal cognitive function.
- Patients with α-dystroglycanopathies can have severe brain malformations including cobblestone lissencephaly.
- Congenital myopathies are traditionally classified by histopathologic findings including nemaline rods, cores, and central nuclei.
- Nemaline myopathies are most frequently caused by mutations in *NEB* and *ACTA1* and can have a very severe neonatal course that is typically not progressive.
- The majority of core myopathies are caused by mutations in *RYR1* and have significant risk for malignant hyperthermia.
- Patients with collagen VI–related muscular dystrophy and *SELENON*-related muscular dystrophy have early respiratory compromise and may require noninvasive ventilation while asleep, even while still ambulatory.
- Variants in the *TTN* gene encoding titin are seen in many healthy people, complicating the interpretation of *TTN* variants in patients with suspected congenital myopathy.

Article 7: Facioscapulohumeral Muscular Dystrophies

Kathryn R. Wagner, MD, PhD. Continuum (Minneap Minn). December 2019; 25 (6 Muscle and Neuromuscular Junction Disorders):1662–1681.

ABSTRACT

PURPOSE OF REVIEW:

Facioscapulohumeral muscular dystrophy (FSHD) is a common muscular dystrophy affecting both pediatric and adult patients. This article reviews the phenotype and pathophysiology of the disease as well as the recent efforts in clinical outcome measures and clinical trials.

RECENT FINDINGS:

As the name implies, FSHD involves weakness of facial muscles, muscles that fix the scapula, and muscles overlying the humerus (biceps and triceps). The distinctive phenotype of FSHD occurs secondary to two different genetic mechanisms. FSHD type 1 (FSHD1) is due to a deletion on chromosome 4q, leading to hypomethylation and derepression of *DUX4*. FSHD type 2 (FSHD2) is due to mutations in *SMCHD1* with resulting hypomethylation of the same subtelomeric region

of chromosome 4q and derepression of *DUX4*. Understanding the central role of *DUX4* has opened up the possibility of disease-modifying treatments. In preparation for clinical trials of novel agents, researchers are in the process of validating a number of clinical trial outcome measures including MRI, the 6-minute walk test, the FSHD Composite Outcome Measure, reachable workspace, electrical impedance myography, and the FSHD Health Index.

SUMMARY:

The treatment of FSHD is currently supportive only. While past clinical trials in FSHD have been largely disappointing, novel agents in development, including antisense oligonucleotides, gene therapy, and small molecules, hold promise for future meaningful therapies.

KEY POINTS

- The two forms of facioscapulohumeral muscular dystrophy are type 1 (95% of cases) and type 2 (5% of cases). The presentations of both types are identical.
- Both facioscapulohumeral muscular dystrophy types 1 and 2 are due to hypomethylation of the subteleomeric region of chromosome 4q, leading to aberrant expression of a normally silent transcription factor DUX4.
- Facioscapulohumeral muscular dystrophy presents with asymmetric weakness of the orbicularis oculi, orbicularis oris, rhomboids, serratus anterior, biceps, triceps, paraspinals, rectus abdominis, and tibialis anterior. Eventually, other muscles of the arms and legs may become involved.
- Facioscapulohumeral muscular dystrophy has few associated signs and symptoms. In those with large deletions, an increased risk of retinal vasculopathy and hearing loss is present.
- The diagnosis of facioscapulohumeral muscular dystrophy rests on the recognition of the clinical phenotype and genetic testing. Creatine kinase is normal to mildly elevated, and EMG and muscle biopsy are nonspecific and not indicated.
- Patients with large deletions in chromosome 4q should be seen by a retina specialist and have a hearing examination.
- Surgical scapular fixation is an extensive procedure and should be undertaken only in specific patients with preserved deltoid strength and should be carried out by experienced surgeons.
- Bone health is important to prevent morbidity. Vitamin D_3 levels should be checked in all patients with facioscapulohumeral muscular dystrophy and supplemented as needed. For those with significant weakness, bone density should be followed by annual dual energy x-ray absorptiometry scans.
- The rectus abdominis and semimembranosus are among the most severely affected muscles in patients with facioscapulohumeral muscular dystrophy, as noted on MRI.
- On imaging, muscle affected by facioscapulohumeral muscular dystrophy may follow a pathologic progression from normal signal intensity to short tau inversion recovery hyperintensity to T1-weighted hyperintensity.
- β_2-Adrenergic agonists have been trialed in patients with facioscapulohumeral muscular dystrophy, and while they show increased muscle mass, they have had mixed results in showing increased strength.
- Aerobic exercise in the form of cycling has shown mixed results with some improvement in fitness and strength observed in patients with facioscapulohumeral muscular dystrophy.
- Future therapies for patients with facioscapulohumeral muscular dystrophy include antisense oligonucleotides, gene therapy, and small molecules all targeting DUX4.

Article 8: Myotonic Muscular Dystrophies

Nicholas E. Johnson, MD, MSc, FAAN. Continuum (Minneap Minn). December 2019; 25 (6 Muscle and Neuromuscular Junction Disorders):1682–1695.

ABSTRACT

PURPOSE OF REVIEW:

This article describes the clinical features, pathogenesis, prevalence, diagnosis, and management of myotonic dystrophy type 1 and myotonic dystrophy type 2.

RECENT FINDINGS:

The prevalence of myotonic dystrophy type 1 is better understood than the prevalence of myotonic dystrophy type 2, and new evidence indicates that the risk of cancer is increased in patients with the myotonic dystrophies. In addition, descriptions of the clinical symptoms and relative risks of comorbidities such as cardiac arrhythmias associated with myotonic dystrophy type 1 have been improved.

SUMMARY:

Myotonic dystrophy type 1 and myotonic dystrophy type 2 are both characterized by progressive muscle weakness, early-onset cataracts, and myotonia. However, both disorders have multisystem manifestations that require a comprehensive management plan. While no disease-modifying therapies have yet been identified, advances in therapeutic development have a promising future.

KEY POINTS

- The myotonic muscular dystrophies are autosomal dominant disorders characterized by a clinical triad of progressive weakness, myotonia, and early-onset cataracts.
- Myotonic dystrophy type 1 is the most common form of muscular dystrophy.
- Myotonic dystrophy type 1 is caused by a CTG repeat expansion in the 3′ untranslated region of the *DMPK* gene. Myotonic dystrophy type 2 is caused by an intronic CCTG repeat expansion in the *CNBP* gene.
- The clinical triad associated with myotonic dystrophy type 1 is distal muscle weakness, myotonia, and early-onset cataracts.
- Cardiac arrhythmias, such as atrioventricular block, are the leading cause of death in myotonic dystrophy type 1.
- The most impactful symptom in myotonic dystrophy type 1 is fatigue, which may be driven by a combination of sleep apnea, respiratory failure, and excessive daytime sleepiness.
- Patients with myotonic dystrophy type 1 may have a symptom complex similar to irritable bowel syndrome.
- If the symptoms of myotonic dystrophy type 1 begin at birth, it is called *congenital myotonic dystrophy*. The neonatal manifestations often include hypotonia, respiratory failure, feeding problems, and talipes equinovarus (clubfoot).
- Childhood-onset myotonic dystrophy is defined as symptoms after the age of 1 and before the age of 10. These early childhood symptoms often include intellectual impairment and gastrointestinal symptoms.
- Muscle weakness in myotonic dystrophy type 2 is predominantly proximal rather than distal and includes the neck flexors, hip flexors, and hip extensors.
- It is possible that pain may be diagnosed as fibromyalgia in the absence of other myotonic dystrophy type 2–associated features.
- Both patients with myotonic dystrophy type 1 and patients with myotonic dystrophy type 2 benefit from moderate-intensity aerobic exercise.
- Skeletal muscle myotonia in patients with myotonic dystrophy type 1 or myotonic dystrophy type 2 may be treated with several different agents that target skeletal muscle sodium channels, such as mexiletine.
- Patients with myotonic dystrophy type 1 or myotonic dystrophy type 2 are at an increased risk of developing life-threatening cardiac arrhythmias. It is recommended that patients have an ECG at diagnosis and annually thereafter.
- It is important to screen patients with myotonic dystrophy type 1 and patients with myotonic dystrophy type 2 for the presence of central or obstructive sleep apnea.

- Patients with myotonic dystrophy type 1 or myotonic dystrophy type 2 should be screened with a glucose breath test for a bacterial overgrowth syndrome and treated appropriately if the test is positive. A high-fiber diet is the first-line treatment for patients with diarrhea or constipation.
- Patients with myotonic dystrophy are at risk of thyroid deficiency, which may exacerbate their fatigue and myotonia without treatment.
- Patients with myotonic dystrophy type 1 are at increased risk with use of general anesthesia. Complications include a hypersensitivity to opiate medications, a paradoxical reaction to muscle-depolarizing agents, or a prolonged ventilatory wean.

Article 9: Episodic Muscle Disorders

Valeria A. Sansone, MD, PhD. Continuum (Minneap Minn). December 2019; 25 (6 Muscle and Neuromuscular Junction Disorders):1696–1711.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the episodic muscle disorders, including benign cramp-fasciculation syndrome, the periodic paralyses, and the nondystrophic myotonias. The core diagnostic criteria for a diagnosis of primary periodic paralysis, including clues to distinguish between the hypokalemic and hyperkalemic forms, and the distinctive elements that characterize Andersen-Tawil syndrome are discussed. Management of patients with these disorders is also discussed.

RECENT FINDINGS:

Childhood presentations of periodic paralysis have recently been described, including atypical findings. Carbonic anhydrase inhibitors, such as dichlorphenamide, have recently been approved by the US Food and Drug Administration (FDA) for the treatment of both hypokalemic and hyperkalemic forms of periodic paralysis. Muscle MRI may be a useful outcome measure in pharmacologic trials in periodic paralysis. Genetic research continues to identify additional gene mutations responsible for periodic paralysis.

SUMMARY:

This article will help neurologists diagnose and manage episodic muscle disorders and, in particular, the periodic paralyses and the nondystrophic myotonias.

KEY POINTS

- Cramp-fasciculation syndrome is a rare condition characterized by persistent muscle cramping and twitching (fasciculations), usually in the legs, in otherwise healthy individuals.
- Abortive attacks of weakness involving one or more limbs may erroneously suggest a psychogenic (functional) neurologic disorder because of the transitory nature of the event and the anxiety patients experience related to the loss of function, no matter how brief.
- Complete paralysis of all four limbs is the typical presentation that leads to the diagnostic workup for periodic paralysis. The most frequent differential diagnosis is Guillain-Barré syndrome.
- Children presenting with leg stiffness, cramps, muscle pain, and fluctuating extraocular movements should be examined for myotonia to rule out an underlying sodium channelopathy.
- Episodes of muscle weakness may also occur in the nondystrophic myotonias (sodium and chloride channelopathies).
- Cardiac involvement in Andersen-Tawil syndrome warrants close monitoring, even in patients who are asymptomatic.

- Testing the patient's serum potassium level during an attack of weakness is crucial to the diagnosis of periodic paralysis.
- Creatine kinase levels are not diagnostic in periodic paralysis.
- EMG may contribute to the diagnosis of periodic paralysis in patients in whom family history and potassium levels during an attack are unavailable or not informative.
- Muscle biopsy is not diagnostic in periodic paralysis; although tubular aggregates may be found in some patients, they are not specific to periodic paralysis.
- Patients can manage their episodes of periodic paralysis by learning to avoid triggers, following a diet based on the type of periodic paralysis, and stabilizing their serum potassium levels by taking oral potassium or diuretics according to the type of periodic paralysis.
- When managing patients with periodic paralysis, clinicians should consider more aggressive pharmacologic treatment with carbonic anhydrase inhibitors (preferably dichlorphenamide), if needed, and closely monitor cardiac function in Andersen-Tawil syndrome, even when no symptoms are present.

Article 10: Toxic Myopathies

Christopher T. Doughty, MD; Anthony A. Amato, MD, FAAN. Continuum (Minneap Minn). December 2019; 25 (6 Muscle and Neuromuscular Junction Disorders):1712–1731.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the pathogenesis, clinical features, and management of toxic myopathy related to common medications, critical illness, and illicit substances.

RECENT FINDINGS:

Muscle symptoms are common among statin users and are usually reversible after discontinuation of the statin; rarely, however, statins trigger an immune-mediated necrotizing myopathy that persists and requires immunomodulatory therapy. Autoantibodies targeting 3-hydroxy-3-methylglutaryl coenzyme A reductase can distinguish the toxic and immune-mediated forms. Immune checkpoint inhibitors, increasingly used in the treatment of advanced cancer, have recently been associated with the development of inflammatory myositis. A reversible mitochondrial myopathy has long been associated with zidovudine, but recent reports elucidate the risk of myopathy with newer antivirals, such as telbivudine and raltegravir.

SUMMARY:

The medications most commonly associated with myopathy include statins, amiodarone, chloroquine, hydroxychloroquine, colchicine, certain antivirals, and corticosteroids, and myopathy can occur with chronic alcoholism. Certain clinical, electrodiagnostic, and histologic features can aid in early recognition. Stopping the use of the offending agent reverses symptoms in most cases, but specific and timely treatment may be required in cases related to agents that trigger immune-mediated muscle injury.

KEY POINTS

- The clinical presentation of toxic myopathy is diverse. Some patients present with severe symptoms soon after initiation of the causative medication, whereas others present with mild symptoms that develop insidiously after months of exposure.

- In most cases, stopping the offending medication leads to improvement and even resolution of symptoms. Statins and immune checkpoint inhibitors, however, can cause an immune-mediated myopathy that may require immunomodulatory treatment.
- The spectrum of myopathic symptoms encountered with cholesterol-lowering agents includes myalgia, cramps, asymptomatic creatine kinase level elevation, proximal muscle weakness, and rhabdomyolysis with myoglobinuria.
- Myalgia and cramps are common among statin users but are not always related to the statin.
- Rhabdomyolysis in statin-treated patients is a rare event, with an estimated incidence of 2 to 3 per 100,000 patient-years.
- Many drugs interact with statins and increase the risk of muscle toxicity, including rhabdomyolysis, when used concurrently. Important examples include other cholesterol-lowering agents and cyclosporine.
- Higher doses, older age, and renal failure all increase the risk of statin myotoxicity.
- Manifestations of statin-associated toxic necrotizing myopathy resolve within 1 week to 3 months after stopping the statin. Persistent symptoms or creatine kinase level elevations thereafter should prompt consideration of immune-mediated necrotizing myopathy or other underlying disorders.
- A markedly elevated creatine kinase level and EMG demonstrating irritable myopathy are seen in both toxic necrotizing and immune-mediated forms of statin myopathy, but serum anti–3-hydroxy-3-methylglutaryl coenzyme A reductase antibodies are specific for the immune-mediated form.
- Fibrates cause a spectrum of muscle symptoms similar to statins. Myopathy has also been reported with niacin and ezetimibe, but mostly when used together with a statin.
- Although less common than other neurologic immune-related adverse events, inflammatory myositis can complicate treatment with immune checkpoint inhibitors. Symptoms typically begin after one or two treatment cycles.
- In addition to proximal and axial weakness, oculomotor and bulbar weakness are common with immune checkpoint inhibitor–associated myositis. Myasthenia gravis can develop concurrently.
- Muscle biopsy has demonstrated histiocytic and lymphocytic inflammatory infiltrates in patients with immune checkpoint inhibitor–associated myositis. The creatine kinase level is typically elevated, and EMG will show fibrillation potentials and positive sharp waves in most patients.
- When patients on an immune checkpoint inhibitor develop myositis or myasthenia gravis, the immune checkpoint inhibitor should be stopped. Most patients should also be treated with corticosteroids. Patients' symptoms markedly improve over a period of weeks.
- Chloroquine, hydroxychloroquine, and amiodarone can all cause clinical neuromyopathy. Vacuolar myopathy is evident on muscle biopsy.
- Recovery from amiodarone neuromyopathy may be partial and prolonged over months.
- Colchicine causes a neuromyopathy associated with vacuoles on muscle biopsy. Prolonged exposure is typically required, with weakness developing gradually over months.
- Zidovudine commonly caused a reversible mitochondrial myopathy but is used less commonly to treat HIV now. Myopathy has been reported with more contemporary antivirals, as well, including telbivudine, lamivudine, entecavir, and raltegravir.
- Proximal weakness related to steroid myopathy typically occurs after prolonged treatment with the equivalent of prednisone 30 mg daily. Creatine kinase values and EMG are commonly normal.
- Sepsis, multiorgan system failure, and hyperglycemia are associated with a higher risk of developing critical illness myopathy. The risk associated with corticosteroids or neuromuscular blocking agents is much less clear than previously thought.
- Recent reports suggest that levetiracetam, febuxostat, and isotretinoin can all rarely cause rhabdomyolysis and/or myopathy. The mechanism is uncertain.
- Mild proximal myopathy is common among patients with chronic alcoholism. Binge drinking and use of cocaine, amphetamines, and phencyclidine can all result in rhabdomyolysis.

Article 11: Mitochondrial and Metabolic Myopathies

Bruce H. Cohen, MD, FAAN. Continuum (Minneap Minn). December 2019; 25 (6 Muscle and Neuromuscular Junction Disorders):1732–1766.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of mitochondrial and metabolic biology, the genetic mechanisms causing mitochondrial diseases, the clinical features of mitochondrial diseases, lipid myopathies, and glycogen storage diseases, all with a focus on those syndromes and diseases associated with myopathy. Over the past decade, advances in genetic testing have revolutionized patient evaluation. The main goal of this review is to give the clinician the basic understanding to recognize patients at risk of these diseases using the standard history and physical examination.

RECENT FINDINGS:

Primary mitochondrial disease **is the current designation for the illnesses resulting from genetic mutations in genes whose protein products are necessary for mitochondrial structure or function. In most circumstances, more than one organ system is involved in mitochondrial disease, and the value of the classic clinical features as originally described early in the history of mitochondrial diseases has reemerged as being important to identifying patients who may have a primary mitochondrial disease. The use of the genetic laboratory has become the most powerful tool for confirming a diagnosis, and nuances of using genetic results will be discussed in this article. Treatment for mitochondrial disease is symptomatic, with less emphasis on vitamin and supplement therapy than in the past. Clinical trials using pharmacologic agents are in progress, with the field attempting to define proper goals of treatment. Several standard accepted therapies exist for many of the metabolic myopathies.**

SUMMARY:

Mitochondrial, lipid, and glycogen diseases are not uncommon causes of multisystem organ dysfunction, with the neurologic features, especially myopathy, occurring as a predominant feature. Early recognition requires basic knowledge of the varied clinical phenotypes before moving forward with a screening evaluation and possibly a genetic evaluation. Aside from a few specific diseases for which there are recommended interventions, treatment for the majority of these disorders remains symptomatic, with clinical trials currently in progress that will hopefully result in standard treatments.

KEY POINTS

- ***Primary mitochondrial disease*** **is the current designation for the illnesses resulting from genetic mutations in genes whose protein products are necessary for mitochondrial structure or function.**
- **Most primary mitochondrial diseases, as defined by the illnesses caused by mutations in mitochondrial-targeted genes, are a result of deficient energy production or excessive free radical production.**
- **Most patients with primary mitochondrial disease have at least one nervous system or special sensory system tissue involved.**
- **For patient care, it is most logical to classify the patient's mitochondrial illness by both genotype and phenotype, if available. It is recognized that no well-structured nomenclature for classifying all the mitochondrial diseases exists.**

- If it is not certain that mitochondrial disease is the cause of the patient's illness, it is highly recommended to avoid using the terms *possible* or *probable* as adjectives or descriptors of the term *mitochondrial disease*. Risks of mislabeling include failing to make the correct diagnosis, creating unnecessary worry, initiating unnecessary therapies, and providing incorrect genetic counseling.
- Treatment for the lipid myopathies depends on the specific enzyme defect; some disorders have no specific therapy and others have treatments, which often involve dietary manipulation or the use of cofactors or vitamins.
- Glycogen storage diseases result from deficiencies in the enzymes that build glycogen, as well as those that interfere with the degradation of glycogen and subsequent mobilization of glucose.
- The glycogen storage diseases that affect muscle present either with exercise intolerance and rhabdomyolysis, as seen with McArdle disease (GSD5) or Tarui disease (GSD7), or with myopathy without rhabdomyolysis, as in Pompe disease (GSD2) or debrancher defect (GSD3a).
- Enzyme replacement with acid maltase can dramatically improve the muscle symptoms of Pompe disease.
- Patients with McArdle disease can demonstrate a "second wind phenomenon" in which symptoms improve or disappear after a period of exercise.
- The creatine kinase level is usually chronically elevated in McArdle disease and Pompe disease.
- Dietary therapy is a mainstay of therapy for the glycogen storage diseases.
- Pompe disease has a specific therapy involving IV infusion of alglucosidase alfa.

Article 12: Myasthenia Gravis and Congenital Myasthenic Syndromes

Emma Ciafaloni, MD. Continuum (Minneap Minn). December 2019; 25 (6 Muscle and Neuromuscular Junction Disorders):1767–1784.

ABSTRACT

PURPOSE OF REVIEW:

Myasthenia gravis (MG) is an autoimmune neuromuscular disease that causes fluctuating weakness in ocular, bulbar, and limb muscles and can, in 15% of cases, cause myasthenic crisis, a neurologic emergency characterized by respiratory failure. Although infrequent, MG needs to be promptly recognized and treated because the potential for improvement and remission is very high. The diagnosis of MG can be challenging and delayed because of the fluctuating nature of muscle weakness and the overlap of signs and symptoms with other neuromuscular diseases.

This article reviews the importance of prompt recognition of the typical signs and symptoms, best tests to confirm the diagnosis, currently available acute and chronic treatment modalities, the role of thymectomy, and the natural history of the disease. Special consideration related to the diagnosis and management in women during pregnancy and in children will also be reviewed. This article also includes an overview of congenital myasthenic syndromes.

RECENT FINDINGS:

Recent significant efforts in standardizing and improving the care of patients with MG have occurred, as well as new momentum in developing new drugs for patients with MG who do not adequately respond to currently available treatments. The number of clinical trials and drugs in development for MG is steadily increasing. Eculizumab has been recently approved by the US Food and Drug Administration (FDA) for adult patients with generalized MG who are acetylcholine receptor–antibody positive, based on the REGAIN (Safety and Efficacy of Eculizumab in Refractory Generalized Myasthenia Gravis) study, a phase 3, randomized,

double-blind, placebo-controlled, multicenter trial. An international, multicenter, randomized trial comparing thymectomy plus prednisone with prednisone alone has demonstrated that thymectomy improves clinical outcome in patients with nonthymomatous MG. Clinical care guidelines have been published, and the recommendations for clinical research standards and the Myasthenia Gravis Foundation of America MGFA clinical classification published in 2000 have become widely accepted by the clinical and research community of MG experts.

SUMMARY:

MG is a highly treatable disease with many effective treatment modalities available and with a natural history that continues to improve thanks to better diagnostic tests and effective drugs. The diagnosis and management of patients affected by MG can be highly rewarding for any neurologist as most patients are able to live normal lives if treated appropriately. Nevertheless, future research is needed to address unresolved clinical issues, such as when and how to discontinue immunosuppressive medications in patients in remission, the role and timing of thymectomy in children, and better treatment options for refractory patients.

KEY POINTS

- Autoimmune myasthenia gravis can occur at any age.
- Thymoma is found in about 15% of patients with myasthenia gravis and should always be surgically removed. Thymoma is more frequently found in males and patients older than 40, and about 50% of patients with thymoma develop myasthenia gravis.
- Antibody testing should be used for diagnostic purpose only and not as a repeat test to assess response to therapy. False-positive results are extremely rare.
- Patients with anti–muscle specific tyrosine kinase–positive myasthenia gravis are more often women and may present with predominant facial, pharyngeal, tongue, and respiratory weakness with or without ocular weakness. Patients respond more frequently to plasma exchange than IV immunoglobulin and may have less improvement and more side effects (prominent fasciculations) from cholinesterase inhibitors.
- In predominantly bulbar myasthenia gravis with minimal or no ocular weakness, the differential diagnosis with bulbar amyotrophic lateral sclerosis can be challenging: the absence of tongue atrophy and fasciculations, jaw jerk, and spastic speech is helpful for diagnosis. Electrodiagnostic tests, including EMG and single-fiber EMG of weak muscles, are most helpful in confirming the correct diagnosis.
- The most limiting side effect of pyridostigmine is abdominal cramping and diarrhea because of its muscarinic effect. One of the advantages of using pyridostigmine is its lack of long-term side effects.
- A common mistake in practice, especially in the inpatient setting, is prescribing pyridostigmine 3 or 4 times a day rather than as needed 30 minutes prior to meals when dysphagia is the targeted symptom.
- Thymectomy improves clinical outcome in patients with nonthymomatous myasthenia gravis who are between 18 and 65 years old. Thymectomy is generally not indicated in patients older than 65. The timing and role of thymectomy in children are not yet standardized.
- Pregnancy outcome in women with myasthenia gravis is generally good. Exacerbation of myasthenia gravis occurs in 20% to 30% of women during pregnancy and more commonly in the first trimester or postpartum period. Myasthenia gravis, per se, is not an indication for Cesarean delivery.
- IV immunoglobulin, plasma exchange, prednisone, and pyridostigmine are generally safe in pregnancy and lactation. Mycophenolate mofetil should be avoided during conception and pregnancy.
- Seronegative autoimmune myasthenia gravis in children can be difficult to differentiate from congenital myasthenic syndrome, and DNA testing, repetitive nerve stimulation, and the response to a trial of IV immunoglobulin or plasma exchange can help establish a definite diagnosis of seronegative autoimmune myasthenia gravis.
- Of newborns of mothers with myasthenia gravis, 10% to 15% develop transient neonatal myasthenia gravis, and it can resolve spontaneously after the maternal antibodies transmitted through the placenta are cleared.

Arthrogryposis multiform congenita can occur, although rarely, in newborns of mothers affected by myasthenia gravis, even of mothers who are asymptomatic.

- The diagnosis of congenital myasthenic syndrome should be considered in children with proximal muscle weakness and facial features consistent with a myopathy but in whom the creatine kinase level and muscle biopsy are normal.

Article 13: Lambert-Eaton Myasthenic Syndrome, Botulism, and Immune Checkpoint Inhibitor–Related Myasthenia Gravis

Amanda C. Guidon, MD. Continuum (Minneap Minn). December 2019; 25 (6 Muscle and Neuromuscular Junction Disorders):1785–1806.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the pathophysiology, epidemiology, clinical presentation, diagnosis, and treatment of Lambert-Eaton myasthenic syndrome (LEMS) and of botulism, and immune-related myasthenia gravis (MG) occurring in the context of immune checkpoint inhibitor therapy for cancer.

RECENT FINDINGS:

The suspicion that LEMS is rare but also likely underdiagnosed is supported by recent epidemiologic data. A validated, LEMS-specific scale now exists to assess and monitor disease, and symptomatic and immunomodulatory treatments are available. As presynaptic disorders of neuromuscular transmission, LEMS and botulism share electrodiagnostic abnormalities but have important distinguishing features. Knowledge of the clinical features of botulism is needed, particularly with continued cases of infant botulism, the opioid epidemic increasing the incidence of wound botulism, and medical use of botulinum toxin, which may cause iatrogenic botulism. Foodborne botulism remains rare. Prompt recognition of botulism and administration of antitoxin can improve outcomes. MG may be exacerbated or may present de novo in the context of immune activation from immune checkpoint inhibitor therapies for cancer. Immune-related MG commonly overlaps with myositis and myocarditis. Corticosteroids typically result in improvement. However, immune-related MG can be more fulminant than its idiopathic counterpart and may cause permanent disability or death.

SUMMARY:

The diagnosis of LEMS, botulism, or immune-related MG can generally be made from the patient's history, supplemented with directed questions, a physical examination designed to demonstrate abnormalities, and laboratory and electrodiagnostic testing. Early diagnosis and carefully selected treatment not only improve outcomes of the neuromuscular disease but can affect the prognosis of underlying malignancy, when present.

KEY POINTS

- In Lambert-Eaton myasthenic syndrome (LEMS), pathogenic P/Q-type voltage-gated calcium channel antibodies cause fewer quanta of acetylcholine to be released from presynaptic nerve terminals.

- Failure of neuromuscular transmission in LEMS results in symptoms of skeletal muscle weakness and autonomic dysfunction.
- LEMS is a rare disease that affects mostly adults and is likely underdiagnosed.
- More than half of patients with LEMS have an underlying cancer, most commonly small cell lung cancer, diagnosed within 2 years of disease onset.
- LEMS is generally a treatable disorder that may even improve the prognosis related to small cell lung cancer, when present.
- Symptoms of LEMS include a triad of gait dysfunction/lower extremity weakness, areflexia or hyporeflexia, and autonomic dysfunction.
- Patients should be specifically asked about autonomic symptoms of LEMS, including constipation, dry mouth, and orthostasis.
- Symptoms of LEMS typically exceed abnormal findings on examination; therefore, a high clinical suspicion is needed for diagnosis.
- Most patients with LEMS have diagnostic P/Q-type voltage-gated calcium channel antibodies.
- Electrodiagnostic studies are warranted in patients with LEMS, even in patients with positive antibody testing, to confirm a presynaptic disorder of neuromuscular transmission.
- In LEMS, low-amplitude compound muscle action potentials that facilitate after 10 seconds of exercise and show a decrement in distal nerve-muscle combinations with 3-Hz repetitive nerve stimulation are seen.
- Once the diagnosis of LEMS is suspected, patients should be screened for malignancy. If initial testing is negative, screening continues for up to 2 years.
- The Triple Timed Up and Go test is a reliable and validated outcome measure that can be easily performed in clinic and is used to monitor disease severity in clinical trials of patients with LEMS.
- Amifampridine phosphate and 3,4-diaminopyridine are the primary symptomatic therapies for LEMS. Immunosuppressive therapies are second- or third-line therapies.
- Botulinum neurotoxin is produced by an anaerobic gram-positive spore-forming bacillus. The toxin inhibits presynaptic acetylcholine release in motor and autonomic nerves.
- Cases of botulism are categorized into one of four major transmission categories: foodborne, wound, infant, and other (which includes iatrogenic).
- Botulism presents as acute descending flaccid weakness and respiratory and autonomic dysfunction. Botulism is considered in the differential diagnosis for the acutely "floppy baby" under 1 year of age.
- Physicians should notify the state or other relevant health department to obtain treatment and work to isolate a source as soon as botulism is suspected.
- Electrodiagnostic studies are critical in helping narrow the differential diagnosis and may demonstrate the presynaptic abnormalities of botulism. However, normal studies do not exclude the diagnosis of botulism, especially early in disease.
- Early public health notification of the suspected botulism diagnosis allows for early treatment with human botulism immunoglobulin intravenous (BIG-IV) or antitoxin, which improves outcomes.
- Mortality from botulism is low; however, recovery can be protracted.
- A myasthenic syndrome is now associated with immune checkpoint inhibitor therapy for cancer. It frequently overlaps with other neurologic and non-neurologic immune-related adverse events.
- Currently, treatment of immune-related myasthenia gravis from immune checkpoint inhibitor therapy first involves treatment interruption and often corticosteroids.

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Article 1: Adult Gliomas

Howard Colman, MD, PhD, FAAN. Continuum (Minneap Minn). December 2020; 26 (6 Neuro-oncology):1452–1475.

ABSTRACT

PURPOSE OF REVIEW:

This article highlights important aspects of the evaluation, diagnosis, and treatment of adult gliomas, including lower-grade astrocytomas and oligodendrogliomas, glioblastomas, and ependymomas.

RECENT FINDINGS:

The appropriate initial evaluation and accurate diagnosis of gliomas require an understanding of the spectrum of clinical and radiographic presentations. Recent advances in the understanding of distinct molecular prognostic subtypes have led to major revisions in the diagnostic classification of gliomas. Integration of these new diagnostic and molecular classifications is an important part of the modern management of gliomas and facilitates better understanding and interpretation of the efficacy of different therapies in specific glioma subtypes.

SUMMARY:

The management of adult gliomas is a multidisciplinary endeavor. However, despite recent molecular and treatment advances, the majority of diffuse gliomas remain incurable, and efforts aimed at the development and testing of new therapies in clinical trials are ongoing.

KEY POINTS

- Adult gliomas are a clinically, radiographically, histologically, and molecularly heterogeneous group of tumors.
- The clinical presentation and symptoms of gliomas are often related to anatomic location.
- The acuity of symptoms and presentation are often related to the tumor growth rate.
- MRI is more sensitive than CT for the diagnosis of potential gliomas and other brain tumors.
- Careful consideration of history, clinical factors, and imaging is needed to develop an accurate differential diagnosis in the evaluation of a newly presenting patient with imaging potentially consistent with glioma.
- The differing molecular features of diffuse gliomas are associated with distinct diagnoses and prognoses.
- The revised 2016 World Health Organization (WHO) classification of gliomas incorporates histologic and molecular features into an integrated diagnosis.
- The major molecular alterations used for diagnosis and classification of gliomas include isocitrate dehydrogenase (*IDH)* mutation status, chromosome 1p/19q status, and H3K27M mutation status.
- The majority of lower-grade (grade II and III) astrocytomas and oligodendrogliomas have *IDH* mutations.

- Loss of chromosomes 1p/19q is the molecular hallmark that distinguishes oligodendroglial from astrocytic gliomas within the *IDH*-mutant group.
- For the diagnosis of either astrocytoma or anaplastic astrocytoma with *IDH* mutation, the presence or absence of other molecular alterations including *CDKN2* loss may be more important than the actual WHO grade for prognosis.
- The vast majority of primary glioblastomas in older adults are *IDH*-wildtype, and even lower-grade *IDH*-wildtype astrocytic tumors with appropriate molecular alterations (*EGFR* or chromosome 7 gain/chromosome 10 loss or *TERT* promoter) can be classified as diffuse astrocytic glioma, *IDH*-wildtype, with molecular features of glioblastoma, WHO grade IV.
- H3K27M mutations are the hallmark of diffuse midline glioma, which most commonly occur in the pons and diencephalon in younger patients and are associated with poor prognosis.
- Initial treatment for most diffuse gliomas starts with maximal safe resection.
- *O*-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation is both a prognostic marker in glioblastoma and a predictive marker of a better outcome with temozolomide.
- Standard treatment options with survival benefit in randomized studies for newly diagnosed glioblastoma include radiation, temozolomide, and tumor treating fields.
- Bevacizumab is US Food and Drug Administration (FDA)-approved for recurrent glioblastoma based on improved progression-free survival in randomized studies, but this agent has not demonstrated an overall survival benefit in glioblastoma.
- In older patients with newly diagnosed glioblastoma, a hypofractionated course of radiation is a consideration with or without temozolomide or tumor treating fields.
- The combination of radiation and chemotherapy (either procarbazine, lomustine [CCNU], and vincristine [PCV] or temozolomide) has been proven more effective for prolonging survival than radiation alone in lower-grade diffuse gliomas with *IDH* mutation.
- Participation in a clinical trial is an important consideration in the treatment of all histologies, grades, and molecular subtypes of glioma.

Article 2: Central Nervous System Lymphomas

Christian Grommes, MD. Continuum (Minneap Minn). December 2020; 26 (6 Neuro-oncology):1476–1494.

ABSTRACT

PURPOSE OF REVIEW:

Primary central nervous system (CNS) lymphoma is a rare, aggressive extranodal non-Hodgkin lymphoma confined to the brain, eyes, CSF, or spinal cord without systemic, non-CNS involvement. This article reviews the clinical presentation, imaging characteristics, diagnostic workup, novel pathophysiologic insights, and treatment of immunocompetent patients with primary CNS lymphoma.

RECENT FINDINGS:

The prognosis of primary CNS lymphoma has significantly improved over the past few decades because of the introduction of and widespread use of high-dose methotrexate, which is now the backbone of all first-line combination chemotherapy treatments. Despite this progress, durable remission is still observed in only approximately 50% of patients. Novel insights into the pathophysiology of primary CNS lymphoma have identified the B-cell receptor pathway as well

as the suppressed tumor immune microenvironment and immune evasion as key mechanisms in the pathogenesis of primary CNS lymphoma. Novel, small molecules and agents targeting these aberrant pathways have been introduced into clinical trials of recurrent/refractory primary CNS lymphomas. Agents such as the Bruton tyrosine kinase (BTK) inhibitor ibrutinib or immunomodulatory drugs such as lenalidomide and pomalidomide have shown promising response rates in the relapsed setting.

SUMMARY:

Diagnosis of primary CNS lymphoma requires a high level of suspicion because clinical signs and deficits can vary and depend on the involved CNS compartments. Rapid initiation of therapy is essential for recovery and prognosis. The optimal treatment regimen has not been defined, but methotrexate-based chemotherapy regimens are considered the standard treatment approach for induction treatment. Novel, targeted agents have recently been introduced into the therapeutic arsenal.

KEY POINTS

- The majority of primary central nervous system (CNS) lymphoma cases are diffuse large B-cell lymphomas that cause neurologic deficits within weeks. Primary CNS lymphoma is highly sensitive to high-dose methotrexate with some long-term survivors after treatment with methotrexate alone. Still, the rate of long-term disease control is lower than in lymphomas outside the brain.
- Neurologic deficits depend on the area of the CNS affected by primary CNS lymphoma. The diagnosis, therefore, requires a high level of suspicion.
- MRI is the standard imaging modality for primary CNS lymphoma. Primary CNS lymphoma lesions are characterized by homogeneous enhancement and usually affect deep brain structures.
- Diagnosis of primary CNS lymphoma should be based on tissue collected through a biopsy. Vitreous biopsy or CSF can also add diagnostic value. Corticosteroid use before diagnosis could lead to partial radiographic response and false-negative biopsy results.
- Surgery is only used to collect tissue for the histopathologic diagnosis through stereotactic biopsy. No survival benefit from surgical resection has been proven.
- The majority of primary CNS lymphomas are of the non–germinal center subtype. The B-cell receptor signaling pathway is affected by frequent recurrent mutations and seems to play an essential role in primary CNS lymphoma pathogenesis. The role of immune evasion markers (programmed cell death 1 or programmed death ligand 1) is currently less clear.
- Baseline evaluations in primary CNS lymphoma should include clinical, laboratory, and radiographic evaluations to document CSF or ocular involvement as well as systemic lymphoma. The detection of systemic lymphoma will lead to a change in management and chemotherapy choice.
- The two most important prognostic factors for primary CNS lymphoma are age and performance status.
- Newly diagnosed primary CNS lymphoma is treated in remission-induction (induction) and remission-consolidation (consolidation) phases.
- Historically, whole-brain radiation therapy has been used with high response rates but poor long-term disease control.
- Chemotherapy regimens used in systemic lymphoma (cyclophosphamide, doxorubicin, vincristine, and prednisone) are ineffective in primary CNS lymphoma, most likely due to poor brain penetration.
- Methotrexate chemotherapy is considered the standard treatment approach in primary CNS lymphoma. Methotrexate-based combination chemotherapies are more effective than methotrexate alone.
- Whole-brain radiation therapy–related neurotoxicity is a significant problem causing morbidities including cognitive impairment, incontinence, and gait disturbance. Older patients are particularly vulnerable.
- The optimal dose and schedule of high-dose methotrexate and the optimal chemotherapy combination have not yet been defined. The role of rituximab and whole-brain radiation in patients with newly diagnosed primary CNS lymphoma remains unclear.

- In patients younger than 65, intensive methotrexate-based chemotherapy followed by consolidative high-dose chemotherapy with autologous stem cell rescue has high clinical efficacy.
- Responses to first-line therapy are high in patients with primary CNS lymphoma. Still, disease relapse is common, mostly occurring in the first 2 years after methotrexate-based first-line treatment. Prognosis at relapse is poor.
- Novel targeted agents have been introduced in the treatment of refractory and relapsed primary CNS lymphoma.
- In the relapsed setting, the choice of therapeutic agent depends on age, performance status, prior treatment history, and response, as well as medical comorbidities. Treatment choices include methotrexate rechallenge, palliative whole-brain radiation therapy, as well as new agents such as pemetrexed, ibrutinib, pomalidomide, and lenalidomide. The role of immune checkpoint inhibitors is not clearly defined yet, and phase 2 data are pending.

Article 3: Nonmalignant Brain Tumors

Rimas V. Lukas, MD; Maciej M. Mrugala, MD, PhD, MPH, FAAN. Continuum (Minneap Minn). December 2020; 26 (6 Neuro-oncology):1495–1522.

ABSTRACT

PURPOSE OF REVIEW:

This article describes the diagnosis and management of meningioma, pituitary adenoma, craniopharyngioma, and glioneuronal tumors.

RECENT FINDINGS:

Both meningiomas and pituitary adenomas are common brain tumors. In many cases, these lesions are found incidentally on imaging when patients are being evaluated for a variety of symptoms and signs. While nonmalignant, these tumors are occasionally associated with significant morbidity due to location and resulting secondary symptoms. Rarely, these tumors can also transform into malignant variants. Surgical techniques allow for more complete resections with minimal complications. Significant progress is being made in understanding the molecular biology of meningioma, which may result in wider availability of targeted therapies, especially for patients who are not candidates for other therapeutic modalities. Medical therapies for secretory pituitary adenomas continue to evolve. Craniopharyngiomas are nonmalignant tumors associated with significant morbidity due to their location. Molecular subtypes exist and may respond to targeted agents. Glioneuronal tumors are low-grade neoplasms potentially cured by gross total resection; however, residual and recurrent disease may require additional therapy. Recent studies have identified potentially targetable molecular alterations in more than half of cases.

SUMMARY:

Meningiomas and pituitary adenomas are frequently encountered in neurologic practice, and familiarity with their presentation and management is essential for a practicing neurologist. Craniopharyngiomas, meningiomas, and glioneuronal tumors are characterized by a high frequency of potentially actionable genetic alterations, and targeted therapies may eventually supplement surgical therapy of these nonmalignant tumors.

KEY POINTS

- Meningiomas are the most common primary brain tumor.
- Most meningiomas grow slowly and may be followed radiographically as the initial management approach as long as they are asymptomatic.
- Surgery is the primary treatment for meningioma in most cases, and recurrence rates are associated with the extent of resection and the grade of the tumor.
- Radiation therapy is usually reserved for unresectable meningiomas, incompletely resected meningiomas, recurrent meningiomas, and higher-grade meningiomas.
- Cytotoxic and hormonal medical therapies are largely ineffective in meningioma.
- Novel medical therapies for meningioma including tyrosine kinase inhibitors are under study.
- Pituitary adenomas are the second most common primary brain tumor and are frequently discovered on imaging incidentally.
- Pituitary adenomas smaller than 10 mm in diameter are termed *microadenomas* whereas pituitary adenomas 10 mm in diameter or larger are termed *macroadenomas*.
- Common categories of pituitary adenomas include functioning/secreting tumors and nonfunctioning/nonsecreting tumors.
- Medical therapies are commonly used for functioning/secreting pituitary adenomas as the primary treatment.
- Large pituitary adenomas may cause compression of adjacent critical structures including the optic pathways and often require prompt surgical intervention.
- Radiation therapy is used for patients with unresectable pituitary adenomas, recurrent pituitary adenomas, or those not responding to medical therapy.
- Craniopharyngiomas are low-grade, slow-growing tumors arising from the suprasellar region.
- Craniopharyngiomas can be divided into two subtypes, *BRAF* mutated (papillary) and *CTNNB1* mutated (adamantinomatous), based on their molecular alterations.
- Current management of craniopharyngiomas consists of resection by either a transcranial or an endoscopic approach.
- Surgery for craniopharyngioma may be followed by radiation, with either protons or photons, for recurrent or residual disease.
- Targeted therapies for craniopharyngioma remain investigational but hold substantial promise.
- Glioneuronal tumors are most often World Health Organization grade I; however, rare high-grade variants with poor prognosis occur.
- Dysembryoplastic neuroepithelial tumors (DNETs) and other glioneuronal tumors are associated with a high incidence of seizures.
- Resection is the primary treatment modality for glioneuronal tumors, and complete resection can often be curative.
- Molecular alterations including *BRAF* mutations and *NTRK* fusions occur in the majority of glioneuronal tumors and should be screened for; targeted agents against these alterations may be effective.

Article 4: Familial Nervous System Tumor Syndromes

Roy E. Strowd III, MD, MEd MS; Scott R. Plotkin, MD, PhD. Continuum (Minneap Minn). December 2020; 26 (6 Neuro-oncology):1523–1552.

ABSTRACT

PURPOSE OF REVIEW:

Although sporadic primary neoplasms account for the majority of nervous system tumors, familial nervous system tumor syndromes are important and clinically relevant conditions for the neurologist to understand. This article reviews common inherited nervous system tumor syndromes including neurofibromatosis type 1, neurofibromatosis type 2, schwannomatosis, tuberous sclerosis complex, and von Hippel-Lindau syndrome. The epidemiology, genetics, approach to diagnosis, neurologic and nonneurologic manifestations, and management options are reviewed.

RECENT FINDINGS:

Awareness of the more common and clinically relevant familial nervous system tumor syndromes is important. These conditions teach us about the underlying biology that drives tumor development in the central and peripheral nervous systems including peripheral nerve sheath tumors (eg, neurofibroma, schwannoma), meningioma, vestibular schwannoma, subependymal giant cell astrocytoma, and hemangioblastoma. Knowledge of the clinical manifestations ensures that the neurologist will be able to diagnose these conditions, recommend appropriate surveillance, refer to specialists, and support optimal management. Important discoveries in the role of the underlying genetics have contributed to the launch of several novel drug trials for these tumors, which are changing therapeutic options for patients.

SUMMARY:

Familial nervous system tumor syndromes are uncommon conditions that require specialized surveillance and management strategies. Coordination across a multidisciplinary team that includes neurologists, neuro-oncologists, radiologists, neurosurgeons, radiation oncologists, otolaryngologists, pathologists, neuropsychologists, physical medicine and rehabilitation specialists, and geneticists is necessary for the optimal treatment of these patients.

KEY POINTS

- **The Knudson two-hit hypothesis refers to an inactivating germline mutation that results in a first "hit," which increases susceptibility to subsequent somatic loss of heterozygosity (ie, a second hit) and resultant tumor formation.**
- **Neurofibromatosis type 1 (NF1) is the most common neurogenetic disorder with clinical manifestations that include café au lait macules, axillary and inguinal freckling, cutaneous and plexiform neurofibromas, optic pathway gliomas, and characteristic bony abnormalities.**
- **Severity of NF1 disease cannot be predicted based on the underlying *NF1* genotype except in cases of microdeletion (eg, when a large portion of the gene, more than 1.4 megabase pairs, is involved), which are associated with a more severe phenotype.**
- **Café au lait macules are frequently the first manifestation of NF1 and typically are present in early infancy and within the first 2 years of life.**
- **Neurofibromas are the hallmark of NF1 and represent benign neoplasms of nonmyelinating Schwann cells in the peripheral nerve.**

- Rapid growth (eg, doubling or tripling in several weeks), new unexplained pain, or new neurologic deficits may herald malignant degeneration of a plexiform neurofibroma into a malignant peripheral nerve sheath tumor.
- Focal areas of signal intensity are common and nearly pathognomonic for NF1; they represent areas of benign hamartomatous brain development, are asymptomatic, do not enhance with contrast, and do not require surveillance monitoring or treatment.
- Selumetinib, an oral selective MEK inhibitor, was approved by the US Food and Drug Administration in April 2020 for the treatment of children age 2 years and older with progressive, symptomatic, inoperable plexiform neurofibromas.
- Neurofibromatosis type 2 (NF2) is characterized by a predisposition to developing vestibular schwannomas, meningiomas, spinal cord ependymomas, peripheral nerve schwannomas, and juvenile posterior subcapsular cataracts.
- Bilateral vestibular schwannomas are pathognomonic for NF2 and typically present with hearing loss, tinnitus, balance difficulty, and, rarely, vertigo.
- Patients with NF2 should initially be monitored with neuroimaging of suspicious lesions and audiometry at 6-month intervals to establish a trajectory of tumor growth and functional impact.
- Removal of every tumor in NF2 is frequently not feasible or clinically necessary. Treatment should focus on the preservation of function and maximizing quality of life.
- Schwannomatosis is a rare neurogenetic syndrome typically presenting with multiple peripheral nerve schwannomas and chronic pain.
- Genetically, schwannomatosis is characterized by germline pathogenic variants in *SMARCB1* or *LZTR1* genes; additional unidentified genes also likely exist.
- Tumor formation in schwannomatosis is caused by concomitant mutational inactivation of two genes including the *NF2* gene as well as either *SMARCB1* or *LZTR1*.
- The most common symptom reported by patients with schwannomatosis is chronic pain, which is reported in more than 65% of patients.
- Tuberous sclerosis complex typically manifests with early-onset epilepsy, characteristic skin lesions, cortical tubers, subependymal nodules, subependymal giant cell astrocytomas (SEGAs), angiomyolipomas in the kidney, and lymphangioleiomyomatosis of the lung.
- Epilepsy is the most common and clinically challenging manifestation of tuberous sclerosis complex. Seizures occur in up to 85% of patients and often develop in infancy.
- The development of contrast enhancement in a subependymal nodule should raise suspicion for transformation to a subependymal giant cell astrocytoma.
- Angiomyolipomas are present in up to 80% of patients with tuberous sclerosis complex; they are frequently asymptomatic and not evident until surveillance imaging is performed.
- Lymphangioleiomyomatosis is uncommon in children with tuberous sclerosis complex and typically develops in the third to fourth decade with symptoms of worsening dyspnea or recurrent pneumothoraces.
- Response rates of greater than 50% are observed when treating SEGAs, renal angiomyolipomas, and pulmonary lymphangioleiomyomatosis with mammalian target of rapamycin (mTOR) inhibitors. Treatment of SEGA also reduces seizure frequency in patients with tuberous sclerosis complex.
- The most common nervous system manifestations of von Hippel-Lindau disease include hemangioblastomas of the cerebellum, spinal cord, and retina.

Article 5: Pediatric Brain Tumors

Sonia Partap, MD; Michelle Monje, MD, PhD. Continuum (Minneap Minn). December 2020; 26 (6 Neuro-oncology):1553–1583.

ABSTRACT

PURPOSE OF REVIEW:

This article focuses on primary brain tumors in the pediatric population with an emphasis on molecular classifications and treatment strategies.

RECENT FINDINGS:

Pediatric brain tumors are a heterogeneous group of tumors that differ from adult brain cancers despite similar nomenclature. With the added complexity of the developing brain, treatment regimens are tailored to protect neurocognitive outcomes without sacrificing long-term survival. The 2016 World Health Organization's classification incorporated molecular characteristics to aid in defining the diagnosis and prognosis of these tumors. These changes have enabled providers to stratify patients, thus intensifying therapies in those with high-risk diseases and modifying treatments to reduce morbidity for children and to provide better outcomes. Recent published findings from clinical trials have been especially helpful for gliomas, embryonal tumors, and ependymomas. By using this new information, molecular factors that correlate with survival have been identified in patients. In addition, genetic findings in tumor tissue have also led to revelations in predisposing germline mutations.

SUMMARY:

New findings from clinical trials and molecular stratification will shape the next generation of therapies in hopes of improving overall outcome, identifying pathways in tumorigenesis, and aiding in genetic counseling for children and their families.

KEY POINTS

- Increasingly, pediatric brain tumors are defined and classified molecularly.
- Despite the histologic appearance of diffuse gliomas, the presence of an *H3K27M* mutation classifies these tumors as World Health Organization grade IV.
- Minimization of steroid use is strongly advised in children with diffuse midline gliomas because these patients tend to receive more steroids than is useful and steroid-related toxicities contribute to morbidity and impaired quality of life.
- Unlike adult high-grade glioma, pediatric high-grade glioma is generally not responsive to temozolomide.
- In approximately 75% of pediatric low-grade astrocytomas, a *KIAA1549-BRAF* truncation/fusion alteration is present and confers a better prognosis than that associated with a *BRAF* V600E mutation. MEK inhibitors hold significant promise in the treatment of these *KIAA1549-BRAF* truncation/fusion pediatric low-grade astrocytomas.
- *BRAF* inhibitors should be avoided in patients with pediatric low-grade astrocytoma with the *KIAA1549-BRAF* truncation/fusion alteration because of paradoxical stimulation of tumor growth.
- Unlike adult low-grade glioma, pediatric low-grade glioma rarely transforms to higher-grade glioma.
- Although posterior fossa tumors can occur at all childhood ages, specific types prevail in various age groups.
- Ependymoma is now subclassified by molecular alterations, which often correlate to location and age at diagnosis.
- Embryonal tumors are highly compact and cellular tumors and, consequently, can demonstrate diffusion restriction on MRI.
- Nonglial tumors and ependymal tumors warrant evaluation for metastasis with contrast-enhanced MRI of the entire spine and lumbar puncture for CSF cytology.

- Embryonal tumors are all small round blue cell tumors that are now distinguished by their molecular alterations and/or location. *Primitive neuroectodermal tumor* is no longer used as a descriptor.
- The most common cerebellar masses in children are pilocytic astrocytomas, medulloblastomas, and ependymomas.
- Risk stratification for medulloblastoma is dependent on extent of surgical resection, evidence of metastasis, patient age, histology, and molecular subgroup.
- Obtaining tumor serum markers for β-human chorionic gonadotropin (βHCG) and α-fetoprotein is an appropriate first step when the differential diagnosis includes a CNS germ cell tumor.
- The differential diagnosis for a suprasellar/pituitary lesion with diabetes insipidus includes lymphocytic hypophysitis, Langerhans cell histiocytosis, and CNS germ cell tumor.
- Craniopharyngiomas, although low grade (WHO grade I), have high morbidity because of their suprasellar location and impact on vision and hypothalamic-pituitary function.

Article 6: Metastasis to the Central Nervous System

Adrienne Boire, MD, PhD. Continuum (Minneap Minn). December 2020; 26 (6 Neuro-oncology):1584–1601.

ABSTRACT

Purpose of Review:

Management of metastasis to the central nervous system (CNS) has evolved, and molecular characterization of metastatic disease is now routinely done. Targeted therapies, once few in number with limited penetration into the CNS, have multiplied in number and increased in CNS coverage. This article addresses recent advances in the evaluation and clinical management of patients with CNS metastasis.

Recent Findings:

Metastasis of cancer to the CNS can be diagnosed and characterized with novel techniques, including molecular analyses of the spinal fluid, so-called *liquid biopsies*. Resected parenchymal CNS metastases are now routinely subjected to genomic sequencing. For patients with CNS metastases displaying targetable mutations, a wide variety of treatment options are available, including deferral of radiation therapy in favor of a trial of an orally bioavailable targeted therapy or immunotherapy. For patients without a molecularly targetable lesion, local treatment in the form of radiation therapy, now most often stereotactic radiosurgery, is supplanting untargeted whole-brain radiation therapy.

Summary:

Technologic advances in diagnosis and management have resulted in new diagnostic and therapeutic approaches to patients with metastasis to the CNS, with resulting improvements in progression-free and overall survival.

KEY POINTS

- Central nervous system metastases are common in patients with cancer and may occur in the brain, spinal cord, leptomeninges, epidural space, or dura.
- Patients may harbor metastases in the brain parenchyma, spinal cord, leptomeninges, and epidural and dural spaces either singly or, more commonly, in combination. If a single discovered metastasis cannot adequately explain a patient's symptoms or signs, imaging of additional sites is warranted.

- Treatment of symptomatic lesions is the initial primary focus of care in patients with metastases to the central nervous system.
- Parenchymal brain metastases grow within the confines of the blood-brain barrier, and systemic therapies must penetrate this space to be effective.
- Leptomeningeal metastasis growth is bound by the blood-CSF barrier; treatments for malignancy within this space include intrathecal therapy and CSF-penetrant systemic therapies.
- Central nervous system metastases are the result of selective genetic pressures and may therefore harbor mutations unlike those of the primary cancer.
- When feasible, surgical resection of the symptomatic lesion(s) is preferred as it enables molecular and genetic characterization of the lesion.
- When not surgically accessible, symptomatic central nervous system metastases may be treated with radiation therapy.
- After surgical resection of central nervous system metastases, radiation is generally applied to the surgical bed to reduce the likelihood of recurrence.
- The indications for the use of whole-brain radiation therapy are more restricted now than in the past.
- Dural and epidural metastases reside outside the blood-brain and blood-CSF barriers and thus can be treated with standard chemotherapies, immunotherapies, and targeted therapies.
- Intrathecal therapy is inappropriate for patients with elevated intracranial pressure or bulky leptomeningeal deposits.
- Delivery of intrathecal therapy through an intraventricular catheter, such as an Ommaya reservoir, is preferable to delivery of the drug into the lumbar cistern.
- Many new central nervous system–penetrating targeted therapies and immunotherapies have emerged that may be used in select cases to treat central nervous system metastases in lieu of radiation therapy.
- Immunotherapy shows promise for parenchymal brain metastases from melanoma and non–small cell lung cancer in certain patient subpopulations.

Article 7: Paraneoplastic Disorders of the Nervous System

Eoin P. Flanagan, MBBCh. Continuum (Minneap Minn). December 2020; 26 (6 Neuro-oncology):1602–1628.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews paraneoplastic neurologic disorders and includes an overview of the diagnostic approach, the role of autoantibody testing, the pathophysiology of these disorders, and treatment approaches. This article also provides an overview of the emerging clinical scenarios in which paraneoplastic and autoimmune neurologic disorders may occur.

RECENT FINDINGS:

The number of autoantibodies associated with paraneoplastic neurologic disorders has rapidly expanded over the past 2 decades. These discoveries have improved our ability to diagnose patients with these disorders and have provided insight into their pathogenesis. It is now recognized that these antibodies can be broadly divided into two major categories based on the location of the target antigen: intracellular and cell surface/synaptic. Antibodies to intracellular antigens are almost always accompanied by cancer, respond less well to immunotherapy, and have an unfavorable outcome. In contrast, antibodies to cell surface or synaptic targets are less

often accompanied by cancer, generally respond well to immunotherapy, and have a good prognosis. Paraneoplastic and autoimmune neurologic disorders are now being recognized in novel settings, including their occurrence as an immune-related adverse effect of immune checkpoint inhibitor treatment for cancer.

SUMMARY:

This article discusses when to suspect a paraneoplastic neurologic syndrome, the diagnostic utility and pitfalls of neural autoantibody testing, how to best detect the underlying tumor, and the treatment approach that involves combinations of antineoplastic treatments, immunosuppressants, and supportive/symptomatic treatments.

KEY POINTS

- Paraneoplastic neurologic syndromes frequently manifest before a cancer diagnosis, and their recognition can lead to the detection of an occult malignancy.
- Major advances have occurred in the field of paraneoplastic neurologic disorders with the discovery of a multitude of autoantibody biomarkers of paraneoplastic disease that can confirm the diagnosis and provide insight into the type and location of the underlying cancer.
- Limbic encephalitis is a characteristic paraneoplastic neurologic syndrome that manifests with subacute memory loss, encephalopathy, and seizures accompanied by mesial temporal MRI T2 hyperintensities; it can be associated with a wide array of antibodies.
- Anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a characteristic paraneoplastic encephalitis that has a predilection for young women and manifests clinically with a combination of psychosis, seizures, encephalitis, orofacial dyskinesia, autonomic dysfunction, and hypoventilation in the setting of an underlying ovarian teratoma.
- Paraneoplastic cerebellar degeneration begins with subacute progressive ataxia and is associated with a wide variety of paraneoplastic antibodies.
- A hallmark subacute sensory neuronopathy is described in association with antineuronal nuclear antibody type 1 (ANNA-1)/anti-Hu antibodies and small cell lung cancer.
- Paraneoplastic Lambert-Eaton myasthenic syndrome typically presents with proximal muscle weakness with depressed reflexes that improve with exercise and is seen in the setting of an underlying small cell lung cancer.
- Myasthenia gravis is most often associated with antibodies targeting the muscle acetylcholine receptor, and 10% of cases are paraneoplastic and associated with an underlying thymoma.
- Paraneoplastic neural antibody testing helps confirm the diagnosis of a paraneoplastic neurologic disorder as the cause of the neurologic syndrome. The antibody detected can also give a clue to the type and location of the underlying cancer and may help guide treatment and predict outcome.
- The techniques for testing neural autoantibodies have evolved over time, and improvements in antibody-detection methods have resulted in improvements in sensitivity and specificity.
- Although a positive antibody can confirm a paraneoplastic neurologic disorder, some antibodies detected with earlier-generation techniques occur at a sufficiently high frequency in the general population, so their detection must be put into clinical context to avoid misdiagnosis.
- The cancers most commonly associated with paraneoplastic neurologic disorders include neuroendocrine tumors, thymomas, gynecologic cancers, testicular germ cell tumors, breast cancers, and hematologic malignancies.
- In patients with a paraneoplastic disorder, a general screening approach should be considered, with CT of the chest, abdomen, and pelvis or body positron emission tomography (PET)-CT obtained while antibody test results are awaited.
- Fludeoxyglucose positron emission tomography (FDG-PET) combined with CT has higher sensitivity for cancer detection and is particularly useful when an antibody with high positive predictive value for cancer is present.
- Antibodies that bind intracellular antigens are almost always associated with cancer, and the immune-mediated damage appears to be driven by a cytotoxic T-cell–mediated process resulting in cell damage or death, which may explain the poor prognosis and the lack of response to immunotherapy.

- When compared with antibodies to intracellular antigens, antibodies that bind cell surface antigens are less commonly associated with cancer, have the potential to be directly pathogenic, and tend to respond better to immunotherapy, particularly treatments that deplete antibodies or B cells.
- The first step in the treatment of a paraneoplastic neurologic disorder is to detect and treat the underlying cancer, and earlier treatment is associated with better outcomes.
- Concurrent or adjuvant immunosuppressive treatment after oncologic treatment should be considered in paraneoplastic neurologic disorders, unless they resolve with cancer treatment alone, which is rare.
- Neurologic immune-related adverse effects can occur in patients with cancer treated with immune checkpoint inhibitors.

Article 8: Neurologic Complications in Patients With Cancer

Eudocia Q. Lee, MD, MPH. Continuum (Minneap Minn). December 2020; 26 (6 Neuro-oncology):1629–1645.

ABSTRACT

PURPOSE OF REVIEW:

Neurologic complications in patients with cancer can significantly impact morbidity and mortality. Although these complications can be seen in patients without cancer as well, the purpose of this review is to highlight how the presentation, etiology, and management of delirium, seizures, cerebrovascular disease, and central nervous system infections may be different in patients with cancer.

RECENT FINDINGS:

Some of the newer anticancer therapies are associated with neurologic complications. Delirium and seizures have been described in patients receiving chimeric antigen receptor (CAR) T-cell therapy and other immune effector cell therapies. Angiogenesis inhibitors can increase the risk of bleeding and clotting, including intracranial hemorrhage and stroke. The risk of opportunistic fungal infections, including aspergillosis, is elevated with the Bruton tyrosine kinase inhibitor ibrutinib.

SUMMARY:

Providers should familiarize themselves with neurologic complications in patients with cancer because early diagnosis and intervention can improve outcomes. The differential diagnosis should be broad, including conventional causes as seen in patients who do not have cancer, with special consideration of etiologies specific to patients with cancer.

KEY POINTS

- Delirium is particularly common in advanced-stage cancer, at the end of life, in advanced age, and in patients with preexisting dementia.
- Precipitants of delirium in patients with cancer include central nervous system (CNS) metastases, infections, nutritional and vitamin deficiencies, metabolic abnormalities (eg, hypercalcemia, hyponatremia), endocrinopathies, organ dysfunction, seizures, paraneoplastic disorders, psychoactive medications (eg, opioids, benzodiazepines, antidepressants, antihistamines, and anticholinergics), chemotherapy, corticosteroids, alcohol, dehydration, surgery, and uncontrolled pain.

- Approximately half of delirium episodes can be reversed, especially those precipitated by medications, infections, and electrolyte abnormalities.
- The risk of brain tumor–related seizures varies depending on the tumor location (higher risk for tumors involving the frontal, temporal, or insular cortical gray matter) and underlying pathology (highest risk for glioneuronal tumors).
- In brain tumor–related seizures, seizure control from tumor resection depends on whether the seizure focus is or is not located in the tumor.
- The 2000 American Academy of Neurology (AAN) practice guideline recommends against prophylactic use of antiepileptic drugs in patients with brain tumors and no history of seizures.
- In patients with cancer, the risk of hemorrhagic and ischemic stroke is highest in the first 6 months after a cancer diagnosis, decreasing after the first 6 months but remaining elevated even more than 10 years after diagnosis.
- Radiation-induced vasculopathy resulting in stroke is a delayed complication of radiation, often occurring years after completion of radiation.
- Acquired immunodeficiency related to hematologic malignancy, chemotherapy, hematopoietic stem cell transplantation, or immunosuppressants increases the risk of opportunistic infections including CNS infections.
- Aspergillosis is an invasive fungal infection observed in immunocompromised patients and can involve the CNS, most notably in the form of brain abscesses.
- Progressive multifocal leukoencephalopathy is an aggressive and often fatal disease caused by JC virus resulting in demyelinating lesions involving subcortical U fibers.
- Unlike its counterpart in immunocompetent hosts, primary CNS lymphoma in immunocompromised patients is driven by Epstein-Barr virus and is more often multifocal and ring-enhancing on brain MRI.

Article 9: Neurotoxicity of Cancer Therapies

Jorg Dietrich, MD, PhD, FAAN. Continuum (Minneap Minn). December 2020; 26 (6 Neuro-oncology):1646–1672.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews neurologic complications associated with chemotherapy, radiation therapy, antiangiogenic therapy, and immunotherapy.

RECENT FINDINGS:

Cancer therapies can cause a wide range of neurologic adverse effects and may result in significant patient morbidity and mortality. Although some treatment-associated neurologic complications manifest acutely and are often reversible and transient, others occur with delayed onset, can be progressive, and are uniquely challenging to patient management. With an increase in multimodality and combination therapies, including targeted therapies and immunotherapies, and prolonged patient survival, novel and unique patterns of neurologic complications have emerged.

SUMMARY:

Both conventional and novel cancer therapies can adversely affect the nervous system, thereby producing a wide range of neurologic complications. Increased awareness among neurologists and early recognition of cancer therapy–induced neurotoxic syndromes is critically important to minimize patient morbidity, prevent permanent injury, and improve patient outcomes.

KEY POINTS

- Cancer-directed therapy can be harmful to the central and peripheral nervous systems, and patients may develop a wide range of acute and delayed neurologic complications.
- Neurotoxicity from cancer therapy is a major cause of impaired quality of life in patients with cancer, especially in long-term survivors.
- Chemotherapy-induced peripheral neuropathy is the most common form of neurotoxicity in patients with cancer, and its manifestation is usually dose dependent.
- The most common form of chemotherapy-induced peripheral neuropathy is characterized by a predominantly sensory, length-dependent, symmetric, and painful polyneuropathy.
- A unique phenomenon referred to as *coasting* is observed after treatment with platinum agents and is characterized by peripheral neuropathy that worsens several months after chemotherapy discontinuation.
- Underlying genetic neuropathies (eg, Charcot-Marie-Tooth disease and other hereditary neuropathies) may confer an elevated risk of developing chemotherapy-induced peripheral neuropathy.
- Most forms of chemotherapy-induced peripheral neuropathy are reversible after discontinuation of the offending drug and with supportive management.
- Acute encephalopathy has been associated with a wide range of chemotherapeutic agents.
- Posterior reversible encephalopathy syndrome (PRES) has been associated with a large number of anticancer agents and can present in the absence of hypertension.
- Diffuse white matter injury, a frequent complication of radiation therapy, may also occur after chemotherapy and can be irreversible.
- Cognitive impairment is one of the most frequent complications of cancer therapy and can negatively impact quality of life in cancer patients.
- Radiation-induced neurotoxicity can be categorized into acute, early-delayed, and late-delayed complications.
- Delayed neurologic complications from radiation therapy are often irreversible.
- Neuroprotective strategies have been increasingly used to prevent or limit radiation-induced neurologic complications. These strategies include radiation therapy, hippocampal avoidance, and the use of pharmacologic interventions during and after radiation therapy. There is a need for prospective, randomized clinical trials to validate the benefit of these strategies.
- Cerebral radiation necrosis is a delayed and severe complication of brain radiation therapy and can mimic tumor recurrence.
- Cerebrovascular complications and secondary tumors are serious delayed complications from radiation therapy, and children and long-term survivors are at the highest risk.
- Immunotherapies such as chimeric antigen receptor T cells and checkpoint inhibitors are associated with unique and serious patterns of neurotoxicity.

Article 10: Palliative and Supportive Care in Neuro-oncology

Deborah A. Forst, MD. Continuum (Minneap Minn). December 2020;
26 (6 Neuro-oncology):1673–1685.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the supportive care needs of patients with primary brain tumors and their caregivers, outlines the management of selected common symptoms of patients with brain tumors, and describes challenges and opportunities in providing palliative care for this population.

RECENT FINDINGS:

Patients with primary malignant brain tumors generally have a poor prognosis and experience progressive neurologic decline and significant physical and psychological symptoms. Management of these symptoms, including fatigue, mood disorders, and the manifestations of cerebral edema, can be challenging. Caregivers for these patients have high rates of psychological distress and report significant caregiving burden. Although the benefit of early palliative care for patients with other advanced solid tumors is well established, our understanding of the role of palliative care in neuro-oncology is incomplete, and thus palliative care and hospice services remain underutilized.

SUMMARY:

Patients with brain tumors and their caregivers have significant supportive care needs, which often differ from the needs of patients with cancers outside of the nervous system. Clinicians face challenges associated with managing patients' symptoms and adequately facilitating prognostic understanding and decision making. Palliative care and hospice services may offer important benefits for this population.

KEY POINTS

- Neurologic palliative care is a relatively new field, and the palliative care needs of patients with serious neurologic illnesses, and neuro-oncologic diseases, in particular, remain understudied.
- As neuro-oncology practitioners treat patients with unique symptoms and needs, the palliative care models that have proven beneficial for other patient populations may not be applicable and may need to be amended to adequately address this specific population.
- Compared with patients with other cancers, patients with primary brain tumors more frequently report drowsiness, irritability, difficulty speaking, cognitive impairment, and confusion, whereas they have lower rates of pain, nausea, vomiting, dyspnea, constipation, and anorexia.
- Corticosteroids, which effectively reduce cerebral edema and lead to associated symptom improvement, have long been the mainstay of treatment for patients with symptomatic cerebral edema related to brain tumors.
- It is often difficult to discontinue steroids in patients with primary brain tumors because of associated symptom worsening as well as symptomatic adrenal insufficiency.
- Patients requiring prolonged steroids for the management of symptomatic cerebral edema should be treated at the lowest dose possible and for the shortest period of time.
- The use of bevacizumab in patients with symptomatic cerebral edema may decrease steroid requirements, reduce neurologic symptoms, and improve quality of life, and it improves progression-free survival in patients with glioblastoma.
- Fatigue is a prevalent symptom in patients with cancer and is particularly problematic for patients with primary brain tumors, occurring in 20% to 95% of these patients.
- No pharmacologic or nonpharmacologic interventions have proven consistently effective for the treatment of brain tumor–associated fatigue.
- Despite negative randomized controlled trials, stimulants such as methylphenidate or dextroamphetamine/amphetamine and wakefulness-promoting agents such as modafinil or armodafinil can be useful for the management of fatigue in selected patients with persistent fatigue despite nonpharmacologic interventions.
- Depression occurs in approximately 15% to 20% of patients with gliomas, and anxiety has been reported in up to 30%.
- The diagnosis of mood disorders in patients with brain tumors may be difficult, as many of the symptoms associated with depression and anxiety can also be observed as a consequence of the cancer or cancer treatment.

- **Decision-making capacity may be impaired in patients with primary brain tumors at the time of diagnosis or early in the disease course.**
- **Advance care planning can help ensure that end-of-life care matches the patient's wishes and can result in less psychological distress for bereaved caregivers after the patient's death.**
- **In addition to the financial, psychosocial, and emotional burden of caring for a loved one with advanced cancer, caregivers of patients with brain tumors are subject to additional stressors associated with their loved ones' loss of cognitive and neurologic functions.**

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Neuro-Ophthalmology

Article 1: The Pupil

Marc A. Bouffard, MD. Continuum (Minneap Minn). October 2019;
25 (5 Neuro-Ophthalmology):1194–1214.

ABSTRACT

PURPOSE OF REVIEW:

The goal of this article is to review the anatomy and physiology of pupillary function and then employ that information to develop a comprehensive framework for understanding and diagnosing pupillary disorders.

RECENT FINDINGS:

The contribution of rods and cones to the pupillary light reflex has long been known. A third photosensitive cell type, the intrinsically photosensitive retinal ganglion cell, has recently been discovered. This cell type employs melanopsin to mediate a portion of the pupillary light reflex independent of rods and cones (the postillumination pupillary response) and photic regulation of circadian rhythm.

SUMMARY:

The autonomic nervous systemregulates pupil size in response to stimuli. The parasympathetic nervous system causes miosis in response to light and near visual stimuli. These stimuli activate supranuclear pathways that project to the Edinger-Westphal nuclei. The sympathetic nervous system causes mydriasis in response to a variety of arousing factors, both physiologic (wakefulness) and pathologic (pain). Abnormalities of physiologic function cause disturbances of pupil size, shape, and response to stimuli. The clinical approach to pupillary abnormalities should focus on the clinical and pharmacologic assessment of the pupil's expected response to diverse stimuli.

KEY POINTS

- **The pupillary sphincter muscle is located concentrically near the inner margin of the iris and mediates pupillary constriction via cholinergic stimulation from parasympathetic neurons.**
- **The pupillary dilator is composed of muscles radially arranged around the pupil that are stimulated by the sympathetic nervous syndrome via adrenergic input.**
- **The pupil constricts to both light and viewing of a near target. These two reflexes share the same anatomic efferent limb, the first-order neuron of which is located in the parasympathetic Edinger-Westphal nucleus and the second-order neuron of which is located in the ciliary ganglion. However, the parasympathetic neurons that mediate the near reflex outnumber those involved in the pupillary light reflex by a ratio of 30:1.**
- **Rods, cones, and intrinsically photosensitive retinal ganglion cells all contribute to the pupillary light reflex.**

- Retinal ganglion cells stimulate the ipsilateral olivary pretectal nucleus in response to light. Each olivary pretectal nucleus innervates the bilateral Edinger-Westphal nucleus, although the contralateral Edinger-Westphal nucleus is more highly innervated.
- The near triad encompasses pupillary miosis, convergence, and accommodation. Accommodation refers to relaxation of the ciliary body and a resulting increase in the concavity of the lens to allow for focus on an object at near; accommodation does not refer to the miosis that accompanies it as part of the near triad.
- Axons originating from the third-order sympathetic neurons in the superior cervical ganglion that innervate the superior and inferior Müller tarsal muscles and the pupillary dilator form a plexus around the internal carotid artery. Axons originating from third-order sympathetic neurons in the superior cervical ganglion that innervate the sweat glands of the face adhere to the external carotid artery on route to their target.
- Every examination of patients with anisocoria should include a detailed assessment of eye movements including cover-uncover testing) and of lid position and function.
- Anisocoria resulting from parasympathetic denervation is maximized in the light (when both pupils should constrict maximally).
- Chronic mydriasis in complete isolation is extraordinarily unlikely to result from a third nerve palsy.
- Tonic pupils are irregular, display sectoral hypokinesis (which may require the aid of a slit lamp to visualize), are slow to redilate after constriction (thus their name), and demonstrate light-near dissociation (reacting better to near stimuli than light). They may be idiopathic, occur frequently in young women, and are only rarely associated with other pathologic processes. Ninety percent of cases are monocular.
- Constriction of a mydriatic pupil by dilute pilocarpine (0.125%) was traditionally thought to be specific to tonic pupils. However, this is incorrect; preganglionic third nerve palsies resulting from compression and trauma may result in a mydriatic pupil responsive to 0.125% pilocarpine.
- Pilocarpine 2% will cause constriction of any mydriatic pupil other than one that is pharmacologically dilated.
- Anisocoria resulting from sympathetic denervation of the pupil is maximized in the dark (when both pupils should dilate maximally).
- The ptosis that results from sympathetic denervation is often subtle (1 mm to 2 mm), and frequently both the upper and lower lids are affected (as both the superior and inferior tarsus receive sympathetic innervation), which sometimes results in the optical illusion of enophthalmos (*pseudoenophthalmos*).
- Apraclonidine, a weak α-2 agonist, has largely supplanted cocaine and hydroxyamphetamine in confirmation of sympathetic denervation of the pupil. Denervation supersensitivity may take up to 1 week to occur; apraclonidine testing will not detect acute sympathetic denervation of the pupil. Apraclonidine cannot be used in young children because of the possibility of respiratory depression.
- Tonic pupils, which are mydriatic at the outset, may eventually become miotic and irregular.
- Bilaterally small pupils may result from bilateral sympathetic denervation of the pupillary dilator, from factors causing predominance of parasympathetic tone over sympathetic tone, or from chronic reinnervation as seen with bilateral tonic pupils.
- Bilaterally small irregular pupils should prompt consideration of chronic tonic pupils and Argyll Robertson pupils. Treponemal syphilis serologies should be ordered.
- When in doubt as to the etiology of an irregularly shaped pupil, enlist the aid of an ophthalmologist who can employ a slit lamp to look for important anatomic details and signs of inflammation that are difficult to observe with the naked eye.
- The most common congenital causes of irregular pupils include coloboma, aniridia, and pupillary decentration, referred to as *corectopia*.
- When evaluating irregular pupils, consider trauma, inflammation with synechiae formation, tonic pupils, and Argyll Robertson pupils.
- Light-near dissociation typically localizes to the ciliary ganglion, dorsal midbrain, or bilateral optic nerves.

Article 2: Ischemic Optic Neuropathy

Mark J. Morrow, MD, FAAN. Continuum (Minneap Minn). October 2019;
25 (5 Neuro-Ophthalmology):1215–1235.

ABSTRACT

PURPOSE OF REVIEW:

Vision is often threatened or lost by acute ischemic damage to the optic nerves. Such pathology most often affects the anterior portion of the nerve and is visible on funduscopic examination. Ischemic optic neuropathy is associated with typical vascular risk factors and with one systemic disease in particular: giant cell arteritis (GCA). This article provides an overview of the three major classes of ischemic optic neuropathy, including information on risk factors, differential diagnosis, evaluation, and management.

RECENT FINDINGS:

Optical coherence tomography provides precise anatomic imaging in ischemic optic neuropathy, showing neural loss weeks before it is visible on examination. Refinements of optical coherence tomography reveal optic nerve microvasculature and may assist in understanding pathogenesis and verifying diagnosis. New diagnostic algorithms and cranial vascular imaging techniques help define the likelihood of GCA in patients with ischemic optic neuropathy. Finally, intraocular drug and biological agent delivery holds promise for nonarteritic ischemic optic neuropathy, whereas newer immunologic agents may provide effective steroid-sparing treatment for GCA.

SUMMARY:

It is essential to recognize ischemic optic neuropathy upon presentation, especially to determine the likelihood of GCA and the need for immediate steroid therapy. A broad differential diagnosis should be considered so as not to miss alternative treatable pathology, especially in cases with retrobulbar optic nerve involvement.

KEY POINTS

- **Anterior ischemic optic neuropathy presents as acute, painless monocular visual loss that may progress over several days.**
- **Anterior ischemic optic neuropathy must be distinguished from optic neuritis, compressive masses, and retinal artery and vein occlusions. This distinction is usually clear-cut after a thorough history and examination, but imaging is occasionally needed in equivocal cases. Blood work for giant cell arteritis and vascular risk factors is indicated in most cases.**
- **Nonarteritic anterior ischemic optic neuropathy is the most common cause of acute optic neuropathy in people older than age 50, peaking in incidence around age 60 and somewhat more common in men than women. It is most strongly linked to congenitally crowded optic discs. Other putative risk factors include hypertension, diabetes mellitus, and obstructive sleep apnea.**
- **Examination in arteritic and nonarteritic anterior ischemic optic neuropathy shows visual field impairment, variable loss of acuity, a swollen optic disc, and a relative afferent pupillary defect in the affected eye. Visual loss and optic disc swelling tend to be worse in the arteritic form (arteritic anterior ischemic optic neuropathy).**
- **The optic disc in the unaffected eye almost always shows a small cup in nonarteritic anterior ischemic optic neuropathy. Over 1 to 3 months, optic disc swelling resolves to a flat, atrophic disc in all cases of anterior ischemic optic neuropathy. Optical coherence tomography shows evidence of retinal ganglion cell body loss after only a few weeks.**

- Because no treatment has been established for nonarteritic cases, it is especially important to exclude giant cell arteritis as a cause of anterior ischemic optic neuropathy.
- Although most patients with nonarteritic anterior ischemic optic neuropathy will show some spontaneous improvement, many are left with significant deficits. No therapy has been proven to improve outcomes, although several clinical trials are ongoing.
- Nonarteritic anterior ischemic optic neuropathy strikes the second eye in 15% to 20% of patients over 5 years. Limited evidence has shown that aspirin may reduce risk over the first few years, but no clear long-term benefit of aspirin or any other preventive treatment has been proven. Vascular risk factors such as hypertension and diabetes mellitus should be addressed as a matter of general health maintenance.
- Arteritic anterior ischemic optic neuropathy, like giant cell arteritis itself, is more common with advancing age (mean 70 to 75 years) and in women by at least 2:1 over men. Although most patients presenting with arteritic anterior ischemic optic neuropathy have signs and symptoms of giant cell arteritis, about 20% present with visual problems alone and have no systemic features; this has been described as *occult giant cell arteritis*. Thus, a high level of suspicion is essential.
- Erythrocyte sedimentation rate and C-reactive protein are the most sensitive tests for giant cell arteritis, each being elevated in about 85% of cases. These test results are nonspecific, however, and both are negative in about 10% of patients. Thrombocytosis and anemia are also common in giant cell arteritis and should increase diagnostic suspicion if present.
- Temporal artery biopsy remains the gold standard for the diagnosis of giant cell arteritis and should be arranged within the first few days of a suspected presentation. Although pathologic findings are eventually altered by therapy, these changes take weeks and are not a consideration with regard to the immediate initiation of corticosteroid treatment.
- For patients at moderate to high risk of giant cell arteritis who present with anterior ischemic optic neuropathy or transient visual loss, most experts recommend immediate initiation of high-dose IV steroids (eg, 1000 mg/d methylprednisolone) followed by oral therapy, typically prednisone 1 mg/kg or 80 mg/d. Many advocate initial hospital admission to monitor for steroid side effects, arrange temporal artery biopsy, and provide patient education.
- Corticosteroids are the mainstay of acute and chronic therapy in giant cell arteritis. They have many side effects, especially in the elderly population at highest risk for the condition.
- In most patients, systemic manifestations of giant cell arteritis respond quickly to treatment. Despite this, steroids must be tapered very slowly over 1 year or more to avoid relapse, while monitoring symptoms, erythrocyte sedimentation rate, and C-reactive protein. Various immune suppressant drugs have been used to augment steroids and reduce their long-term risks.
- Tocilizumab recently became the first US Food and Drug Administration–approved option for giant cell arteritis.
- The diagnosis of posterior ischemic optic neuropathy requires contrast imaging of the brain and orbits to exclude inflammatory and compressive conditions. Outside of the postoperative setting, giant cell arteritis should be suspected and thoroughly excluded.
- Posterior ischemic optic neuropathy is a diagnosis of exclusion because no confirmatory funduscopic findings are seen and many other processes may affect the retrobulbar optic nerve. It is reasonable to anticipate an ischemic cause of acute, fundus-negative optic neuropathy after major surgery and in giant cell arteritis.
- No specific treatment for posterior ischemic optic neuropathy has been established, other than in those cases presumed to be of arteritic origin.

Article 3: Optic Neuritis

Jeffrey L. Bennett, MD, PhD, FAAN. Continuum (Minneap Minn). October 2019; 25 (5 Neuro-Ophthalmology):1236–1264.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses the clinical presentation, evaluation, and management of the patient with optic neuritis. Initial emphasis is placed on clinical history, examination, diagnostic testing, and medical decision making, while subsequent focus is placed on examining specific inflammatory optic neuropathies. Clinical clues, examination findings, neuroimaging, and laboratory testing that differentiate autoimmune, granulomatous, demyelinating, infectious, and paraneoplastic causes of optic neuritis are assessed, and current treatments are evaluated.

RECENT FINDINGS:

Advances in technology and immunology have enhanced our understanding of the pathologies driving inflammatory optic nerve injury. Clinicians are now able to interrogate optic nerve structure and function during inflammatory injury, rapidly identify disease-relevant autoimmune targets, and deliver timely therapeutics to improve visual outcomes.

SUMMARY:

Optic neuritis is a common clinical manifestation of central nervous system inflammation. Depending on the etiology, visual prognosis and the risk for recurrent injury may vary. Rapid and accurate diagnosis of optic neuritis may be critical for limiting vision loss, future neurologic disability, and organ damage. This article will aid neurologists in formulating a systematic approach to patients with optic neuritis.

KEY POINTS

- The classic presentation of optic neuritis associated with multiple sclerosis is unilateral, moderate, painful vision loss with an afferent pupillary defect and normal fundus examination. Bilateral vision loss, lack of pain, and severe loss of vision should raise concern for an alternative inflammatory optic neuropathy.
- Neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein (MOG)–IgG optic neuritis cause severe vision loss and are more frequently bilateral. MOG–IgG optic neuritis frequently causes significant optic disc edema.
- Ophthalmic testing is not generally helpful in differentiating acute optic neuropathies. Visual evoked potentials may help to detect subtle optic nerve injury when clinical examination findings are uncertain.
- Optical coherence tomography may be useful in detecting subtle retinal pathology or documenting the extent of prior injury in cases of recurrent optic neuritis.
- MRI of the orbits is the most sensitive diagnostic test (90%) for optic neuritis; however, a normal orbital MRI scan does not exclude optic neuritis.
- The pattern of inflammation of the optic nerve on MRI may provide diagnostic information. NMOSD optic neuritis more often affects the optic chiasm, intracranial optic nerve, and optic tracts; MOG-IgG optic neuritis frequently inflames the intraorbital optic nerve and optic nerve sheath. Both disorders may be bilateral with longitudinally extensive lesions.
- Antinuclear autoantibodies are observed in many patients with optic neuritis; however, they are much less frequent in multiple sclerosis–associated optic neuritis.
- CSF pleocytosis may be highest in MOG-IgG optic neuritis, whereas CSF eosinophils are suggestive of NMOSD.
- Oligoclonal bands should suggest multiple sclerosis–associated optic neuritis, especially if they persist.

- Aquaporin-4 IgG is rarely, if ever, isolated to the CSF.
- High-dose IV methylprednisolone (1000 mg/d IV for 3 days) is effective at improving the speed of recovery of optic neuritis. Small studies have demonstrated that the type of steroid and mode of delivery (oral versus IV) are likely inconsequential. Lower dosages of oral prednisone (1 mg/kg) are contraindicated for acute optic neuritis treatment because of a higher risk of relapse.
- Plasma exchange may be useful in treating steroid-resistant optic neuritis, severe optic neuritis due to NMOSD, and recurrent optic neuritis at risk for poor recovery. Time to administration of plasma exchange may be critical to treatment success.
- Optic neuritis is the initial presentation of multiple sclerosis in 25% of individuals. The presence of enhancing and nonenhancing brain MRI lesions meeting dissemination in space criteria by the 2017 McDonald criteria is diagnostic of multiple sclerosis. If no enhancing lesions are present, oligoclonal bands may provide dissemination in time criteria according to the 2017 McDonald criteria.
- It is important to differentiate optic neuritis due to NMOSD from that due to multiple sclerosis. The prognosis for visual recovery is poorer for NMOSD optic neuritis, and the risk for recurrence is high.
- NMOSD optic neuritis should prompt consideration for early plasma exchange.
- Treatments for multiple sclerosis, such as interferon beta, fingolimod, and natalizumab, have been documented to exacerbate NMOSD disease activity.
- MOG-IgG disease frequently causes recurrent optic neuritis. Bilateral optic neuritis, longitudinal optic nerve lesions, optic nerve sheath enhancement, and steroid responsiveness are important clinical and radiologic clues.
- GFAP-IgG encephalomyelitis is commonly associated with optic nerve papillitis. As a result, disc edema is prominent, but vision loss is rare.
- Perivascular radial enhancement on MRI is highly suggestive of GFAP-IgG disease. GFAP-IgG may be isolated to the CSF in a large fraction of patients.
- Autoimmune optic neuropathy, relapsing isolated optic neuritis, and chronic relapsing inflammatory optic neuropathy are idiopathic seronegative optic neuropathies characterized by their responsiveness to or dependency on steroid immunosuppression. They are currently a diagnosis of exclusion for patients with recurrent optic neuritis seronegative for AQP4-IgG and MOG-IgG.
- Isolated optic neuritis associated with systemic lupus erythematosus or Sjögren syndrome is rare. Patients diagnosed with systemic lupus erythematosus or Sjögren syndrome and optic neuritis should be tested for AQP4-IgG.
- Patients with systemic lupus erythematosus or Sjögren syndrome with optic neuritis who are seropositive for AQP4-IgG are at higher risk for poor visual recovery than patients with systemic lupus erythematosus or Sjögren syndrome without AQP4-IgG.
- Paraneoplastic optic neuritis associated with collapsin response mediator protein-5 (CRMP-5) autoantibodies may mimic idiopathic optic neuritis. Bilateral, asynchronous optic neuritis with prominent vitreitis and retinal leakage in an older adult should raise clinical concern.
- CRMP-5 optic neuritis is frequently accompanied by central or peripheral neurologic injury. The presence of transverse myelitis may mimic NMOSD.
- Sarcoid optic neuropathy may be extremely difficult to diagnose in the absence of ocular inflammation or systemic disease.
- Angiotensin-converting enzyme levels in the serum and CSF are notoriously insensitive for neurosarcoidosis. When suspicious, CT chest, gallium scan, or fludeoxyglucose positron emission tomography are recommended for identifying involved tissue amenable to biopsy.
- While multiple infectious agents have been associated with neuroretinitis, many cases are idiopathic. Exposure to common infectious causes should be evaluated. When the infectious workup is negative, alternative noninflammatory causes of optic disc edema with a macular star should be considered.
- Optic neuritis with disc edema and cranial neuropathies should be investigated for Lyme disease in endemic areas.

- Syphilitic optic neuritis is often associated with ocular inflammation. Optic disc edema, when present, is usually prominent. A detailed social history identifying high-risk behavior for HIV should be performed in suspicious cases.
- Optic neuritis due to direct viral infection is rare. Clinical and examination clues include recent zoster ophthalmicus, encephalitis, immunosuppression, risk for mosquito-borne illness, or associated retinitis or chorioretinitis.
- Optic neuritis from tuberculosis is often associated with uveitis and orbital apex syndrome. MRI brain findings include leptomeningeal enhancement, ependymitis, abscess, infarct, encephalitis, and tubercles.

Article 4: Toxic-Metabolic and Hereditary Optic Neuropathies

Cristiano Oliveira, MD. Continuum (Minneap Minn). October 2019;
25 (5 Neuro-Ophthalmology):1265–1288.

ABSTRACT

PURPOSE OF REVIEW:

The diagnosis of visual loss from toxic-metabolic and hereditary optic neuropathies may be delayed in some cases because of a failure to elicit important information in the clinical history or to recognize typical examination findings. An understanding of the features specific to each type of toxic-metabolic and hereditary optic neuropathy, and of the underlying mechanism of insult to the optic nerve, could lead to earlier recognition, diagnosis, and treatment (when available).

RECENT FINDINGS:

Understanding of the role of mitochondria in toxic-metabolic and hereditary optic neuropathies is growing, particularly regarding the mechanism of insult of certain agents (medications and toxins) and of vitamin B_{12} deficiency. New developments in the quest for treatment for hereditary optic neuropathy, specifically Leber hereditary optic neuropathy, are being seen.

SUMMARY:

Toxic-metabolic and hereditary optic neuropathies present in a similar fashion, with painless, progressive, bilateral visual loss with dyschromatopsia and cecocentral visual field defects. The associated retinal ganglion cell and axonal loss is typically due to mitochondrial dysfunction caused by an exogenous agent (toxic), by insufficient or deficient substrate (metabolic or nutritional), or by abnormal proteins or mitochondrial structure determined by a genetic mutation (hereditary).

KEY POINTS

- Optic neuropathies present with visual acuity loss, dyschromatopsia (color vision dysfunction), and visual field defect. Toxic-metabolic and hereditary neuropathies should be considered when vision loss is bilateral, particularly when central or cecocentral (central defect extending to the physiologic blind spot) visual field loss is present.
- The underlying mechanism of retinal ganglion cell and axonal loss in toxic-metabolic and hereditary neuropathies is mitochondrial dysfunction caused by an exogenous agent (toxic), insufficient or deficient substrate (metabolic or nutritional), or abnormal proteins or structure of the mitochondria determined by a genetic mutation (hereditary).
- The mitochondria are responsible for adenosine triphosphate production via oxidative phosphorylation that occurs in the respiratory chain polypeptide complexes. They are also the major site of production of free radicals, which are highly reactive molecular fragments that can cause oxidative cellular damage.

- Mitochondrial dysfunction leads to damage of retinal ganglion cells and their axons through a double-hit mechanism. The first hit results from impaired axon organelle transportation and impulse conduction due to adenosine triphosphate deficit, and the second hit results from superoxide-induced oxidative damage and signaling of apoptosis.
- The papillomacular bundle is formed by the retinal ganglion cell axons located between the perineural macula and the optic disc, and its injury results in cecocentral visual field loss. The small diameter of the papillomacular bundle axons is thought to be the basis of their greater vulnerability when facing adenosine triphosphate deficit and increased superoxide production in the setting of mitochondrial dysfunction.
- Obtaining information regarding ongoing or previous toxic exposure (medications or other substances), prior surgery (bariatric or gastrointestinal resections and bypass), and dietary habits/restrictions is an essential step in the investigation of patients presenting with bilateral progressive visual loss.
- Ethambutol affects mitochondrial function by interfering with complexes I and IV and cytochrome coxidase. The ocular toxicity is dose related and more likely to occur in patients treated with 25 mg/kg/d or higher (dose must be adjusted for renal insufficiency). In addition to the bilateral cecocentral field defect, patients may present with bitemporal field defects, some with evidence of chiasmal abnormal signal. Early diagnosis and drug cessation are essential and may result in visual recovery.
- Antibiotics such as linezolid, chloramphenicol, and ciprofloxacin have been implicated in toxic optic neuropathies through inhibition of mitochondrial protein synthesis.
- Amiodarone has been associated with an optic neuropathy with optic disc swelling and visual acuity and field loss, similar to nonarteritic anterior ischemic optic neuropathy. However, it is more often bilateral, with an insidious course and protracted resolution of the disc edema.
- Toxic optic neuropathies due to tumor necrosis factor-α inhibitors and tacrolimus can be unilateral, bilateral, or sequential. As patients receiving these agents may be immunosuppressed, a thorough investigation to exclude infectious and neoplastic etiologies is particularly important.
- Vigabatrin causes retinal toxicity and a peculiar pattern of secondary optic nerve atrophy with nasal disc pallor sparing the temporal region (spared papillomacular bundle). Patients present with progressive concentric constriction sparing central vision.
- Nutritional optic neuropathies have a clinical presentation indistinct from most cases of toxic optic neuropathy and should be considered in patients who have had gastrointestinal bypass surgery, have stringent dietary restrictions, or have a history of substance abuse and secondary malnourishment.
- Vitamin B_{12} (cobalamin) is an intracellular superoxide scavenger, which is particularly important for unmyelinated axons in the papillomacular bundle. Cobalamin deficiency may cause superoxide accumulation, which is a signal for retinal ganglion cell apoptosis, therefore causing retinal ganglion cell and axon loss.
- Toxins and malnutrition can have a synergistic effect, causing optic neuropathy and visual loss. Carriers of genetic mutations determining mitochondrial dysfunction may be more vulnerable to both toxic and metabolic optic neuropathies.
- More than 90% of all Leber hereditary optic neuropathy cases have been associated with one of the three primary mitochondrial DNA mutations of genes coding for protein subunits of complex I (m.11778G>A, m.14484T>C, m.3460G>A), with the first being the most prevalent mutation.
- Leber hereditary optic neuropathy presents with sudden unilateral painless central visual loss with fellow eye involvement within weeks to months (sequential optic neuropathy). More than 90% of the carriers become symptomatic before 50 years of age, with peak onset in the second and third decades of life.
- In Leber hereditary optic neuropathy, dilated funduscopy may be completely normal or may show a hyperemic optic nerve with swelling of the retinal nerve fiber layer and tortuosity of the central retinal vessels. Optic disc temporal pallor is typically seen within 6 weeks of onset of visual loss, and cupping may also be observed.
- Because of the level of visual loss at presentation and the infrequent visual recovery, the visual prognosis in Leber hereditary optic neuropathy is typically poor. Patients with the 14484 mutation are the most likely to recover, followed by those with the 3460 mutation.

- No treatment has been proven effective for Leber hereditary optic neuropathy. The early use of idebenone, an antioxidant that can transport electrons directly to complex III bypassing a dysfunctional complex I, may be beneficial. Gene therapy trials are currently under way.
- Most patients with and carriers of autosomal dominant optic atrophy harbor mutations in the *OPA1* gene, a nuclear gene on chromosome 3 that codes for an inner mitochondrial membrane protein essential for maintenance of the mitochondrial cristae network. The mutation results in a decrease in adenosine triphosphate production and increased formation of reactive oxygen species.
- Typical patients with autosomal dominant optic atrophy present with a history of insidious, bilateral, painless loss of visual acuity and color vision beginning in the first or second decades of life, with cecocentral field loss and the finding of optic disc temporal pallor. Of patients with autosomal dominant optic atrophy, 50% to 75% will experience further visual decline later in life, and no spontaneous recovery has been reported.
- The assessment of patients with a history of progressive bilateral visual loss and bilateral optic disc pallor should include a thorough medical history and examination, followed by laboratory testing for vitamins B_{12}, B_1, and B_6; folate; methylmalonic acid; copper; and zinc and contrast-enhanced MRI of the brain and orbits. Genetic testing is typically done as a subsequent step in the workup.
- No proven treatment is available for autosomal dominant optic atrophy. Routine follow-up examinations to assess visual acuity and color vision as well as Humphrey visual field testing and optical coherence tomography to assess structural changes help ensure that patients are following the natural history of the disease and can identify concurrent pathology when deviation from the expected clinical evolution is seen.
- Although a 50% risk of transmission to offspring exists in autosomal dominant optic atrophy, because of variable penetrance, the risk of developing visual loss is 60% to 88%. Even among those who develop the disease, great variability may exist in the level of visual dysfunction.

Article 5: Idiopathic Intracranial Hypertension

Matthew J. Thurtell, MBBS, MSc, FRACP. Continuum (Minneap Minn). October 2019; 25 (5 Neuro-Ophthalmology):1289–1309.

ABSTRACT

PURPOSE OF REVIEW:

Idiopathic intracranial hypertension is a syndrome of increased intracranial pressure of unclear etiology that most often occurs in obese women of childbearing age but can also occur in men, children, and older adults. This article reviews the diagnostic criteria, clinical features, neuroimaging findings, differential diagnosis, and management options for this condition.

RECENT FINDINGS:

Recent population studies have found that the annual incidence of idiopathic intracranial hypertension is increasing in association with obesity rates, whereas recent scientific studies indicate a possible role for androgen sex hormones and adipose tissue in the pathogenesis of the disease. Prospective clinical trials have demonstrated a role for weight loss, acetazolamide, and topiramate in the management of mild disease. A recently begun randomized multicenter trial of surgical interventions will provide insight into the indications for surgical intervention, optimal timing and choice of intervention, and long-term outcomes.

SUMMARY:

Idiopathic intracranial hypertension is a disorder producing symptoms and signs of increased intracranial pressure in the absence of an alternative cause. The main goals of treatment are to

preserve visual function and alleviate symptoms, which can usually be achieved with a combination of weight loss, medical therapies, and surgical interventions depending on the severity of symptoms and vision loss, response to treatment, and subsequent clinical course.

KEY POINTS

- Idiopathic intracranial hypertension is a syndrome of increased intracranial pressure that usually occurs in obese women of childbearing age.
- Idiopathic intracranial hypertension is a diagnosis of exclusion. Therefore, other etiologies of increased intracranial pressure must be ruled out based on clinical history, neuroimaging, and CSF examination.
- The incidence of idiopathic intracranial hypertension appears to be increasing and is strongly correlated with obesity rates.
- Greater levels of weight gain are associated with increased risk of idiopathic intracranial hypertension, although the condition can also develop in the setting of moderate weight gain in patients who are not obese.
- Headache is the most common symptom of idiopathic intracranial hypertension. However, many patients have headaches that have features of other primary headache disorders, such as migraine and tension headache.
- Headache in idiopathic intracranial hypertension is often disabling and associated with poorer quality of life but is not correlated with intracranial pressure and, thus, may not improve with lowering of intracranial pressure.
- Transient visual obscurations are the second most common symptom of idiopathic intracranial hypertension. They are thought to result from transient ischemia of the optic nerve head and are associated with higher grades of papilledema.
- Progressive visual field loss may not be appreciated by patients, underscoring the importance of formal perimetry (visual field testing) in the evaluation and monitoring of idiopathic intracranial hypertension.
- Pulse-synchronous (pulsatile) tinnitus occurs in about half of patients with idiopathic intracranial hypertension and is thought to arise because of turbulent blood flow across transverse venous sinus stenoses.
- Papilledema is the most common and important sign in idiopathic intracranial hypertension. It is usually bilateral and symmetric. The threat of vision loss is correlated with its severity.
- If untreated, papilledema can result in progressive and irreversible vision loss with optic atrophy.
- Visual field loss is difficult to exclude with confrontation visual field testing. Consequently, formal perimetry is mandatory in the evaluation and monitoring of idiopathic intracranial hypertension.
- An enlarged physiologic blind spot is the first visual field defect to develop in idiopathic intracranial hypertension, followed by arcuate visual field defects (initially in the inferonasal visual field) and, subsequently, progressive constriction with sparing of central vision until late.
- Sixth and seventh nerve palsies can occur as false localizing signs in patients with idiopathic intracranial hypertension.
- Ophthalmic investigations are necessary to determine the severity of vision loss and papilledema. In patients with equivocal papilledema or possible pseudopapilledema, consultation with an ophthalmologist or, ideally, a neuro-ophthalmologist is suggested.
- In patients with an atypical or fulminant presentation of idiopathic intracranial hypertension, magnetic resonance venography of the head with contrast should be obtained to exclude cerebral venous sinus thrombosis.
- Common imaging findings in idiopathic intracranial hypertension include an empty sella turcica, increased optic nerve sheath dilation and tortuosity, posterior globe flattening, optic disc elevation and enhancement, inferior cerebellar tonsillar descent, and transverse venous sinus stenosis.
- In adults, a CSF opening pressure of greater than 25 cm H_2O is high, while an opening pressure of 20 cm H_2O to 25 cm H_2O is probably abnormal if symptoms, signs, and imaging findings are consistent with increased intracranial pressure. In children, recent studies suggest that a CSF opening pressure of greater than 28 cm H_2O is high.
- Retinal nerve fiber layer thickness from optical coherence tomography correlates with papilledema severity. However, retinal nerve fiber layer thickness measurements must be interpreted with caution in patients who could have combined optic disc edema and atrophy.

- Raster scans obtained through the optic nerve head with optical coherence tomography may show biomechanical changes that correlate with increased intracranial pressure and might be useful for monitoring response to treatment.
- Several medications (eg, tetracycline antibiotics, retinoids, and lithium) and cerebral venous outflow obstruction (eg, due to cerebral venous sinus thrombosis) can cause a clinical syndrome that mimics idiopathic intracranial hypertension.
- Weight loss of 6% to 10% of initial body weight can be effective in inducing a remission of idiopathic intracranial hypertension. Bariatric surgery can be effective in patients who are morbidly obese and struggle to lose weight.
- Treatment of idiopathic intracranial hypertension with acetazolamide produces improvement in visual field loss, papilledema, symptoms, and quality of life. Common side effects of acetazolamide therapy include paresthesia, dysgeusia, nausea, vomiting, and diarrhea.
- Topiramate is effective in treatment of mild to moderate idiopathic intracranial hypertension and can be considered in patients who are unable to tolerate acetazolamide or when headache is prominent. Common side effects of topiramate therapy include mental slowing, lethargy, paresthesia, and loss of appetite.
- Surgical therapies are usually reserved for patients with idiopathic intracranial hypertension who have a fulminant presentation and for patients who fail to improve or worsen despite maximally tolerated medical therapy.
- CSF shunting is effective for rapidly reducing intracranial pressure. Complications can include infection, obstruction, and migration of shunt tubing; shunt revision is often needed.
- Optic nerve sheath fenestration is effective in relieving pressure on the optic nerve, thereby reducing papilledema and improving visual function. Complications can include vision loss, tonic pupil, and diplopia.
- Transverse venous sinus stenting has been reported to improve symptoms, signs, visual function, and intracranial pressure. Complications can include in-stent thrombosis, subdural hemorrhage, and development of new stenoses proximal to the stent.
- The indications for surgical intervention in idiopathic intracranial hypertension, the timing and choice of surgical intervention, and long-term outcomes remain unclear.
- The main goals of treatment of idiopathic intracranial hypertension are to preserve vision and alleviate symptoms. Thus, the management is tailored depending on the severity of vision loss, papilledema, and symptoms as well as the patient's response to medical therapy and ability to tolerate medical therapy.
- Patients with idiopathic intracranial hypertension with minimal to mild vision loss can usually be managed with weight loss and medical therapy, whereas patients with moderate to severe vision loss often need a combination of weight loss, aggressive medical therapy, and, occasionally, surgical intervention.
- Patients with idiopathic intracranial hypertension should be managed in coordination with an ophthalmologist or neuro-ophthalmologist, since formal perimetry and monitoring of papilledema severity is needed to guide management.

Article 6: Chiasmal and Postchiasmal Disease

Heather E. Moss, MD, PhD, FAAN. Continuum (Minneap Minn). October 2019; 25 (5 Neuro-Ophthalmology):1310–1328.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the anatomy, symptoms, examination findings, and causes of diseases affecting the optic chiasm, optic tracts, optic radiations, and occipital lobes.

RECENT FINDINGS:

Modern ophthalmic imaging can be used to monitor the effects of diseases of the optic chiasm and tract on the retinal ganglion cells. It can also be used to visualize transsynaptic degeneration of the anterior visual pathway in the setting of acquired retrogeniculate lesions. Visual prostheses that directly stimulate the occipital lobe are a potential strategy for rehabilitation that is in active clinical trials.

SUMMARY:

Detecting and characterizing visual deficits due to optic chiasm and retrochiasmal disease are important for the diagnosis, localization, and monitoring of neurologic disease; identifying patient disability; and guiding rehabilitation.

KEY POINTS

- Central vision can be affected in chiasmal lesions but is spared in unilateral retrochiasmal lesions.
- If a homonymous field defect is complete, localization beyond a retrochiasmal location is not possible based on peripheral vision testing alone.
- Confrontation visual field deficits are specific but not sensitive for peripheral vision loss.
- Optic nerve head pallor in both eyes is diagnostic of chronic injury to the retinal ganglion cells in both optic nerves, the chiasm, or one optic tract.
- Lack of optic nerve head pallor does not exclude injury to the ganglion cells in the optic nerves, chiasm, or optic tracts.
- Relative afferent pupillary defects can occur in asymmetric chiasm and unilateral optic tract lesions.
- Lesions affecting the anterior chiasm affect the peripheral temporal fields, whereas those affecting the posterior chiasm affect the central temporal fields with sparing of the periphery.
- The optic chiasm is best viewed on coronal or sagittal MRI or CT sequences obtained with narrow slice spacing.
- Homonymous peripheral vision loss affects navigation, and homonymous visual field loss that reaches central vision affects reading.
- Homonymous visual field loss with an afferent pupillary defect on the same side of the visual field loss suggests a contralateral optic tract lesion.
- Visual symptoms due to optic radiation disease are usually accompanied by other neurologic symptoms localizing to the affected territory.
- Congruous homonymous visual field loss is a hallmark of occipital lobe disease.
- Posterior cerebral artery infarcts often spare central vision and far peripheral vision in the affected field, which can limit disability from vision loss.
- Posterior cortical atrophy and Creutzfeldt-Jakob disease can cause homonymous visual field loss with only subtle neuroimaging findings.

Article 7: Higher Cortical Visual Disorders

Sashank Prasad, MD; Marc Dinkin, MD. Continuum (Minneap Minn). October 2019; 25 (5 Neuro-Ophthalmology):1329–1361.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the disorders that result from disruption of extrastriate regions of the cerebral cortex responsible for higher visual processing. For each disorder, a historical perspective is offered and relevant neuroscientific studies are reviewed.

RECENT FINDINGS:

Careful analysis of the consequences of lesions that disrupt visual functions such as facial recognition and written language processing has improved understanding of the role of key regions in these networks. In addition, modern imaging techniques have built upon prior lesion studies to further elucidate the functions of these cortical areas. For example, functional MRI (fMRI) has identified and characterized the response properties of ventral regions that contribute to object recognition and dorsal regions that subserve motion perception and visuospatial attention. Newer network-based functional imaging studies have shed light on the mechanisms behind various causes of spontaneous visual hallucinations.

SUMMARY:

Understanding the regions and neural networks responsible for higher-order visual function helps the practicing neurologist to diagnose and manage associated disorders of visual processing and to identify and treat responsible underlying disease.

KEY POINTS

- After initial processing in the primary visual cortex, numerous adjacent cortical areas continue the work of analyzing specific aspects of visual information. These areas, which are situated in the occipital, temporal, and parietal lobes, are given names such as V2, V3, V4, V5, lateral occipital area, or fusiform face area.
- Anton syndrome refers to cortical blindness with lack of awareness (ie, anosognosia) of the deficit.
- Visual agnosia refers to a specific impairment of the ability to recognize or interpret visually presented information although elementary aspects of vision remain intact.
- In apperceptive visual agnosia, although spatial acuity is preserved, the remaining steps of visual processing are disrupted at a very early stage, rendering patients unable to perceive even the most basic geometric relationships that create the contours of a visual object.
- Associative visual agnosia describes a disorder in which basic visual perception is preserved, including grouping of visual forms, but visual percepts cannot be associated with relevant stored semantic knowledge.
- Central hemiachromatopsia describes loss of color recognition in the hemifield contralateral to a lesion of V4, a region in which neurons are selectively responsive to specific wavelengths of light. In clinical practice, lesions often encompass this area as well as the adjacent inferior striate cortex (V1), causing an overlapping superior quadrantanopia, so that the achromatopsia is only evident in the seeing inferior visual field.
- Processing in V4 adjusts for the spectral balance of incident light so that the apparent color of an object is perceived as being fairly constant despite considerable differences in lighting environments. This phenomenon is known as *color constancy*.
- Alexia without agraphia, also referred to as *pure alexia* or *pure word blindness*, describes the loss of the ability to read, although the ability to write remains spared. It is often the result of a lesion affecting both the left occipital cortex and the splenium of the corpus callosum. A right homonymous hemianopia ensues, while visual information in the right occipital cortex cannot reach the left-sided language areas to allow linguistic analysis of the visualized symbols.
- Alexia without agraphia may also result from a single lesion in the visual word form area within the fusiform gyrus.
- Prosopagnosia is a specific form of visual agnosia in which face perception is impaired while elementary aspects of vision, such as acuity and visual field, remain intact.
- Facial recognition in the visual system is particularly sensitive to the orientation of an image, much more so than other types of object processing.
- Riddoch syndrome describes the preserved ability to detect motion in an otherwise blind visual field.
- Balint syndrome describes a profound disruption of visuospatial attention mechanisms resulting from bilateral parietal lesions. Its key features are simultanagnosia, optic ataxia, and ocular apraxia.
- Simultanagnosia refers to an ability to perceive the local elements of a scene but not the global elements in their totality.

- Optic ataxia refers to impaired reaching under visual guidance, in which reaching under proprioceptive guidance (ie, back to one's own nose) is preserved. Ocular apraxia refers to inaccurate saccades stemming from a disorder of visuospatial attention.
- Unilateral parietal lobe lesions, especially of the right parietal cortex, often cause hemispatial neglect to the contralateral side.
- Charles Bonnet syndrome refers to "release" hallucinations that occur in the context of visual loss, often due to anterior lesions such as cataracts or macular degeneration.
- Lhermitte peduncular hallucinosis describes vivid, dreamlike hallucinations that occur during normal wakefulness and may result from lesions to areas of the midbrain and thalamus that regulate the sleep-wake state and normally prevent dreams from encroaching on wakefulness.

Article 8: Approach to Diplopia

Christopher C. Glisson, DO, MS, FAAN. Continuum (Minneap Minn). October 2019; 25 (5 Neuro-Ophthalmology):1362–1375.

ABSTRACT

PURPOSE OF REVIEW:

"Double vision" is a commonly encountered concern in neurologic practice; the experience of diplopia is always sudden and is frequently a cause of great apprehension and potential disability for patients. Moreover, while some causes of diplopia are benign, others require immediate recognition, a focused diagnostic evaluation, and appropriate treatment to prevent vision- and life-threatening outcomes. A logical, easy-to-followapproach to the clinical evaluation of patients with diplopia is helpful in ensuring accurate localization, a comprehensive differential diagnosis, and optimal patient care. This article provides a foundation for formulating an approach to the patient with diplopia and includes practical examples of developing the differential diagnosis, effectively using confirmatory examination techniques, determining an appropriate diagnostic strategy, and (where applicable) providing effective treatment.

RECENT FINDINGS:

Recent population-based analyses have determined that diplopia is a common presentation in both ambulatory and emergency department settings, with 850,000 such visits occurring annually. For patients presenting to an outpatient facility, diagnoses are rarely serious. However, potentially life-threatening causes (predominantly stroke or transient ischemic attack) can be encountered. In patients presenting with diplopia related to isolated cranial nerve palsy, immediate neuroimaging can often be avoided if an appropriate history and examination are used to exclude worrisome etiologies.

SUMMARY:

Binocular diplopia is most often due to a neurologic cause. The onset of true "double vision" is debilitating for most patients and commonly prompts immediate access to health care services as a consequence of functional impairment and concern for worrisome underlying causes. Although patients may seek initial evaluation through the emergency department or from their primary care/ophthalmic provider, elimination of an ocular cause will not infrequently result in the patient being referred for neurologic consultation. A logical, localization-driven, and evidence-based approach is the most effective way to arrive at the correct diagnosis and provide the best outcome for the patient.

KEY POINTS

- A detailed history and systematic examination can often accurately localize the cause of diplopia.
- Monocular diplopia is rarely due to neurologic pathology.
- Eliciting the orientation of the double image (horizontal, vertical, or oblique),whether diplopia is present at distance or near, and whether the diplopia worsens in any direction of gaze are fundamental to accurate localization.
- Diplopia that occurs with fatigue does not necessarily imply myasthenia gravis; long-standing and decompensated ocular misalignment can also become symptomatic when patients are tired or under stress or in the setting of concomitant illness.
- Diplopia/ocular misalignment that does not change with the direction of gaze is classified as comitant; diplopia that varies depending on the direction of gaze is termed incomitant and most often indicates extraocular muscle dysfunction.
- Assessment of fixation is commonly overlooked during the ocular motility examination but is essential in identifying potential pathologic features that may be associated with diplopia.
- Neuroimaging has a low diagnostic yield in isolated fourth, pupil-sparing third, and sixth nerve palsies in older patients with vascular risk factors. However, a small number of patients older than 50 years of age may have other causes including neoplasm, infarction, and giant cell arteritis.
- While the localization of isolated diplopia can be relatively straightforward, the complex nature of ocular motility and coordination makes them susceptible to disruption by more diffuse cerebral dysfunction.
- Internuclear ophthalmoplegia is best identified by testing saccades.
- Patients presenting with cranial nerve VI palsy should be evaluated for signs and symptoms of increased intracranial pressure, which includes fundus examination.
- Myasthenia gravis can mimic any pupil-sparing ocular motility deficit.
- Antibody and electrophysiologic testing for myasthenia gravis may be supportive, but this remains a primarily clinical diagnosis.
- Patients with known or suspected thyroid ophthalmopathy should have periodic monitoring with formal visual fields because of the possibility of peripheral vision constriction by compression of the optic nerves as a consequence of enlarging extraocular muscles.
- For patients with new-onset (eg, microvascular) or transient (eg, myasthenia gravis–related) diplopia, monocular occlusion for mitigation of symptoms is immediately effective and can be employed as needed when symptoms are present.
- Prism correction is useful for patients with stable or comitant ocular misalignment; eye alignment surgery is useful for patients with incomitant diplopia.

Article 9: Nystagmus and Saccadic Intrusions

Janet C. Rucker, MD. Continuum (Minneap Minn). October 2019;
25 (5 Neuro-Ophthalmology):1376–1400.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of nystagmus and saccadic intrusions with the goal of facilitating recognition and differentiation of abnormal eye movements to assist with accurate diagnosis of neurologic disease and evidence-based specific treatment of oscillopsia. Myriad advances have been made in the understanding of several types of nystagmus and saccadic intrusions, even in the past 5 to 10 years, especially regarding underlying pathophysiology, leading to pharmacologic advances rooted in physiologic principles.

RECENT FINDINGS:

Specific recent advances in the study of nystagmus and saccadic intrusions include (1) improved understanding of the underlying etiologies and mechanisms of nystagmus enhanced or unmasked by provocative maneuvers such as supine position or head shaking; (2) recognition of the differences in behavior and treatment responsivity of acquired pendular nystagmus in demyelinating disease versus oculopalatal myoclonus; (3) recognition that oculopalatal myoclonus results froma dual mechanism of abnormal inferior olivary gap junction connection formation and maladaptive cerebellar learning; and (4) well-controlled clinical trials to evaluate the efficacy of pharmacologic interventions, such as memantine for acquired pendular nystagmus and 4-aminopyridine for downbeat nystagmus.

SUMMARY:

Accurate recognition of nystagmus and saccadic intrusions, including familiarity with the subtleties of examination techniques that allow such eye movements to be unmasked, is critical to proper diagnosis and ultimate alleviation of the visual impairment these patients experience.

KEY POINTS

- Nystagmus can be congenital or acquired; it tends to be rhythmic and regular and, if present in central gaze, continuous and sustained. Saccadic intrusions are more often nonrhythmic, intermittent, and unsustained.
- The initial abnormal eye movement with nystagmus is always a slow drift of the eyes that is also called a *slow phase*; in contrast, saccadic intrusions are initiated by a fast saccadic eye movement.
- The two main types, or waveforms, of nystagmus are jerk and pendular, both of which may have horizontal, vertical, and/or torsional trajectories, which may be different in the two eyes, especially for pendular nystagmus.
- Even if no nystagmus is seen on standard examination with the patient in the upright position, provocative maneuvers often unmask nystagmus and assist with diagnosis. Thus, they should be incorporated into the examination of any patient with symptoms of oscillopsia, imbalance, or vertigo.
- Saccadic intrusions are divided into two broad categories: those with an intersaccadic interval between subsequent saccades and those lacking such an interval.
- Saccadic intrusions with an intersaccadic interval include square-wave jerks, macro–square-wave jerks, and macrosaccadic oscillations. Saccadic intrusions without an intersaccadic interval include ocular flutter and opsoclonus.
- Square-wave jerks are pairs of small saccades, typically in the horizontal plane, that remove the eyes from and then return them to the midline without crossing it and have an intersaccadic interval.
- Square-wave jerks occur excessively, sometimes nearly continuously, in patients with Friedreich ataxia, multisystem atrophy, or progressive supranuclear palsy, although they may also occur in idiopathic Parkinson disease at any stage of the illness.
- Macrosaccadic oscillations are runs of horizontal saccades that are larger than square-wave jerks, have an intersaccadic interval, cross the midline, and build and decay around the central fixation point in a crescendo-decrescendo pattern.
- Ocular flutter and opsoclonus consist of erratic bursts of very-high-frequency, high-velocity, back-to-back saccades that oscillate about the midline and have no intersaccadic interval between subsequent saccades. This is termed *ocular flutter* when the saccades occur only in the horizontal plane. *Opsoclonus*, in contrast, contains saccades in all trajectories: horizontal, vertical, and torsional.
- Flutter and opsoclonus occur in two main clinical settings: paraneoplastic conditions and parainfectious brainstem encephalitis.
- Acquired pendular nystagmus occurs most often in the setting of demyelinating disease or within the context of oculopalatal myoclonus following a brainstem ischemic or hemorrhagic stroke.
- Acquired pendular nystagmus is typically very visually disabling because of the constant slow to-and-fro foveal drifting it creates.

- Nystagmus induced by the vestibular system, via peripheral or central disruption, is jerk nystagmus with linear-velocity slow phases that tends to follow the Alexander law, with worsening of the amplitude and frequency of fast phases in the direction of gaze of the nystagmus fast phases (ie, right-beat jerk nystagmus worsens in right gaze).
- Posterior canal benign paroxysmal positional vertigo represents over 80% of benign paroxysmal positional vertigo cases and is confirmed by the presence of a vertical-torsional nystagmus induced by the Dix-Hallpike maneuver.
- Observation of the patient over several minutes is required when pure horizontal jerk nystagmus is present, as this type of nystagmus may also occur with periodic alternating nystagmus. However, with periodic alternating nystagmus, the nystagmus will reverse horizontal direction approximately every 90 to 120 seconds, often with a few beats of vertical nystagmus during the transition zone.
- In nearly all cases, vertical and torsional nystagmus should be present in central gaze fixation with the patient upright, although the oscillations may be of very tiny amplitude in this patient position and only visible with magnified views of the eye, such aswith high-resolution infrared video or during ophthalmoscopy.
- Upbeat nystagmus is most commonly seen with Wernicke encephalopathy secondary to thiamine deficiency (in combination with horizontal gaze deficits and often with accompanying gaze-evoked nystagmus), demyelinating disease, or stroke of the medulla or midbrain.
- Downbeat nystagmus, one of the most common forms of acquired central nystagmus seen clinically, is jerk nystagmus induced by slow upward drifts of the eyes followed by resetting downward fast phases. It may or may not follow the Alexander law by increasing in downward gaze (and often does not), but it nearly always increases in amplitude and frequency in downward lateral gaze.
- Downbeat nystagmus, in most cases, represents cerebellar dysfunction, typically with lesions involving the vestibulocerebellum (flocculus, paraflocculus, nodulus, and uvula), although cases are also reported due to primary brainstem lesions, usually involving a group of brainstem neurons called the paramedian tracts.
- One of the prevalent forms of physiologic nystagmus commonly seen on clinical examination is gaze-evoked nystagmus, which is also variably called *end-gaze nystagmus* or *direction-changing nystagmus*.

Article 10: Paraneoplastic Syndromes in Neuro-ophthalmology

Lynn Gordon, MD, PhD; Marc Dinkin, MD. Continuum (Minneap Minn). October 2019; 25 (5 Neuro-Ophthalmology):1401–1421.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses the varied types of paraneoplastic syndromes that commonly have neuro-ophthalmologic manifestations. Diagnostic considerations and therapeutic options for individual diseases are also discussed.

RECENT FINDINGS:

Paraneoplastic syndromes can affect the afferent and efferent visual systems. Paraneoplastic syndromes may result in reduced visual acuity from retinal degeneration, alterations in melanocyte proliferation and uveal thickening, or acquired nystagmus. Ocular motor abnormalities related to paraneoplastic syndromes may present with symptoms from opsoclonus or from neuromuscular junction disease. Diagnosis remains challenging, but serologic identification of some specific antibodies may be helpful or confirmatory. Treatment, in addition to directed therapies against the underlying cancer, often requires systemic corticosteroids, plasma exchange, or immunosuppression, but some specific syndromes improve with use of targeted pharmacologic therapy.

SUMMARY:

Diagnosis and therapy of paraneoplastic syndromes presenting with neuro-ophthalmic symptoms remain a challenge, but strategies are evolving and new approaches are on the horizon.

KEY POINTS

- Neuro-ophthalmologic paraneoplastic syndromes arise from remote tumor effects largely through autoimmune responses against normal tissue that arise or are triggered by tumor expression of neuronal proteins that elicit immune responses.
- Detection of specific antibodies against neuronal antigenic targets can be helpful in identifying paraneoplastic disease. However, the practitioner should be aware of false-negative and false-positive errors, the possibility of novel antibodies not yet described or available for testing, and the spectrum of varied clinical presentations for any one antibody.
- Paraneoplastic syndromes may precede a cancer diagnosis by months or even years.
- The characteristic afferent visual paraneoplastic syndromes involve the retina in conditions such as cancer-associated retinopathy, melanoma-associated retinopathy, and bilateral diffuse uveal melanocytic proliferation, but a paraneoplastic optic neuropathy may also occur, although rarely.
- Workup for possible paraneoplastic syndromes affecting the afferent visual system should include visual acuity, color vision, pupillary testing, formal visual field testing, funduscopy, optical coherence tomography of the retina, and electroretinogram.
- The symptoms of cancer-associated retinopathy reflect its target cell: the photoreceptor. Loss of acuity, color vision, and central visual field as well as sensitivity to light and glare, photopsia, and flickering lights all result from cone dysfunction, while paracentral (ring) scotomas, impaired dark adaptation, and nyctalopia (difficulty seeing at night) result from damage to the rods.
- Testing for paraneoplastic antibodies should not be used as a screening tool for paraneoplastic disease in the absence of a suspicious clinical presentation.
- Antibodies against recoverin, a photoreceptor protein involved in phototransduction, were the first to be described in cancer-associated retinopathy. Cancer-associated retinopathy associated with antibodies against α-enolase is more likely to involve pure cone dysfunction and to present months or years after the cancer diagnosis.
- Some of the identified antibodies in cancer-associated retinopathy initiate retinal degeneration by entering retinal photoreceptors and inducing cell death, while others appear to be induced by release of immunologic proteins from the dying photoreceptors and may either further propagate retinal cell death or, in some cases, serve only as markers of the disease.
- Some evidence exists for reversal of some of the retinal findings in cancer-associated retinopathy with treatment.
- Rarely, melanoma-associated retinopathy can precede the diagnosis of melanoma.
- Melanoma-associated retinopathy is typically associated with a response on the electroretinogram that reflects bipolar cell dysfunction.
- Management of melanoma-associated retinopathy includes immunosuppression and treatment of the underlying cancer. However, checkpoint inhibitors used to treat melanoma have been associated with the occurrence or exacerbation of melanoma-associated retinopathy in rare cases.
- POEMS is a paraneoplastic syndrome whose name describes the protean clinical manifestations of cytokine production, driven in part by vascular endothelial growth factor, all resulting from a monoclonal plasma cell disorder. Papilledema may accompany the disorder, in which case CSF evaluation may reflect an increase in protein and intracranial pressure.
- Management of paraneoplastic optic neuropathy includes treatment of the underlying cancer with or without the use of adjunctive therapy, including systemic corticosteroids, mycophenolate mofetil, or plasma exchange.
- Opsoclonus is a form of saccadic intrusion characterized by omnidirectional, chaotic, high-frequency saccadic movements that may be of large amplitude and lack an intersaccadic interval.

- Reflective of brainstem or cerebellar damage, opsoclonus may result from paraneoplastic disease, with or without myoclonus, typically from neuroblastoma in children and small cell lung carcinoma or ovarian cancer in adults. Responsible antibodies include antineuronal nuclear antibodies type 1 (anti-Hu) and type 2 (anti-Ri).
- Lambert-Eaton myasthenic syndrome is a disease in which antibodies against the P/Q voltage-gated calcium channel located on the presynaptic terminal of the neuromuscular junction result in their dysfunction and secondary weakness that improves with exercise. Neuro-ophthalmic manifestations may include diplopia and ptosis, the latter of which may improve with upgaze. The underlying cause may be paraneoplastic or primary immune.
- Myasthenia gravis is an autoimmune disease in which an antibody-mediated attack on the acetylcholine receptors on the postsynaptic junction of the neuromuscular junction result in fatigable generalized weakness, often accompanied by ptosis and ophthalmoparesis. A minority of cases are associated with thymoma, which, despite its typically indolent nature, can be invasive and, rarely, malignant.
- Involvement of bilateral medial rectus muscles in myasthenia gravis may mimic a bilateral internuclear ophthalmoplegia.
- The Cogan lid twitch is an overshoot of the eyelid when the patient looks upward following a period of fixation on a target in downgaze. Although not pathognomonic for myasthenia gravis, it may provide supporting clinical evidence for the disease.

Article 11: Infectious Optic Neuropathies

Eric R. Eggenberger, DO, FAAN. Continuum (Minneap Minn). October 2019; 25 (5 Neuro-Ophthalmology):1422–1437.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews common infectious optic neuropathies, focusing on the more common and globally important entities.

RECENT FINDINGS:

Novel infections continue to emerge and drift geographically over time; not infrequently, these have important neurologic or ocular features. Malarial retinal findings comprise a relatively specific set of findings and serve as an invaluable aid in the diagnosis of cerebral malaria. Therapy continues to evolve and is best formulated in concert with an infectious disease expert.

SUMMARY:

Infectious optic neuropathies are less common than inflammatory or ischemic optic neuropathies; may present with varied, overlapping, and nonspecific clinical appearances; and comprise an important differential consideration demanding specific therapy.

KEY POINTS

- Infectious optic neuropathy often presents with a nonspecific clinical picture including adjacent structures, most commonly the retina and vitreous. Travel and increasingly global exposures influence the differential diagnosis. New pathogens continue to emerge and frequently involve ocular structures.
- Tuberculosis is a common worldwide infection and shares a synergistic interconnection with HIV. Diagnosis can be challenging; however, interferon-based laboratory tests represent a useful advance.
- Tuberculosis can affect any part of the visual system from the globe, optic nerve, chiasm, and tracts to the occipital lobe. Optic nerve and ocular involvement are accompanied by uveitis in the vast majority of cases.
- Neuroretinitis is a nonspecific clinical syndrome that may be related to any of several different infectious agents in addition to inflammatory or neoplastic pathophysiologies.

- Although *Borrelia* is an important neuropathogen, retrobulbar optic neuropathy related to Lyme disease is extremely rare.
- Syphilis rates are increasing, and diagnostic testing can be challenging; diverse clinical presentations and a well-earned reputation as "the great mimic" make syphilis an important treatment-altering point in the differential of many clinical neuro-ophthalmologic presentations.
- Syphilis may involve the brain and ocular structures at any stage. When syphilis affects the eye, uveitis is the most common form; however, the disease is notoriously variable and may affect the bulbar or retrobulbar segment of the optic nerve with granulomatous, nongranulomatous, or ischemic pathophysiologies.
- Acute retinal necrosis is an important ocular condition producing rapidly progressive retinal vasculitis with retinal necrosis, often with coincident or subsequent papillitis.
- Zika virus is the latest in novel infectious epidemics, with a relatively distinct congenital syndrome of microcephaly and retinal/optic nerve changes.
- Cerebral malaria is often associated with relatively distinct retinal changes, including retina whitening, retinal vascular changes, retinal hemorrhage, and occasional papilledema.
- Toxoplasmosis is widespread geographically and the most common infectious cause of uveitis in many clinics. Treatment is effective at preventing visual loss in most patients.
- Fungal infections are rapidly progressive in the immunocompromised host, with frequent lethal outcomes in the absence of early diagnosis and aggressive therapy.

Article 12: Imaging in Neuro-ophthalmology

Fiona Costello, MD, FRCPC; James N. Scott, MD, MSc. Continuum (Minneap Minn). October 2019; 25 (5 Neuro-Ophthalmology):1438–1490.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses an approach to imaging in patients with neuro-ophthalmologic disorders, with emphasis on the clinical-anatomic localization of lesions affecting afferent and efferent visual function.

RECENT FINDINGS:

Advances in MRI, CT, ultrasound, and optical coherence tomography have changed how neuro-ophthalmic disorders are diagnosed and followed in the modern clinical era.

SUMMARY:

The advantages, disadvantages, and indications for various imaging techniques for neuro-ophthalmologic disorders are discussed, with a view to optimizing how these tools can be used to enhance patient care.

KEY POINTS

- The diagnostic pursuit of "what" the problem is in neuro-ophthalmology is often spearheaded by knowledge of "where" the problem is because of the elegant topographic organization of the afferent and efferent visual systems.
- The diagnosis of optic neuritis associated with neuromyelitis optica spectrum disorder can be aided by adding orbital MRI sequences to cranial imaging; orbital views typically reveal longitudinal lesion(s) that extend back to the optic chiasm.

- MRI of the brain, orbits, and spinal cord can help identify patterns of central nervous system inflammation that are pathognomonic for neuromyelitis optica spectrum disorder.
- Anti–myelin oligodendrocyte glycoprotein IgG–associated optic neuritis commonly presents with optic disc edema and MRI evidence of perineural enhancement of the optic nerve extending into surrounding tissues in the orbit.
- Autoimmune glial fibrillary acidic protein–IgG astrocytopathy presents with a highly characteristic radial pattern of periventricular enhancement best seen with cranial MRI.
- Optic perineuritis with MRI evidence of a tram-track sign is a nonspecific radiologic finding and may be seen in a variety of inflammatory and neoplastic disorders affecting the optic nerve. Complementary CT images can reveal calcification in suspected cases of optic nerve sheath meningioma, but in other cases a systemic evaluation of the patient may be needed to render the diagnosis.
- Enhanced-depth optical coherence tomography can be used to detect buried optic disc drusen, which appear as signal-poor structures surrounded by a hyperreflective rim.
- Tortuosity of the optic nerve sheaths, flattening of the posterior globes, an empty sella turcica, and transverse venous sinus stenosis are radiologic signs of raised intracranial pressure in patients with idiopathic intracranial hypertension.
- Optical coherence tomography–derived ganglion cell–inner plexiform layer analysis can detect the presence of a compressive lesion in the region of the optic chiasm, sometimes in advance of visual field loss. Moreover, the extent of optical coherence tomography– measured retinal nerve fiber layer thinning and ganglion cell–inner plexiform layer loss in the preoperative phase can help predict the extent of postoperative visual recovery after surgical or medical decompression of compressive lesions.
- In cases of tumefactive multiple sclerosis, lesions can appear masslike and may be confused with neoplasms. In this setting, the so-called open pattern of ring enhancement is a useful radiologic sign to help distinguish demyelinating lesions.
- Recently, a punctate pattern depicted with MRI (referring to T2-weighted hyperintense or enhancing punctate lesions) has been shown to be a highly specific feature of progressive multifocal leukoencephalopathy and may be the first detectable imaging feature.
- Specific MRI patterns of brainstem involvement are highly suggestive of neuromyelitis optica spectrum disorder, including lesions of the dorsal medulla and area postrema structures.
- In addition to vascular insults, the brainstem is also vulnerable to demyelinating, neoplastic, neurodegenerative, inflammatory, infectious, and metabolic disorders.

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ARTICLE 1: APPROACH TO THE HISTORY AND EVALUATION OF VERTIGO AND DIZZINESS

Terry D. Fife, MD, FAAN, FANS. Continuum (Minneap Minn). April 2021;
27 (2 Neuro-otology):306–329.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews a method of obtaining the medical history of patients presenting with dizziness, vertigo, and imbalance. By combining elements of the history with examination, the goal is to identify patterns and an effective differential diagnosis for this group of patients to help lead to an accurate diagnosis.

RECENT FINDINGS:

Studies over the past dozen years have changed the historical approach to patients with dizziness from one based primarily on how the patient describes the sensation of dizziness. This older approach can lead to misdiagnosis, so a preferred method puts greater emphasis on whether the dizziness is acute or chronic, episodic or continuous, or evoked by or brought on by an event or circumstance so that a pattern may be derived that better narrows the differential diagnosis and focused examination can further narrow to a cause or causes.

SUMMARY:

Dizziness is a common symptom of many possible causes. This article will help clinicians navigate gathering the history and examination to formulate a working diagnosis in patients affected by dizziness.

KEY POINTS

- Dizziness is a common symptom that occurs at all ages but especially in patients aged between 41 and 70 years.
- Peripheral vestibular disorders are common, but half of patients with dizziness have a nonvestibular mechanism, and approximately one in six patients present with two different causes of dizziness at the same time.
- Many patients with dizziness see multiple health care providers in evaluation of the dizziness and feel frustrated, misdiagnosed, or misdirected.

- Overreliance on a patient's description of the dizziness and using it as the main piece of information to choose among causes leads to mistakes in the diagnosis.
- All aspects of history (symptom description, onset, frequency, duration, and provoking or aggravating circumstances) should be questioned until understood as well as possible because any part of the history can be miscommunicated by a patient or misunderstood by the health care provider.
- History-taking is best started with an open-ended question to allow patients to relay how the symptoms began and what they experience, although patients may need to be redirected in some cases.
- Excessive reliance on the patient's description of dizziness or vertigo leads to mistakes in diagnosis, but some patients accurately describe spinning, whirling, rotational sensations that do indeed imply a higher likelihood of a vestibular process.
- For patients who describe clear vertigo (spinning, whirling, rotation), if spells last less than 1 minute, then benign paroxysmal positional vertigo may be the cause. If the spells last minutes, transient ischemic attack or vestibular migraine should be considered. If the spells last hours, Ménière disease or vestibular migraine may be the cause.
- It is helpful to ask patients about the impact the dizziness or vertigo has on their quality of life and ascertain their goal for the visit and evaluation because some patients just want to be reassured that the cause is benign but can live with the symptom if need be, whereas others are desperate for treatment to relieve the symptoms.
- Spontaneous downbeat nystagmus should be considered a central finding that localizes to the cerebellar vermis or cervicomedullary junction.
- In peripheral vestibular horizontal nystagmus, the nystagmus stays in one direction, intensifying with gaze in the direction of the fast phase and diminishing or abating with gaze in the direction away from the fast phase of nystagmus.
- Delayed orthostatic hypotension (having onset beyond 3 minutes after standing or head-up tilt) may be missed by routine orthostatic vital signs but can be detected by a tilt-table test.

ARTICLE 2: VESTIBULAR TESTING

Timothy C. Hain, MD; Marcello Cherchi, MD, PhD, FAAN. Continuum (Minneap Minn). April 2021; 27 (2 Neuro-otology):330–347.

ABSTRACT

PURPOSE OF REVIEW:

Vestibular testing, both at the bedside and in the laboratory, is often critical in diagnosing patients with symptoms of vertigo, dizziness, unsteadiness, and oscillopsia. This article introduces readers to core concepts, as well as recent advances, in bedside and instrumented vestibular assessments.

RECENT FINDINGS:

Vestibular testing has improved immensely in the past 2 decades. While history and bedside testing is still the primary method of differential diagnosis in patients with dizziness, advances in technology such as the ocular vestibular-evoked myogenic potential test for superior canal dehiscence and the video head impulse test for vestibular neuritis have capabilities that go far beyond the bedside examination. Current vestibular testing now allows clinicians to test all five vestibular sensors in the inner ear.

SUMMARY:

Contemporary vestibular testing technology can now assess the entire vestibular periphery. Relatively subtle conditions, such as superior canal dehiscence or a subtle vestibular neuritis, can now be diagnosed with far greater certainty.

KEY POINTS

- The function of all five vestibular sensors in the inner ear, including the otolith organs (saccule and utricle) and all three semicircular canals, can now be tested.
- The assessment of the balance of a patient with dizziness starts when the patient is met in the waiting room and walked to the examination room.
- Frenzel goggles are critical to the rapid and efficient evaluation of patients with dizziness because they improve the clinician's ability to detect vestibular nystagmus.
- Vestibular spontaneous nystagmus is suppressed by fixation.
- Congenital nystagmus is enhanced by fixation.
- The ophthalmoscope can be used to assess spontaneous nystagmus if Frenzel goggles are not available.
- The Alexander law can be used to assess for spontaneous jerk nystagmus.
- The neck-vibration test is a sensitive and durable test of unilateral vestibular weakness.
- Hearing testing is critical to assess for Ménière disease and contributes greatly to the diagnosis of a vestibular schwannoma.
- The combination of a subjective hearing test such as the audiogram with an objective test such as otoacoustic emissions can help with the diagnosis of functional hearing loss.
- False-positive videonystagmography findings of bilateral vestibular weakness or central vestibular disturbance are common sources of referrals to neurologists.

ARTICLE 3: EPISODIC POSITIONAL DIZZINESS

Kevin A. Kerber, MD, MS. Continuum (Minneap Minn). April 2021; 27 (2 Neuro-otology): 348–368.

ABSTRACT

PURPOSE OF REVIEW:

This article provides a summary of the evaluation and treatment of patients presenting with episodic positional dizziness.

RECENT FINDINGS:

Positional components are nearly ubiquitous among diagnoses of dizziness, so it can be challenging to classify patients with episodic positional dizziness simply based on the history of present illness. Overreliance on the presence of a report of positional components has likely resulted in misapplication or misinterpretation of positional testing and negative experiences with maneuvers to treat positional dizziness. The prototypical episodic positional dizziness disorder is benign paroxysmal positional vertigo (BPPV). BPPV is caused by free-floating particles in a semicircular canal that move in response to gravity. The diagnosis is made by identifying the characteristic patterns of nystagmus on the Dix-Hallpike test. Particle repositioning for BPPV is supported by randomized controlled trials, meta-analyses, and practice guidelines. Other disorders that can present with episodic positional dizziness are migraine dizziness, central lesions, and light cupula syndrome.

SUMMARY:

Episodic positional dizziness is a common presentation of dizziness. Neurologists should prioritize identifying and treating BPPV; doing so provides an important opportunity to deliver effective and efficient care. Providers should also recognize that positional components are

common in most causes of dizziness and, therefore, should not over-rely on this part of the history of presentation when considering the diagnosis and management plan.

KEY POINTS

- Patients with any cause of dizziness typically report positional components. As a result, providers should be cautious in relying on the self-report of positional components to make a diagnosis of benign paroxysmal positional vertigo (BPPV).
- Patients with dizziness are often not reliable in their self-report of the type of dizziness. As a result, BPPV should be considered a diagnostic possibility even in patients who do not report vertigo.
- The ocular motor examination starts with observing the eyes in primary gaze for 5 to 10 seconds and specifically looking for any spontaneous movements such as nystagmus or saccadic intrusions.
- When impaired smooth pursuit is identified in patients who are cognitively intact and without other large motor deficits (eg, hemiplegia), it is a strong indicator of cerebellar dysfunction.
- Eye movement testing, including pursuit tracking, gaze testing, and saccadic eye movement observation, takes very little time but can be the key factor in identifying a cerebellar or vestibular disorder.
- The Dix-Hallpike test is designed to identify posterior canal BPPV but can also identify the horizontal and anterior canal variants and central causes of dizziness.
- Some patients with BPPV report a constant milder dizziness before and even for a time after treatment for unclear reasons.
- The gold standard test for BPPV is the Dix-Hallpike test. A positive finding is a triggered and transient nystagmus.
- *Direction-changing positional nystagmus* refers to nystagmus that changes direction with changes in head position and should not be confused with gaze-evoked nystagmus in which nystagmus changes direction with changes in the direction of gaze.
- Clinicians should not think of the Dix-Hallpike test as a test only for peripheral disorders; it is also a test for central positional dizziness.
- The most common patterns of central positional nystagmus are downbeat, apogeotropic horizontal, geotropic horizontal, and multiplanar.
- Vestibular migraine can closely mimic BPPV by presenting with purely positional dizziness.
- Patients with light cupula syndrome typically have profound positional vertigo and a constant sense of imbalance. The nystagmus is persistent geotropic direction-changing positional nystagmus without latency or fatigability.
- The Dix-Hallpike test should be performed by moving the patient from the sitting to head-hanging position at a pace a bit more quickly than he or she would ordinarily lie down and trying to tilt the head back approximately 20 degrees.
- A Cochrane collaboration meta-analysis of eight randomized controlled trials found that conversion from a positive to a negative Dix-Hallpike test significantly favored the Epley treatment group when compared with a sham maneuver or control.
- Horizontal canal BPPV can be treated by using the barbeque roll maneuver, the Gufoni maneuver, or the forced prolonged position.
- If a patient is suspected of having BPPV but the positional testing does not trigger nystagmus, it is possible that the patient had spontaneous resolution, the positional testing was not adequately performed, or the patient developed an anxiety response to previous BPPV.

ARTICLE 4: EPISODIC SPONTANEOUS DIZZINESS

Scott D. Z. Eggers, MD. Continuum (Minneap Minn). April 2021;
27 (2 Neuro-otology):369–401.

ABSTRACT

PURPOSE OF REVIEW:

Conditions causing recurrent spontaneous episodes of dizziness or vertigo span several medical specialties, making it challenging for clinicians to gain confidence in evaluating and managing the spectrum of episodic vestibular disorders. Patients are often asymptomatic and have normal examinations at the time of evaluation. Thus, diagnosis depends heavily on eliciting key features from the history. Overreliance on symptom quality descriptions commonly leads to misdiagnosis. The goal of this article is to provide the reader with a straightforward approach to the diagnosis and management of conditions that cause episodic spontaneous dizziness.

RECENT FINDINGS:

Consensus diagnostic criteria have been established for vestibular migraine, Ménière disease, vestibular paroxysmia, and hemodynamic orthostatic dizziness/vertigo. Vertigo has been recognized as a common symptom in vertebrobasilar ischemia, cardiogenic dizziness, and orthostatic hypotension. Treatment recommendations for vestibular migraine still lack high-quality evidence, but controlled trials are occurring.

SUMMARY:

The evaluation should start with a detailed description of the episodes from the patient and any observers. Rather than focusing first on whether the symptom quality is most consistent with vertigo, dizziness, lightheadedness, or unsteadiness, the clinician should clarify the timing (episode frequency and duration), possible triggers or circumstances (eg, position changes, upright posture), and accompanying symptoms. History should identify any auditory symptoms, migraine features, posterior circulation ischemic symptoms, vascular risk factors, clues for anxiety, and potentially relevant medications. Carefully selected testing can help secure the diagnosis, but excessive and indiscriminate testing can lead to more confusion. Treatments for these conditions are vastly different, so an accurate diagnosis is critical.

KEY POINTS

- Patients with episodic spontaneous dizziness are often asymptomatic at the time of evaluation and most often have normal examinations. The diagnostic history should focus on the timing, triggers, circumstances, and accompanying symptoms rather than placing too much emphasis on the patient's description of the quality of dizziness.
- Dizziness is a common accompaniment of migraine that is not associated with other headache types.
- Vestibular migraine is the most common cause of episodic spontaneous vertigo, affecting between 1% and 2.7% of the population.
- Migraine headache typically precedes vertigo onset by several years; although they may begin concurrently, headaches may have resolved decades before vertigo begins.
- The wide spectrum of clinical manifestations and vestibular laboratory findings in vestibular migraine suggests heterogeneous pathophysiologic mechanisms.

- The character of vestibular symptoms varies widely in vestibular migraine. Vertigo may be external or internal spinning, rocking, tilting, swaying, falling, or floating. Symptoms may be spontaneous or may be triggered or aggravated by position changes, head movements, or visual stimuli.
- The temporal relationship between headaches and vertigo is quite variable in vestibular migraine, but few patients experience vertigo consistently as a typical aura.
- Auditory symptoms occur during episodes in about half of patients with vestibular migraine and can create diagnostic confusion with Ménière disease.
- Most patients with vestibular migraine have nystagmus during episodes, although tools to block visual fixation may be needed to appreciate it. It may be present in the upright position or only during positional testing, may look central or peripheral, and may be horizontal, vertical, or torsional. However, very intense horizontal nystagmus is more suggestive of Ménière disease.
- Between episodes, patients with vestibular migraine experience higher rates of motion sickness, head motion–induced dizziness, and visually induced dizziness with complex or moving visual stimuli.
- Patients with vestibular migraine have higher rates of other coexisting vestibular disorders such as benign paroxysmal positional vertigo and persistent postural perceptual dizziness, as well as higher rates of anxiety and depression than the general population.
- The general neurologic, ocular motor, and vestibular examinations are typically normal between episodes of vestibular migraine, although minor nonspecific peripheral or central vestibular and ocular motor findings are common during the symptom-free period when carefully evaluated with quantitative tools such as videonystagmography.
- A variety of vestibular laboratory tests are more commonly abnormal in patients with vestibular migraine than in controls, but none of them is specific for the diagnosis.
- Vestibular migraine is diagnosed based on symptoms meeting diagnostic criteria, with consideration of the differential diagnosis and sometimes investigations to exclude those conditions.
- Diagnosing vestibular migraine requires a patient meets International Headache Society criteria for migraine with or without aura, have recurrent episodes of vestibular symptoms lasting 5 minutes to 72 hours, and have at least one migrainous feature besides nausea with more than half of vestibular episodes.
- Patients can often be diagnosed with vestibular migraine based on a characteristic history meeting diagnostic criteria, a normal examination between episodes, and an absence of any red flags. Further investigations to exclude alternative diagnoses may include positional testing, audiometric evaluation, neuroimaging, or vestibular laboratory testing.
- Treatment recommendations for vestibular migraine come largely from case series, retrospective reviews, expert opinion, a few small controlled trials, and adaptation from the much larger migraine headache literature.
- Identifying and treating comorbid conditions is critical in the management of vestibular migraine.
- Ménière disease is an inner ear disorder whose clinical syndrome consists of spontaneous episodes of vertigo associated with typically unilateral fluctuating sensorineural hearing loss, tinnitus, and aural fullness.
- Ménière disease attacks typically produce severe spinning vertigo lasting 2 to 3 hours on average. If examined during an attack, most patients have intense spontaneous horizontal jerk nystagmus that ultimately reverses direction during the attack.
- Although the sensorineural hearing loss in Ménière disease fluctuates and initially recovers after attacks, it progressively worsens over time, generally still affecting lower frequencies but eventually flattening out to affect all frequencies and becoming less varying.
- Audiometrically documenting low- to medium-frequency sensorineural hearing loss is important for establishing the diagnosis of Ménière disease early on, especially because tinnitus and even subjective hearing loss can occur with episodes of vestibular migraine.
- Transient ischemic attacks are an uncommon cause of episodic vertigo across the population, but they are an important and dangerous cause to consider, especially in older patients with recent-onset symptoms and vascular risk factors.

- Isolated vertigo is the most common warning symptom before vertebrobasilar stroke. Most such vertebrobasilar TIAs last minutes to 1–2 hours.
- New hearing loss accompanied by vertigo can occur in lateral pontine or inner ear stroke.
- *Vestibular paroxysmia* refers to recurrent spontaneous or sometimes triggered episodes of vertigo lasting seconds to 1 minute that can occur up to dozens of times per day. It is most often attributed to neurovascular cross-compression of the vestibulocochlear nerve. Sometimes time-locked tinnitus aids localization.
- Most patients with vestibular paroxysmia respond to carbamazepine or oxcarbazepine.
- Panic attacks commonly cause dizziness, unsteadiness, or lightheadedness, but intense vertigo is uncommon.
- Anxiety disorders, including panic disorder, can be the cause of vestibular symptoms, the result of a vestibular disorder, or a comorbidity that is necessary to identify and manage simultaneously. Psychiatric disorders may also trigger functional vestibular disorders such as persistent postural perceptual dizziness.
- Patients with delayed orthostatic hypotension have a gradual fall in blood pressure that takes more than 3 minutes of upright posture to develop. Thus, the relationship between the trigger (upright position) and dizziness may be less clear, and patients may present with what appears to be episodic spontaneous dizziness.
- Patients with orthostatic hypotension may describe symptoms of vertigo or unsteadiness rather than lightheadedness or faintness.
- Dizziness is a prominent symptom in patients with bradycardia, tachycardia, or other low cardiac output states, and it is commonly experienced as vertigo lasting seconds to minutes.

ARTICLE 5: ACUTE VESTIBULAR SYNDROME

Kristen K. Steenerson, MD. Continuum (Minneap Minn). April 2021;
27 (2 Neuro-otology):402-419.

ABSTRACT

PURPOSE OF REVIEW:

This article provides a practical approach to acute vestibular syndrome while highlighting recent research advances.

RECENT FINDINGS:

Acute vestibular syndrome is defined as sudden-onset, continuous vertigo lasting longer than 24 hours with associated nausea and vomiting, all of which are worsened with head movement. Acute vestibular syndrome is provoked by a variety of central and peripheral causes, the most common of which are vestibular neuritis and acute stroke (posterior circulation). A clinical approach focusing on timing, associated history, and ocular motor findings can improve diagnostic accuracy and is more sensitive and specific than early neuroimaging. Because of the shared neurovascular supply, both peripheral and central vestibular disorders can manifest overlapping signs previously considered solely peripheral or central, including vertical skew, nystagmus, abnormal vestibular ocular reflex, hearing loss, and gait instability. Although acute vestibular syndrome is typically benign, stroke should be considered in every person with acute vestibular syndrome because it can act as a harbinger of stroke or impending cerebellar herniation. Treatment is focused on physical therapy because the evidence is minimal for the long-term use of medication.

SUMMARY:

The diagnosis of acute vestibular syndrome first requires the elimination of common medical causes for dizziness. Next, underlying pathology must be determined by distinguishing between the most common causes of acute vestibular syndrome: central and peripheral vestibular disorders. Central vestibular disorders are most often the result of ischemic stroke affecting the cerebellar arteries. Peripheral vestibular disorders are assumed to be caused mostly by inflammatory sources, but ischemia of the peripheral vestibular apparatus may be underappreciated. By using the HINTS Plus (Head Impulse test, Nystagmus, Test of Skew with *Plus* referring to hearing loss assessment) examination in addition to a comprehensive neurologic examination, strokes are unlikely to be missed. For nearly all acute vestibular disorders, vestibular physical therapy contributes to recovery.

KEY POINTS

- Acute vestibular syndrome describes the sudden onset of continuous vertigo lasting longer than 24 hours and associated with nausea, head motion intolerance, and unstable balance.
- Nausea, vomiting, and unsteadiness are symptoms of acute vestibular syndrome that are common to several causes, so additional measures are needed to narrow the diagnostic possibilities.
- The posterior circulation (vertebral arteries, posterior inferior cerebellar artery, anterior inferior cerebellar artery, and less often superior cerebellar artery) supplies the brainstem and cerebellar regions causing stroke that might present with acute vestibular syndrome.
- Cerebellar strokes that can present with vertigo, nystagmus, and imbalance if left unrecognized and untreated could lead to brain edema that can rarely lead to herniation and death.
- CT may miss posterior fossa strokes because of considerable bony artifact from the skull, and MRI may be diffusion negative up to the first 48 hours of symptoms.
- Strictly defined acute vestibular syndrome is most commonly due to acute unilateral vestibulopathy (vestibular neuritis or ischemic labyrinthopathy). If all types of acute dizziness are included, about one-third are due to vestibular causes.
- Orthostatic hypotension and other cardiac causes of dizziness can classically cause near-syncope and possibly brief bouts of vertigo but rarely sustained vertigo as is classic for acute vestibular syndrome.
- Vitamin B_1 deficiency causing Wernicke encephalopathy can rarely present as acute vestibular syndrome, although often with additional neurologic findings.
- Phenytoin toxicity may present with acute vertigo, nausea, ataxia, and gaze-evoked nystagmus.
- Acute intoxication with alcohol, phencyclidine, opiates, marijuana, and barbiturates can cause nystagmus and vertigo.
- Vertigo is a disorder of motion perception and encompasses false spinning sensations (spinning vertigo) and other false sensations such as swaying, tilting, bobbing, bouncing, or sliding (nonspinning vertigo).
- Spontaneous vertigo classic to acute vestibular syndrome continues even when the patient is motionless but worsens with any kind of head movement; in contrast, the vertigo of benign paroxysmal positional vertigo ensues after only certain provocative head maneuvers that evoke vertigo lasting less than 1 minute rather than continuously for 24 hours.
- Recurrent attacks that are new and increasing may rarely be a sign of stuttering transient ischemic attack of the posterior circulation.
- In patients with acute vertigo, nystagmus may be obvious with the naked eye, but when it is not, removal of fixation by some means (eg, Frenzel goggles, Fresnel lenses, magnifying sheet, bright penlight, or fundoscopy) improves detection of more subtle nystagmus.
- Although ideally hearing should be assessed in every patient with suspected acute vestibular syndrome, emergency settings are rarely equipped for formal audiometry. Bedside testing with hearing test smartphone applications or finger-rub testing followed by an eventual outpatient formal audiogram can provide valuable vascular risk factor information.

- Grading truncal ataxia in acute vestibular syndrome patients can increase anterior inferior cerebellar artery stroke detection sensitivity to 100%.
- If the HINTS Plus (Head Impulse test, Nystagmus, Test of Skew plus hearing loss assessment) examination demonstrates a central pattern consisting of no catch-up saccade on head impulse testing, central pattern nystagmus (direction-changing, vertical, unaffected by fixation), vertical skew deviation, and/or new, sudden asymmetric hearing loss, stroke is likely.
- The internal auditory artery, also known as the labyrinthine artery, supplies the cochlea, saccule, and posterior semicircular canal. Greater than 90% of anterior inferior cerebellar artery infarctions affect hearing and have evidence of peripheral vestibulopathy superimposed on central vestibulopathy.
- Antivirals have not been found to be effective medications and are not recommended in acute vestibular syndrome or acute unilateral vestibulopathy in isolation. Ramsay Hunt syndrome, which may cause acute vestibular syndrome in addition to vesicles around the ear and multiple cranial neuropathies, requires immediate antiviral therapy.
- Peripheral-pattern nystagmus for the majority of patients with acute unilateral vestibulopathy is direction-fixed, horizontal nystagmus that beats away from the affected side. It intensifies with gaze in the direction of the fast phase and diminishes or abates with gaze in the direction of the slow phase (known as the Alexander law).
- A catch-up saccade on head impulse testing is an abnormality that indicates ipsilateral peripheral vestibular hypofunction. It is a cortically generated response to the loss of the normal vestibular ocular reflex. A catch-up saccade with a quick turn to the right indicates the right is hypofunctional, and a catch-up saccade with a quick turn to the left indicates the left is hypofunctional.
- Abnormalities in the pathways, peripheral to central, of the ocular tilt reaction can result in skew deviation; although skew deviation is usually a central finding, it can sometimes be present with acute unilateral vestibular loss.
- HINTS Plus in acute vestibular syndrome due to vestibular neuritis consists of an abnormal head impulse test with a catch-up saccade toward the side affected, spontaneous unidirectional nystagmus with fast phases away from the affected ear, and the absence of skew eye deviation on cover-uncover testing.
- Mood disorders and inactivity can prolong or cause incomplete recovery from symptoms of acute unilateral vestibulopathy.
- Evidence-based guidelines support the use of vestibular physical therapy alone in the treatment of classic acute unilateral vestibulopathy resulting from acute vestibular syndrome.
- Physical and barotrauma can cause central and peripheral vestibular dysfunction.
- An empiric steroid trial for autoimmune inner ear disease should be considered in patients with aggressive, subacute, fluctuating, bilateral vestibular, and cochlear symptoms.

ARTICLE 6: CHRONIC DIZZINESS

Yoon-Hee Cha, MD, FAAN. Continuum (Minneap Minn). April 2021;
27 (2 Neuro-otology):420–446.

ABSTRACT

PURPOSE OF REVIEW:

Determining the etiology of disorders that manifest with chronic dizziness can seem a daunting task, but extracting some basic elements of the patient's history can reduce the differential diagnosis significantly. This includes determining initial triggers, timing of symptoms, associated features, and exacerbating factors. This article covers distinct causes of chronic dizziness including persistent postural perceptual dizziness, mal de débarquement syndrome, motion sickness and visually induced motion sickness, bilateral vestibulopathy, and persistent dizziness after mild concussion.

RECENT FINDINGS:

To date, none of the disorders above has a cure but are considered chronic syndromes with fluctuations that are both innate and driven by environmental stressors. As such, the mainstay of therapy for chronic disorders of dizziness involves managing factors that exacerbate symptoms and adding vestibular rehabilitation or cognitive-behavioral therapy alone or in combination, as appropriate. These therapies are supplemented by serotonergic antidepressants that modulate sensory gating and reduce anxiety. Besides expectation management, ruling out concurrent disorders and recognizing behavioral and lifestyle factors that affect symptom severity are critical issues in reducing morbidity for each disorder.

SUMMARY:

Many syndromes of chronic dizziness can be diagnosed by recognition of key features, although many symptoms overlap between these groups. Symptoms may be manageable and improve with time, but they are often incompletely relieved.

KEY POINTS

- Persistent postural perceptual dizziness is a chronic disorder of postural instability that lasts at least 3 months but can have fluctuations that are both innate as well as driven by environmental stimuli such as passive or active motion and visual stimuli.
- Persistent postural perceptual dizziness may be triggered by any severe homeostatic perturbation such as a vestibular disorder or medical, neurologic, or psychological process. Symptoms may continue despite resolution of the initial trigger or can coexist with an ongoing trigger.
- A slowly progressive disorder without a clear precipitant is not consistent with persistent postural perceptual dizziness.
- The mainstays of therapy for persistent postural perceptual dizziness include vestibular rehabilitation, cognitive-behavioral therapy, and serotonergic antidepressants.
- Mal de débarquement syndrome is a disorder of post–motion-induced persistent oscillating vertigo lasting more than 48 hours.
- The perception of motion in mal de débarquement syndrome is usually described as rocking, bobbing, or swaying. This perception decreases when the individual is back in motion such as when driving.
- Symptoms associated with mal de débarquement syndrome include chronic fatigue, visually induced dizziness, headaches, tinnitus, and anxiety. It is not typical for mal de débarquement syndrome to be associated with nystagmus, extraocular movement abnormalities, hearing loss, or spinning vertigo.
- Clinically available treatments for mal de débarquement syndrome include serotonergic antidepressants and benzodiazepines; vestibular therapy is generally not helpful.
- Motion sickness and visually induced motion sickness are generally self-limited processes that end when the stimulus is over. Symptoms may include nausea/vomiting, stomach awareness, headache, sweating/pallor, dizziness, drowsiness, or eyestrain.
- Motion sickness susceptibility peaks at the ages of 7 to 12 years, is stable through adult years, and declines after age 60 years. Visually induced motion sickness generally worsens with age.
- Certain disorders such as migraine, vestibular migraine, and Ménière disease can increase susceptibility to motion sickness. Motion sickness susceptibility can increase with vestibular neuritis but return to normal if the vestibular paresis is compensated. Individuals with bilateral vestibulopathy have very low motion sickness susceptibility.
- Habituation exercises, medications (antimuscarinic, anticholinergic, antihistaminergic, or diazepam), controlled breathing, music, or pleasant smells can modify motion sickness severity.
- Core symptoms of bilateral vestibulopathy include gait unsteadiness, postural instability, visual blurring with head movement, and sometimes oscillopsia.
- Bilateral vestibulopathy can be diagnosed by rotational chair testing, caloric irrigation, or video head impulse testing; the most reliable method is rotational chair testing.

- Bilateral vestibulopathy may occur after sequential inner ear injury such as from Ménière disease, vestibular neuritis, or vestibular schwannomas, from extension of intracerebral processes such as meningitis, carcinomatosis, or other processes in the subarachnoid space into the inner ear, or secondary to vestibulotoxic medications such as aminoglycoside antibiotics.
- Vestibular rehabilitation, protecting vision, and avoiding deconditioning are helpful in reducing morbidity from bilateral vestibulopathy. Safety measures should emphasize care in low-light settings.
- Postconcussion dizziness includes categories such as positional vertigo, exertional dizziness, vestibular migraine, spatial disorientation, and visual disorders.
- Concurrent ocular motor dysfunction and visual processing disorders may occur with postconcussion dizziness and can significantly add to morbidity.
- It is important to rule out structural injury to the inner ear after head trauma, particularly if severe vertigo or concurrent hearing loss is present.
- Graded vestibular rehabilitation is generally required for postconcussive dizziness along with a multipronged approach to address concurrent cognitive slowing, headache, anxiety, and mood dysregulation.

ARTICLE 7: VERTIGO RELATED TO CENTRAL NERVOUS SYSTEM DISORDERS

Kamala Saha, MD. Continuum (Minneap Minn). April 2021;
27 (2 Neuro-otology):447–467.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of the numerous causes of vertigo and dizziness that are due to central nervous system (CNS) pathology and guides clinicians in formulating a differential diagnosis and treating patients with CNS causes of vertigo.

RECENT FINDINGS:

Specific autoimmune vestibulocerebellar syndromes may now be tested for, and this article discusses the antibodies known to cause such syndromes. Superficial siderosis can be more accurately diagnosed with imaging studies, and treatment using iron chelation has recently been studied but has not yet been established as an effective treatment. Central autonomic network damage in the brain can cause central orthostatic hypotension in some neurodegenerative diseases, and medication has been approved for treatment.

SUMMARY:

CNS causes of vertigo are numerous and important for clinicians to recognize. Examination findings are still an extremely valuable way to diagnose central vertigo; therefore, learning how to differentiate central from peripheral vertigo based on examination is an important skill. CNS causes of vertigo often have available treatments.

KEY POINTS

- Multiple sclerosis lesions causing vertigo occur most frequently in the root entry zone of cranial nerve VIII and the medial vestibular nucleus.
- Treatment of vertigo as part of a multiple sclerosis exacerbation is usually with steroids, plus a very short course of a vestibular suppressant.
- Although known to experience central positional vertigo, patients with multiple sclerosis are much more likely to be experiencing benign paroxysmal positional vertigo if positional vertigo is the presenting symptom.

- Anterior inferior cerebellar artery territory infarcts can cause vertigo due to a peripheral lesion or central lesion, or both.
- Central vertigo in vestibular schwannoma often results from brainstem compression.
- Cavernous malformations are seen in the posterior fossa 25% of the time, and posterior fossa cavernous malformations have higher rates of hemorrhage than supratentorial cavernous malformations.
- Hemangioblastoma is typically associated with von Hippel-Lindau disease.
- Medulloblastoma causes vertigo and increased intracranial pressure from fourth ventricle involvement.
- *Listeria monocytogenes* is the most common infectious cause of rhombencephalitis.
- Chiari malformation type 1 is a radiographic diagnosis usually made by measuring cerebellar tonsil herniation greater than or equal to 5 mm below the foramen magnum.
- Downbeat nystagmus in patients with Chiari malformations localizes to the cervicomedullary junction.
- Infratentorial superficial siderosis most commonly causes hearing loss, but ataxia and vertigo are often also present.
- Imaging, usually MRI with gradient recalled echo and susceptibility-weighted imaging sequences, shows the findings of hemosiderin damage in superficial siderosis but does not necessarily correlate with clinical symptoms in a patient.
- Treatment of superficial siderosis is symptomatic, but identifying any possible underlying structural lesion causing the superficial siderosis is imperative. Surgery and iron chelators are being investigated but have not yet been established as effective treatments.
- Patients with cerebellar ataxia often have paroxysmal vertigo along with central nystagmus findings on examination.
- The central autonomic network is damaged in some neurodegenerative diseases and can lead to central orthostatic hypotension.
- Diagnosis of autoimmune vestibulocerebellar disorders depends on both a clinical syndrome that is characteristic and a positive antibody result.
- To improve test yield, both serum and CSF samples should be obtained for antibody testing for autoimmune vestibulocerebellar disorders.
- Identifying the specific antibody causing an autoimmune vestibulocerebellar disorder can help prognosticate and determine the likelihood of a malignancy eventually being found.

ARTICLE 8: SELECTED OTOLOGIC DISORDERS CAUSING DIZZINESS

Gail Ishiyama, MD. Continuum (Minneap Minn). April 2021;
27 (2 Neuro-otology):468–490.

ABSTRACT

PURPOSE OF REVIEW:

This article details updated clinical presentations and current treatment paradigms of the common otologic disorders that may present to the neurologist for vertigo, including Ménière disease, superior semicircular canal dehiscence syndrome, perilymphatic fistula, barotrauma, cholesteatoma, Ramsay Hunt syndrome, enlarged vestibular aqueduct syndrome, and autoimmune inner ear disease including Cogan syndrome.

RECENT FINDINGS:

The recent data on modern imaging techniques with three-dimensional delayed IV contrast in Ménière disease, findings on the clinical and testing parameters to diagnose semicircular canal dehiscence and barotrauma, and clinical findings in Ramsay Hunt syndrome, cholesteatoma, and enlarged vestibular aqueduct syndrome are discussed in the article. The most recent

findings on the treatment and evaluation of autoimmune inner ear disease and Cogan syndrome are also covered.

SUMMARY:

This article discusses the common clinical otologic entities in patients who may present to the neurologist for vertigo, and it can be used as a guide in the diagnosis of these conditions with the use of auditory, vestibular, and imaging results.

KEY POINTS

- Ménière disease may be caused by oxidative damage of the microvasculature resulting in degeneration of the blood-labyrinthine barrier.
- Tumarkin attacks occur in some patients with Ménière disease and are important to recognize because the falls are unpredictable and may lead to serious injury and are nearly always an indication for ablative treatment.
- The normal acoustic reflex helps distinguish the conductive hearing loss of superior semicircular canal dehiscence from that of otosclerosis, which is associated with an absent acoustic reflex.
- The demonstration of a thinning or dehiscence of the superior semicircular canal on CT of the temporal bone does not necessarily indicate the presence of superior semicircular canal dehiscence syndrome.
- All cases of superior semicircular canal dehiscence should have radiographic evidence, but CT alone overestimates the diagnosis by 6-fold to 20-fold. Patients diagnosed with superior semicircular canal dehiscence should meet criteria based on clinical presentation and audiologic and vestibular testing.
- The absence of a fistula sign at bedside testing does not rule out the diagnosis of a perilymphatic fistula.
- In trauma associated with hearing loss and/or vertigo, the CT should be evaluated in the coronal view for air bubbles (pneumolabyrinth), which is evidence of a traumatic perilymphatic fistula. Pneumolabyrinth, ossicular fracture or dislocation, or a temporal bone fracture through the otic capsule may be indications for urgent surgical exploration to preserve inner ear function.
- Clinicians should have a high level of suspicion in children presenting with hearing loss and should rule out perilymphatic fistula in the setting of inner ear anomaly as etiology.
- Mild symptoms consistent with perilymphatic fistula may be treated conservatively with avoidance of a Valsalva maneuver or with rest. However, conservative treatment is not recommended for traumatic perilymphatic fistula secondary to penetrating inner ear injury, temporal bone fracture, or ossicular damage.
- Acoustic hyperacusis with bone conduction thresholds less than 0 dB, autophony, and abnormal cervical vestibular-evoked myogenic potentials can help distinguish superior semicircular canal dehiscence from perilymphatic fistula.
- Barotrauma related to scuba diving is often associated with hearing loss (90%) and variably associated with vertigo (averaging 50%).
- High-resolution CT of the temporal bone is always indicated in audiovestibular loss in the setting of diving to rule out anatomic risk factors, ossicular disruption, hemorrhage, or pneumolabyrinth.
- Vestibular symptoms and vertigo in inner ear barotrauma should be referred to an otologic surgeon because surgical correction results in a high rate of symptom relief.
- The distinction between barotrauma and decompression inner ear syndromes in diving is critical, as inner ear barotrauma can be managed with an observational period. In contrast, decompression inner ear disease, which presents with a predominance of vestibular symptoms, should be treated with hyperbaric oxygen within 5 hours of injury as any further delay usually results in permanent inner ear damage.
- Early recognition of chronic otitis media and invasive cholesteatoma is critical. Because of the proximity of the middle ear canal to the facial nerve, the horizontal semicircular canal, and overlying dura, invasive cholesteatoma can cause hearing loss, vertigo, facial paresis, meningitis, and intracranial abscess.
- Surgical eradication of cholesteatoma is indicated and aims to prevent the extension through the dura membrane and the associated intracranial complications.

- Evaluation for fistulization of the bony labyrinth may be tested at the bedside with the fistula test using a pneumatic otoscope (the Hennebert test). However, the fistula test may be falsely negative in the case of a cholesteatoma abundantly filled with keratin debris.
- The patient presenting with a gradual onset of facial weakness, often incomplete in the setting of otalgia and otorrhea, likely has chronic otitis media with cholesteatoma causing dehiscence of the facial nerve canal.
- The classical signs of meningitis may be masked in the patient with invasive cholesteatoma due to antibiotics.
- A diffusion-weighted imaging sequence on MRI can be used to follow a cholesteatoma, which will be hyperintense on diffusion-weighted imaging.
- Chronic otitis media with headache, nausea, and vomiting should trigger a workup for meningitis.
- Areas of vesicular rash eruption in Ramsay Hunt syndrome involve the sensory distribution of the facial nerve, which can include vesicles in the ipsilateral ear (concha and antihelix, antitragus, and a portion of the lobule and adjacent mastoid), ipsilateral hard palate, and anterior two-thirds of the tongue, which has the special taste sensory fibers.
- In addition to evaluation of the external ear for vesicles in Ramsay Hunt syndrome, the clinician should evaluate the back of the ear and conduct an otoscopic examination of the external canal and the tympanic membrane.
- Facial paralysis occurs in nearly all and hearing loss in up to half of patients with Ramsay Hunt syndrome. About 30% to 50% have vestibular neuritis–like vertigo and subsequent imbalance.
- A key factor in the recovery of cranial nerve function after Ramsay Hunt syndrome appears to be an earlier onset of treatment. Treatment within 1 to 3 days of symptom onset ensures 75% of patients recover function, but only 30% recover if treated after 7 days.
- Up to 15% of children with sensorineural hearing loss have an enlarged vestibular aqueduct.
- An enlarged vestibular aqueduct and pathogenic sequence alteration in the *SLC26A4* gene are associated with bilateral hearing loss and recurrent spells of episodic vertigo.
- An enlarged vestibular aqueduct, like superior semicircular canal dehiscence, can present with cervical vestibular-evoked myogenic potentials with low thresholds and high amplitudes, but the Tullio phenomenon and the Hennebert sign are generally less prominent. A Ménière disease–like presentation with recurrent spells of vertigo can be associated with an enlarged vestibular aqueduct.
- An enlarged vestibular aqueduct can be diagnosed by using either CT of the temporal bone or MRI of the internal auditory canal.
- Many patients with an enlarged vestibular aqueduct have been advised to avoid contact sports, but current data may not support an association with minor head trauma and drops in hearing. Also, cochlear implantation in these patients is safe and effective.
- Deafness associated with autoimmune inner ear disease occurs over weeks and not 1 or 2 days, as in sudden sensorineural hearing loss. One-third of the patients with autoimmune inner ear disease have or will develop a systemic autoimmune disease.
- Up to 50% of patients with autoimmune inner ear disease report vertigo or dizziness or have tinnitus and aural fullness, mimicking Ménière disease.
- Corticosteroids are the mainstay of treatment for autoimmune inner ear disease, with serial audiograms to evaluate hearing with taper. Referral to rheumatology for consideration of steroid-sparing medications and evaluation for systemic autoimmune disease should be considered.
- The vasculitis and audiovestibular dysfunction of Cogan syndrome usually respond to high-dose corticosteroids, with the expectation of a beneficial response within 2 to 3 weeks. In intractable Cogan syndrome, the progression to deafness occurs in more than half of patients.
- In both autoimmune inner ear disease– and Cogan syndrome–associated deafness, cochlear implantation is often restorative of hearing with good to excellent results.
- The finding of immunoglobulin deposition in the stria vascularis and spiral ganglia in Sjögren syndrome associated with hearing loss indicates that the hearing loss in autoimmune inner ear disease and systemic autoimmune disease may be mediated in part by immunoglobulin deposition in the inner ears.

ARTICLE 9: TINNITUS, HYPERACUSIS, OTALGIA, AND HEARING LOSS

Terry D. Fife, MD, FAAN, FANS; Roksolyana Tourkevich, MD. Continuum (Minneap Minn). April 2021; 27 (2 Neuro-otology):491–525.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the causes of tinnitus, hyperacusis, and otalgia, as well as hearing loss relevant for clinicians in the field of neurology.

RECENT FINDINGS:

Important causes of unilateral and bilateral tinnitus are discussed, including those that are treatable or caused by serious structural or vascular causes. Concepts of hyperacusis and misophonia are covered, along with various types of neurologic disorders that can lead to pain in the ear. Hearing loss is common but not always purely otologic.

SUMMARY:

Tinnitus and hearing loss are common symptoms that are sometimes related to a primary neurologic disorder. This review, tailored to neurologists who care for patients who may be referred to or encountered in neurology practice, provides information on hearing disorders, how to recognize when a neurologic process may be involved, and when to refer to otolaryngology or other specialists.

KEY POINTS

- Among the most serious causes of unilateral pulse-synchronous tinnitus are a dural arteriovenous fistula, arteriovenous malformation, or a glomus tumor arising from the jugular foramen or middle ear.
- Many forms of unilateral and bilateral tinnitus are more bothersome to patients with coexistence of depression, insomnia, stress, anxiety, and excessive caffeine use.
- Otologic causes of unilateral pulse-synchronous tinnitus include ceruminous impaction and middle ear disorders leading to conductive hearing loss such that bone-conducted sounds from vascular and other internal structures are heard more loudly.
- Unilateral pulse-synchronous tinnitus may be caused by sounds transmitted from the carotid artery (bruit) or the heart (murmur), increased intracranial pressure, or conditions that cause high-flow states such as pregnancy, anemia, and hyperthyroidism.
- "Typewriter tinnitus" is a term for a pulse-asynchronous tapping or Morse code–like staccato tinnitus that may respond to treatment with carbamazepine, oxcarbazepine, gabapentin, or pregabalin.
- Myoclonus of the stapedius or tensor tympani may cause a benign type of unilateral fluttering or thumping tinnitus that is rhythmic but not synchronous with the heart rate.
- Bilateral high-pitched subjective tinnitus that is constant but varies with ambient noise is the most common form of tinnitus and is often associated with some degree of sensorineural hearing loss.
- Palatal myoclonus and oculopalatal myoclonus cause an objective clicking sound audible to the patient and others and that persists during sleep.
- While phonophobia is an aversion to loud sounds as may occur during migraine headaches, hyperacusis is a rare disorder with constant intolerance to sounds of ordinary loudness that do not bother most people.
- Unilateral continuing otalgia without an evident structural cause can sometimes be attributable to hemicranial headache disorders, herpes zoster oticus, or postherpetic neuralgia, giant cell arteritis, or neuralgia of cranial nerves V, VII, IX, and X or of the sphenopalatine or greater occipital nerves.

- In a patient presenting with hearing impairment, the first step is to distinguish conductive from sensorineural hearing loss.
- Vestibular schwannoma can occasionally present with sudden unilateral hearing loss, although it is usually more gradual and progressive.
- When acute unilateral hearing loss is present, labyrinthine ischemia should be considered, but a viral/inflammatory cause is considered to be more common.
- Occlusion of the posterior inferior cerebellar artery can rarely cause acute audiovestibular symptoms.
- If any part of HINTS (Head Impulse, Nystagmus, Test of Skew) suggests central localization, the etiology must be assumed to be central until proven otherwise.
- Isolated labyrinthine stroke is unlikely to be visible on standard MRI.
- Ménière disease presents with an abrupt onset of recurrent vertiginous attacks with associated fluctuating unilateral low-frequency sensorineural hearing loss.
- Intracranial hypotension can present with tinnitus, altered hearing, dizziness, or vertigo.
- Among the more prevalent etiologies of chronic bilateral sensorineural hearing loss are age-related hearing loss, heritable factors, and noise exposure.

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NEUROCRITICAL CARE

ARTICLE 1: MANAGEMENT OF CEREBRAL EDEMA, BRAIN COMPRESSION, AND INTRACRANIAL PRESSURE

Eric M. Liotta, MD, MS. Continuum (Minneap Minn). October 2021; 27 (5 Neurocritical Care):1172–1200.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the pathophysiology and management of cerebral edema, brain compression, and elevated intracranial pressure (ICP). It also provides a brief introduction to the concept of the glymphatic system and select cellular contributors to cerebral edema.

RECENT FINDINGS:

Cerebral edema and brain compression should be treated in a tiered approach after the patient demonstrates a symptomatic indication to start treatment. All patients with acute brain injury should be treated with standard measures to optimize intracranial compliance and minimize risk of ICP elevation. When ICP monitors are used, therapies should target maintaining ICP at 22 mm Hg or less. Evidence exists that serial clinical examination and neuroimaging may be a reasonable alternative to ICP monitoring; however, clinical trials in progress may demonstrate advantages to advanced monitoring techniques. Early decompressive craniectomy and hypothermia are not neuroprotective in traumatic brain injury and should be reserved for situations refractory to initial medical interventions. Medical therapies that acutely lower plasma osmolality may lead to neurologic deterioration from osmotic cerebral edema, and patients with acute brain injury and renal or liver failure are at elevated risk.

SUMMARY:

A tiered approach to the management of cerebral edema and brain compression can reduce secondary brain injury when implemented according to core physiologic principles. However, our knowledge of the pathophysiology of acute brain injury is incomplete, and the conceptual framework underlying decades of clinical management may need to be revised in response to currently evolving discoveries regarding the pathophysiology of acute brain injury.

KEY POINTS

- **Cerebral edema is a major cause of secondary brain injury through compression of brain structures, distortion and herniation of brain tissue, and compromise of cerebral blood flow through increased intracranial pressure.**

- Clinicians should be aware of four forms of cerebral edema: vasogenic, cytotoxic, hydrostatic, and osmotic. Vasogenic and cytotoxic edema are the most frequently encountered.
- Vasogenic edema results from dysfunction of the blood-brain barrier, the physical and metabolic barrier between the brain and the systemic circulation. It is associated with brain tumors, cerebral abscesses, and posterior reversible encephalopathy syndrome.
- Cytotoxic edema results from derangements in cellular metabolism with resulting alterations in ionic gradients and movement of water into the brain tissue. Cytotoxic edema is classically associated with ischemic stroke and acute liver failure.
- Hydrostatic cerebral edema results from displacement of CSF from the ventricular space into the brain interstitium; this occurs as a consequence of hydrocephalus when hydrostatic pressure pushes CSF through the ependymal lining.
- Osmotic cerebral edema occurs when an acute osmotic gradient develops between the brain and serum favoring water entry into the brain. Patients with brain injuries receiving medical interventions that reduce serum osmolality, such as dialysis, are at particular risk for acute deterioration from this edema.
- Rapid identification and treatment of osmotic cerebral edema by returning serum osmolality to prior levels may be lifesaving.
- The intracranial compartment can be thought of as a rigid box with a balloon attached to the side. The balloon buffers volume added to the box and minimizes pressure increases until the balloon is full. The balloon represents intracranial compliance.
- CSF functions as the primary buffer responsible for intracranial compliance. CSF can be displaced to the spinal cisterns and cranial nerve sheaths. Once intracranial compliance is exhausted, intracranial pressure increases exponentially.
- Lundberg A waves reflect critically exhausted intracranial compliance with elevated risk for brain herniation. Lundberg A waves are characterized by rapid increases in intracranial pressure to 50 mm Hg to 80 mm Hg lasting 5 to 20 minutes.
- The Brain Trauma Foundation recommends treatment for intracranial pressure greater than 22 mm Hg. Intracranial pressure should be elevated for about 10 minutes before treatment to avoid overtreatment of spontaneously resolving intracranial pressure elevations.
- Cerebral perfusion pressure is calculated by subtracting the intracranial pressure from the mean arterial blood pressure. The latest Brain Trauma Foundation guidelines recommended revising the cerebral perfusion pressure goal to 60 mm Hg to 70 mm Hg.
- Currently, intracranial pressure monitoring is not routine in the management of hemorrhagic or ischemic stroke, brain tumors, or meningitis but may be considered in select cases of coma, herniation, or hydrocephalus occurring in these diseases.
- Intracranial pressure monitoring should be considered in patients who are comatose after traumatic brain injury with abnormal CT scans of the head or normal CT scans with two or more of the following: age older than 40 years, motor posturing, or systolic blood pressure below 90 mm Hg.
- Although intracranial pressure monitoring does not have a proven outcome benefit, it still has considerable clinical utility. However, clinicians could also consider alternative strategies, including clinical assessment and serial neuroimaging.
- Normal intracranial pressure values should not be comforting when in conflict with other concerning clinical data. Significant pressure gradients may exist in the skull, and brain herniation can occur with normal intracranial pressure monitor readings.
- Intracranial pressure–targeted therapy should follow a tiered approach in which therapies from higher tiers are introduced after ensuring optimization of lower-tier interventions.
- Systemic resuscitation and goal-directed supportive medical care are critical to avoid secondary brain injury. Numerous studies have demonstrated that hypotensive and hypoxic episodes are associated with worse outcome.

- Because of their numerous side effects, steroids should be reserved for the treatment of significant symptoms that are referrable to peritumoral edema rather than the tumor itself.
- Steroids are contraindicated in the treatment of traumatic brain injury because of increased mortality.
- In urgent situations, the osmotic agent used to treat cerebral edema or elevated intracranial pressure should be dictated by availability and familiarity. Many emergency departments do not stock and are not familiar with hypertonic saline but are familiar with mannitol.
- Osmotic therapy should be reserved for patients with cerebral edema or elevated intracranial pressure and with symptomatic clinical deterioration that is likely to benefit from improved intracranial compliance and should not be used prophylactically.
- Initiating osmotic therapy before it is needed for intracranial compliance may actually promote an earlier development and greater magnitude of edema through increased blood-brain barrier permeability; this may ultimately obligate clinicians to maintain a higher osmolality later in the disease course than might otherwise be needed.
- In patients 60 years of age and younger with malignant middle cerebral artery infarcts who neurologically deteriorate despite medical therapy, decompressive craniectomy within 48 hours of stroke is recommended to improve mortality and functional outcome.
- In patients with posterior fossa lesions causing brainstem compression or obstructive hydrocephalus, posterior fossa decompression is considered first-line therapy.
- Therapeutic hypothermia may be used for refractory intracranial pressure elevation, but prophylactic hypothermia does not improve outcome in severe traumatic brain injury and might be harmful.
- Hyperventilation should primarily be used as a transient intervention to bridge a patient to a more definitive intracranial pressure therapy because it can induce cerebral ischemia.
- The glymphatic system consists of perivascular spaces through which CSF flows into the brain, driven by the pulsations of the arterial wall and facilitated by aquaporin-4 channels on astrocyte end feet.
- CSF influx along perivascular spaces may provide the source of early cerebral edema after acute ischemic stroke.

ARTICLE 2: SUBARACHNOID HEMORRHAGE

Sherry Hsiang-Yi Chou, MD, MSc, FNCS, FCCM. Continuum (Minneap Minn). October 2021; 27 (5 Neurocritical Care):1201–1245.

ABSTRACT

PURPOSE OF REVIEW:

Subarachnoid hemorrhage (SAH) remains an important cause of mortality and long-term morbidity. This article uses a case-based approach to guide readers through the fundamental epidemiology and pathogenesis of SAH, the approach to diagnosis and management, the results of clinical trials and evidence to date, prognostic considerations, controversies, recent developments, and future directions in SAH.

RECENT FINDINGS:

Historically, management of SAH focused on prevention and treatment of subsequent cerebral vasospasm, which was thought to be the primary cause of delayed cerebral ischemia. Clinical and translational studies over the past decade, including several therapeutic phase 3 randomized clinical trials, suggest that the pathophysiology of SAH-associated brain injury is multiphasic and multifactorial beyond large vessel cerebral vasospasm. The quest to reduce

SAH-associated brain injury and improve outcomes is shifting away from large vessel cerebral vasospasm to a new paradigm targeting multiple brain injury mechanisms, including early brain injury, delayed cerebral ischemia, microcirculatory dysfunction, spreading cortical depolarization, inflammation, and the brain-body interaction in vascular brain injury with critical illness.

Despite multiple negative randomized clinical trials in search of potential therapeutic agents ameliorating the downstream effects after SAH, the overall outcome of SAH has improved over recent decades, likely related to improvements in interventional options for ruptured cerebral aneurysms and in critical care management. Emerging clinical evidence also suggests potential harmful impact of historic empiric treatments for SAH-associated vasospasm, such as prophylactic induction of hypertension, hypervolemia, and hemodilution (triple H therapy).

With decreasing mortality, long-term SAH survivorship and efforts to reduce chronic morbidity and to improve quality of life and patient-centered outcome are growing areas of unmet need. Despite existing guidelines, significant variabilities in local and regional practices and in scientific terminologies have historically limited advancement in SAH care and therapeutic development. Large global collaborative efforts developed harmonized SAH common data elements in 2019, and studies are under way to examine how existing variabilities in SAH care impact long-term SAH outcomes.

SUMMARY:

Although the overall incidence and mortality of SAH is decreasing with advances in preventive and acute care, SAH remains a major cause of long-term morbidity in survivors. Significant variabilities in care settings and empiric treatment protocols and inconsistent scientific terminologies have limited advancement in patient care and therapeutic clinical studies. Large consensus efforts are under way to introduce clinical guidelines and common data elements to advance therapeutic approaches and improve patient outcome.

KEY POINTS

- Subarachnoid hemorrhage (SAH) is the least common type of stroke syndrome (1% to 6% of all strokes) but leads to significant morbidity and disproportionately high societal health care costs and economic impact.
- The incidence of SAH increases with age and peaks in the fifth and sixth decades; is higher in females; and is more common in African American, Hispanic, Japanese, and Finnish populations.
- Although familial clustering is seen in SAH, most cases of SAH are sporadic. People with two or more first-degree relatives with cerebral aneurysm or SAH are at increased risk for aneurysmal SAH. The American Heart Association/American Stroke Association guidelines recommend screening in those with two or more first-degree relatives with aneurysm or SAH.
- The classic SAH presentation is characterized by the sudden development of a severe headache, often referred to as the worst headache of life, which can be associated with nausea, vomiting, meningismus, altered mental status, loss of consciousness, seizure or seizurelike events, and acute focal strokelike deficits.
- SAH is a neurologic emergency that requires immediate diagnosis and rapid transfer to a high-volume center. Delayed or missed diagnosis of SAH is common and often associated with severe consequences, including death and severe morbidity. The most common diagnostic error leading to missed or delayed diagnosis of SAH is the failure to obtain a head CT scan.
- Diagnostic head CT is most sensitive for SAH in the first 6 to 12 hours following aneurysm rupture. For subacute or chronic phases of SAH, MRI with gradient recalled echo, susceptibility-weighted imaging, or fluid-attenuated inversion recovery sequences has superior sensitivity compared to noncontrast head CT.
- In cases of negative or equivocal imaging and high clinical suspicion for SAH, lumbar puncture to evaluate for CSF xanthochromia is recommended.

- After initial resuscitation and stabilization of a patient with SAH, a key next step is to rapidly identify and secure the bleeding source to minimize the risk for aneurysm rerupture. Cerebral CT angiography is often the first-line imaging modality, with 90% to 97% sensitivity in detecting an intracranial aneurysm. Digital subtraction angiography with three-dimensional reconstructions remains the gold standard diagnostic modality for cerebral aneurysms.
- The most common cause of spontaneous SAH is a ruptured cerebral aneurysm (85%). Approximately 10% to 15% of patients with SAH do not have an identifiable bleeding source; of these, approximately 38% have nonaneurysmal perimesencephalic SAH, which is a benign variant of SAH with generally excellent prognosis.
- Hyperacute life-threatening complications that can occur shortly after initial aneurysm bleeding include acute cardiopulmonary failure, acute hydrocephalus, diffuse cerebral edema, and aneurysm rebleeding.
- Acute symptomatic hydrocephalus can develop within minutes to days of aneurysm rupture and occurs in 20% of patients with SAH. Timely insertion of an external ventricular catheter for acute symptomatic hydrocephalus is lifesaving.
- Acute cardiopulmonary dysfunction is common in SAH and often requires critical care resuscitation and support. In severe cases, SAH may present with cardiac arrest. It is important to recognize aneurysmal SAH as a potential etiology in patients presenting with cardiac arrest, as delayed diagnosis is associated with high mortality.
- Neurogenic myocardial stunning with acute left ventricular dysfunction occurs in up to 30% of patients with SAH and can lead to reduced cardiac output and cardiogenic shock. A classic appearance of neurogenic stunned myocardium is left ventricle apical akinesis leading to ballooning of the apex during systole, often referred to as *takotsubo cardiomyopathy*. Timely appropriate critical care support is important to maintain adequate perfusion to the brain and body in patients with SAH with neurogenic stunned myocardium.
- Acute pulmonary dysfunction and hypoxic respiratory insufficiency are common after SAH and have multiple etiologies. Timely diagnosis and treatment of acute respiratory insufficiency in SAH is important to minimize further brain injury due to hypoxia.
- Aneurysm rerupture in SAH leads to high mortality and morbidity. Timely obliteration of a bleeding aneurysm by endovascular or microsurgical techniques very effectively reduces the risk of rerupture. Endovascular treatment of bleeding aneurysms is associated with higher survival and better outcomes and, when possible, is the preferred treatment modality. However, some aneurysms may not be amenable to endovascular approaches and may require microsurgical clipping.
- A prominent clinical feature of SAH is that a subset of patients will develop progressive neurologic deterioration and additional brain injury despite the successful obliteration of the bleeding cerebral aneurysm and critical care support. Brain injury following SAH is multiphasic and caused by multiple pathophysiologic processes, including ischemia from vasospasm.
- Early brain injury following SAH begins at the time of acute cerebral aneurysm rupture when sudden intracranial pressure elevation causes transient global cerebral ischemia and brain tissue damage by intracranial hematoma.
- Delayed cerebral ischemia is an SAH-associated brain injury process that typically develops 3 to 21 days following aneurysm rupture and remains the strongest predictor of poor outcome. The term *ischemia* is misleading, as many different pathophysiologic mechanisms contribute to this phase of brain injury.
- Multiple overlapping terminologies used to describe secondary neurologic deterioration and brain injury lead to confusion over clinical entities and monitoring approaches. Consensus common data elements and definitions for clinical deterioration due to delayed cerebral ischemia, cerebral infarction due to delayed cerebral ischemia, angiographic cerebral vasospasm, and symptomatic cerebral vasospasm are available and should be used to minimize confusion.
- Up to 70% of all patients with aneurysmal SAH may subsequently develop visible cerebral vasoconstriction on digital subtraction angiography between 3 and 21 days following initial aneurysm rupture, but only 30% will develop clinical symptoms attributable to ischemia from vasospasm. Symptomatic vasospasm is associated with delayed cerebral ischemia and unfavorable SAH outcome, whereas angiographic vasospasm is not.

- Transcranial Doppler (TCD) ultrasound is a common modality used to monitor for the development of vasospasm. TCD has adequate sensitivity to detect vasospasm in the circle of Willis vessels but is less reliable for distal vessel segments and posterior circulation vessels. The sensitivity and specificity of TCD are operator and laboratory dependent. TCD results must be interpreted with clinical correlation. Negative TCD studies do not rule out the presence of clinically significant vasospasm.
- In patients with acute neurologic deterioration attributable to ischemia from vasospasm, accepted empiric treatments include hemodynamic augmentation to increase blood pressure and endovascular rescue therapy such as intraarterial vasodilator infusion and cerebral angioplasty. Prophylactic use of these interventions is associated with increased complications and morbidity and is not recommended.
- To date, the only therapeutic agent with Class I evidence for decreasing the risk of poor outcome in SAH is nimodipine started within 96 hours of the initial hemorrhage and continued for 21 consecutive days.
- A common misconception is that nimodipine exerts therapeutic benefit through reducing cerebral vasospasm. In a randomized clinical trial, nimodipine use reduced delayed cerebral ischemia but had no impact on the rate of radiographic vasospasm.
- No high-quality data support the use of fasudil, cilostazol, intrathecal fibrinolytics, and intrathecal vasodilators for delayed cerebral ischemia treatment or prevention in SAH.
- The use of hypervolemic, hypertensive, and hemodilutional (Triple H) therapy is associated with increased cardiopulmonary complications and is not recommended in modern neurocritical care for SAH.
- Intravascular hypovolemia is associated with delayed cerebral ischemia and unfavorable SAH outcomes and should be avoided. Guidelines recommend maintenance of normal intravascular volume in critical care support during the high-risk period for delayed cerebral ischemia.
- Up to 26% of patients with SAH may present with seizurelike symptoms at onset. Nonconvulsive seizures and nonconvulsive status epilepticus are seen in up to 18% of patients with SAH who are comatose, and they are associated with unfavorable outcome. Continuous EEG studies are recommended in patients with high clinical suspicion for seizures. Prolonged empiric anticonvulsant use, particularly phenytoin, is associated with less favorable outcome and neurocognitive dysfunction.
- Fever is common following SAH and is associated with higher SAH clinical severity and unfavorable outcome. Current guidelines recommend fever control in patients at higher risk of delayed cerebral ischemia.
- Hyponatremia is common following SAH and is most commonly caused by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or cerebral salt wasting syndrome. The correct diagnosis of SIADH versus cerebral salt wasting is very important as treatment approaches are divergent.
- Without timely diagnosis and treatment, cerebral salt wasting syndrome can rapidly lead to hypovolemia, worsen brain ischemia, and cause symptomatic delayed cerebral ischemia. Treatment of cerebral salt wasting should focus on restoring and maintaining intravascular euvolemia with fluid resuscitation.
- Although SIADH is typically treated with fluid restriction, this may not be an option in patients with SAH at high risk for delayed cerebral ischemia. Use of hypertonic fluid with high sodium content is a reasonable approach to correct moderate to severe hyponatremia while maintaining a euvolemic state in SAH patients with SIADH.
- A large number of patients with SAH develop progressive anemia. Whether transfusion is beneficial in SAH and the optimal hemoglobin target are currently unknown. A large multicenter randomized control trial comparing a liberal versus a restrictive red blood cell transfusion strategy in SAH is ongoing.

ARTICLE 3: INTRACEREBRAL HEMORRHAGE

Christa O'Hana S. Nobleza, MD, MSCI. Continuum (Minneap Minn). October 2021; 27 (5 Neurocritical Care):1246–1277.

ABSTRACT

PURPOSE OF REVIEW:

Nontraumatic intracerebral hemorrhage (ICH) is the second most common type of stroke. This article summarizes the basic pathophysiology, classification, and management of ICH and discusses the available evidence on therapy for hematoma, hematoma expansion, and perihematomal edema.

RECENT FINDINGS:

Current available data on potential therapeutic options for ICH are promising, although none of the trials have shown improvement in mortality rate. The literature available on reversal of anticoagulation and antiplatelet agents after an ICH and resumption of these medications is also increasing.

SUMMARY:

ICH continues to have high morbidity and mortality. Advances in therapeutic options to target secondary brain injury from the hematoma, hematoma expansion, and perihematomal edema are increasing. Data on reversal therapy for anticoagulant-associated or antiplatelet-associated ICH and resumption of these medications are evolving.

KEY POINTS

- The American Heart Association's 2020 stroke statistics show that a persistent racial disparity of intracerebral hemorrhage (ICH) exists, with higher age-adjusted incidence of first-ever ICH in Blacks than in Whites. In women, late menopause, gestational hypertension, pregnancy-associated hypertensive disorders, preterm delivery, and stillbirth increase risk for ICH.
- Classification schemes for ICH may have implications for both clinical management and patient outcomes; however, this has not been well established, and their application should still be individualized.
- Hypertension can be present in patients with either lobar or nonlobar ICH, although it is more prominent in those with nonlobar ICH.
- Hypertension as the etiology, elevated systolic blood pressure on admission, and lower calcium levels all are associated with worse outcome in ICH.
- Important aspects in history taking for patients on anticoagulant or antiplatelet medications include the dose, administration, and last time the medication was taken.
- Differentiation of cerebral amyloid angiopathy from hypertensive ICH has clinical implications that may affect future antiplatelet and anticoagulant medication risk assessments for these patients who are also at high risk for cardiovascular disease, since cerebral amyloid angiopathy carries a higher ICH recurrence risk.
- Prior or known cerebral microbleeds are not established to be a contraindication to the use of IV recombinant tissue plasminogen activator for acute ischemic stroke, and MRI before thrombolysis administration is not recommended.
- The most common clinical presentation of arteriovenous malformation is ICH followed by seizures.
- Approximately 30% of patients with moyamoya disease can present with an ICH because of friable collateral vessels that may have formed micro and/or false aneurysms. Herpes simplex virus, varicella-zoster virus,

syphilis, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections have been implicated as causes of ICH, with the primary pathology of vasculitic infiltration of the blood vessels.

- Solid or hematologic malignancy can cause ICH because of vasculature involvement, primary brain tumor, or metastatic disease.
- The insult from the intracerebral hematoma after the onset of ICH may result in secondary brain injury from the mass effect of the hematoma, hematoma expansion, or the inflammatory cascade that ensues as reflected by perihematomal edema and perihematomal expansion rate. An inflammatory reaction after ICH has implicated release of inflammatory cytokines and chemokines after the focal brain injury in ICH.
- Patients with acute neurologic change should be called into the emergency systems as stroke alerts.
- A nationwide US sample showed mortality was higher in patients with ICH with coagulopathy, liver disease, acquired immunodeficiency syndrome, and congestive heart failure and, paradoxically, significantly lower in those with hypertension, obesity, and hypothyroidism.
- Immediate diagnosis of ICH is important to be able to institute measures to stabilize the patient and, it is hoped, prevent hematoma expansion.
- The initial diagnostic modality of choice for ICH is a noncontrast head CT.
- The presence of herniation is an important radiologic feature that should be recognized and correlated with the clinical examination of the patient.
- Noncontrast head CT indicators of herniation include midline shift, hydrocephalus, or new areas of infarction adjacent to displaced structures.
- Blood pressure control is recommended upon confirmation of the diagnosis of ICH, although the timing and target blood pressure remain controversial.
- Increased blood pressure variability, defined as the mean of the absolute differences between two consecutive blood pressure variations, variation of blood pressure during a period of time, or coefficient of variation, in patients with ICH has been found to be associated with worsening neurologic status and poor outcome.
- Prophylactic hyperosmolar therapy is not recommended in patients with ICH as it does not improve outcomes.
- American Heart Association/American Stroke Association guidelines do not recommend seizure prophylaxis in ICH.
- The target temperature for patients with ICH in consensus guidelines is 36.5 °C to 37.5 °C (97.7 °F to 99.5 °F).
- Neurosurgical management of ICH may include external ventricular drain placement for CSF diversion, intracranial pressure monitoring, and hematoma evacuation.
- In patients with cerebellar ICH, low Glasgow Coma Scale score (<8), obstructed quadrigeminal cistern, and hydrocephalus were independent predictors of in-patient mortality and poor functional outcome at discharge.
- Recommendations for restarting anticoagulation after ICH involve meticulous analysis of the benefits of anticoagulation and the risk of ICH recurrence.
- Prognostic scoring systems for ICH should only be used to provide guidance in evaluating the risk of ICH intervention and in research but not to precisely predict outcome. It is recommended to delay any change in goals of care for patients with ICH who did not have treatment-limiting orders on admission, because early treatment limitations in ICH are associated with increased mortality in some patients who could have survived with good functional outcome.

ARTICLE 4: MODERATE AND SEVERE TRAUMATIC BRAIN INJURY

Christopher P. Robinson, DO, MS. Continuum (Minneap Minn). October 2021; 27 (5 Neurocritical Care):1278–1300.

ABSTRACT

PURPOSE OF REVIEW:

Traumatic brain injury (TBI) encompasses a group of heterogeneous manifestations of a disease process with high neurologic morbidity and, for severe TBI, high probability of mortality and poor neurologic outcomes. This article reviews TBI in neurocritical care, hence focusing on moderate and severe TBI, and includes an up-to-date review of the many variables to be considered in clinical care.

RECENT FINDINGS:

With advances in medicine and biotechnology, understanding of the impact of TBI has substantially elucidated the distinction between primary and secondary brain injury. Consequently, care of TBI is evolving, with intervention-based modalities targeting multiple physiologic variables. Multimodality monitoring to assess intracranial pressure, cerebral oxygenation, cerebral metabolism, cerebral blood flow, and autoregulation is at the forefront of such advances.

SUMMARY:

Understanding the anatomic and physiologic principles of acute brain injury is necessary in managing moderate to severe TBI. Management is based on the prevention of secondary brain injury from resultant trauma. Care of patients with TBI should occur in a dedicated critical care unit with subspecialty expertise. With the advent of multimodality monitoring and targeted biomarkers in TBI, patient outcomes have a higher probability of improving in the future.

KEY POINTS

- Traumatic brain injury (TBI) is a leading cause of death and disability worldwide.
- The leading cause of TBI in low- to middle-income countries is vehicular trauma, whereas the leading cause of TBI in high-income countries is falls.
- TBI is a heterogeneous group of diseases with multiple chemical and biomechanical pathologies.
- Acute classifications for moderate and severe TBI exist within the clinical, radiographic, and mechanistic domains.
- Clinical classification of TBI describes mild, moderate, and severe levels of injury based on presentation Glasgow Coma Scale score.
- Mechanistic classification of TBI includes closed head, penetrating head, crash, and blast injuries.
- Primary injury in TBI is defined as the initial traumatic insult resulting in hemorrhage, edema, and axonal injury.
- Secondary injury in TBI is defined as injury related to cellular and biochemical activation, including inflammation, calcium overload, free radical formation, and blood-brain barrier breakdown.
- A severe TBI with Glasgow Coma Scale score of 8 or less with an abnormal CT scan is an acute indication for intracranial pressure monitoring.
- Neurocritical care for acute TBI follows a tiered approach based on consensus guidelines.
- Physiologic targets in the management of TBI include intracranial pressure, cerebral perfusion pressure, brain tissue oxygen tension, and cerebral blood flow.
- Acute coagulopathy in TBI is a powerful predictor of outcome and prognosis.

- Treatments for refractory intracranial pressure include hyperosmolar fluids, sedation, neuromuscular paralysis, and surgical decompression.
- Early recognition and management of paroxysmal sympathetic hyperactivity following TBI can result in decreased length of stay and decreased iatrogenic complications.
- Management of neurobehavioral syndromes following TBI is a key component in improving long-term outcomes.
- Determination of prognosis of TBI is difficult because of the heterogeneity of the disease and dynamic evolution of pathologic processes.
- The management of refractory intracranial pressure in pediatric patients with TBI follows a tiered approach similar to that suggested for adult TBI, with guidelines focused on specific physiologic targets.

ARTICLE 5: POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME AND REVERSIBLE CEREBRAL VASOCONSTRICTION SYNDROME AS SYNDROMES OF CEREBROVASCULAR DYSREGULATION

Aneesh B. Singhal, MD, FAAN, FANA, FAHA. Continuum (Minneap Minn). October 2021; 27 (5 Neurocritical Care):1301–1320.

ABSTRACT

PURPOSE OF REVIEW:

This article describes the causes, clinical and imaging features, management, and prognosis of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS), in which the underlying pathophysiology is related to reversible dysregulation of the cerebral vasculature.

RECENT FINDINGS:

PRES and RCVS are descriptive terms, each bringing together conditions with similar clinical-imaging manifestations. Headache, visual symptoms, seizures, and confusion occur in both syndromes. RCVS is usually heralded by recurrent thunderclap headaches, whereas encephalopathy and seizures are typical in PRES. In PRES, brain imaging shows reversible vasogenic edema that is typically symmetric and located in subcortical regions (mostly posterior predominant). In RCVS, brain imaging is often normal; cerebral angiography shows segmental vasoconstriction-vasodilatation affecting the circle of Willis arteries and their branches. Aside from shared clinical features, significant imaging overlap exists. Both PRES and RCVS can be complicated by ischemic and hemorrhagic brain lesions; angiographic abnormalities frequently occur in PRES and vasogenic edematous lesions in RCVS. Common triggers (eg, eclampsia, vasoconstrictive and chemotherapeutic agents) have been identified. Abnormal cerebrovascular tone and endothelial dysfunction may explain both syndromes. Management of these syndromes includes the removal of identified triggers, symptomatic treatment of headache or seizures, and moderate blood pressure control. Both syndromes are self-limited, with clinical recovery occurring within days to weeks. Long-term deficits and mortality are uncommon.

SUMMARY:

PRES and RCVS have been well characterized and acknowledged to have significant overlap. Advances in our understanding of pathophysiology and risk factors for poor outcome are expected to optimize the management of these not uncommon syndromes.

KEY POINTS

- Reversible cerebral vasoconstriction syndrome (RCVS) predominantly affects women, even after accounting for postpartum cases.
- Brain imaging to investigate for posterior reversible encephalopathy syndrome (PRES) is warranted in patients with altered mental status in high-risk clinical settings.
- Cortical visual symptoms are common in both PRES and RCVS.
- Although a single thunderclap headache carries a broad differential diagnosis, recurrent thunderclap headaches occurring over a span of a few days are diagnostic for RCVS.
- The word *reversible* in the term reversible cerebral vasoconstriction syndrome refers to the spontaneous reversibility of cerebral angiographic abnormalities, observed in 97% to 100% of cases. Patients who develop stroke as a complication can have permanent clinical deficits.
- Vasogenic edema indicates disruption of the blood-brain barrier, which is central to the pathophysiology of PRES.
- In RCVS, despite widespread and often severe intracranial artery narrowing, brain parenchymal imaging typically remains normal at onset.
- RCVS can be easily and accurately diagnosed based on clinical-imaging features alone, for example by using the $RCVS_2$ score. Biomarkers and advanced imaging techniques such as high-resolution vessel wall MRI and invasive cerebral angiography have limited diagnostic utility.
- Thunderclap headache is a neurologic emergency.
- Angiographic progression in RCVS is often associated with iatrogenic factors such as glucocorticoid therapy, exposure to vasoconstrictive agents, or changing levels of female reproductive hormones as in the postpartum state.
- Accurate diagnosis of PRES and RCVS rests on thorough evaluation of the clinical setting, presenting symptoms, and neuroimaging features.
- In RCVS, headaches are of extreme severity, often warranting opioid administration.
- Intraarterial vasodilator therapy carries risks and should not be routinely used for the diagnosis of RCVS.
- The time course of resolution of the clinical and imaging abnormalities may be dissociated in PRES and RCVS.

ARTICLE 6: SEIZURES, STATUS EPILEPTICUS, AND CONTINUOUS EEG IN THE INTENSIVE CARE UNIT

Eric S. Rosenthal, MD. Continuum (Minneap Minn). October 2021;
27 (5 Neurocritical Care):1321–1343.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses the evolving definitions of seizures and status epilepticus in the critical care environment and the role of critical care EEG in both diagnosing seizure activity and serving as a predictive biomarker of clinical trajectory.

RECENT FINDINGS:

Initial screening EEG has been validated as a tool to predict which patients are at risk of future seizures. However, accepted definitions of seizures and nonconvulsive status epilepticus encourage a treatment trial when the diagnosis on EEG is indeterminate because of periodic or rhythmic patterns or uncertain clinical correlation. Similarly, recent data have demonstrated the diagnostic utility of intracranial EEG in increasing the yield of seizure detection. EEG has additionally been validated as a diagnostic biomarker of covert consciousness, a predictive biomarker of cerebral ischemia and impending neurologic deterioration, and a prognostic biomarker of coma recovery and status epilepticus resolution. A recent randomized trial concluded that patients allocated to continuous EEG had no difference in mortality than those undergoing intermittent EEG but could not demonstrate whether this lack of difference was because of studying heterogeneous conditions, examining a monitoring tool rather than a therapeutic approach, or examining an outcome measure (mortality) perhaps more strongly associated with early withdrawal of life-sustaining therapy than to a sustained response to pharmacotherapy.

SUMMARY:

Seizures and status epilepticus are events of synchronous hypermetabolic activity that are either discrete and intermittent or, alternatively, continuous. Seizures and status epilepticus represent the far end of a continuum of ictal-interictal patterns that include lateralized rhythmic delta activity and periodic discharges, which not only predict future seizures but may be further classified as status epilepticus on the basis of intracranial EEG monitoring or a diagnostic trial of antiseizure medication therapy. In particularly challenging cases, neuroimaging or multimodality neuromonitoring may be a useful adjunct documenting metabolic crisis. Specialized uses of EEG as a prognostic biomarker have emerged in traumatic brain injury for predicting language function and covert consciousness, cardiac arrest for predicting coma recovery, and subarachnoid hemorrhage for predicting neurologic deterioration due to delayed cerebral ischemia.

KEY POINTS

- Electrographic seizures and status epilepticus can be diagnosed by an electroclinical response to antiseizure medication.
- Although most seizures are detected in the first 48 hours of monitoring, shorter-duration monitoring may be sufficient in patients without any epileptiform abnormalities and longer-duration monitoring may be required in patients with subarachnoid hemorrhage.
- Seizure detection is significantly augmented by the implantation of a single intraparenchymal or subdural strip electrode.
- Because of changes in protein binding, large-magnitude errors are common when estimating free phenytoin applying standard phenytoin correction equations to patients who are critically ill; correction equations adjusting for age, renal function, hepatic function, and critical illness are necessary to avoid significant errors if free phenytoin levels are unavailable.
- High-frequency periodic discharges may be transient when weaning patients from anesthetic coma following status epilepticus; pausing and observing the patient and EEG, evaluating background activity, and examining for frank seizures may avoid delaying anesthetic liberation.
- The quantified initial or peak burden of ictal-interictal continuum activity and electrographic seizures are independently associated with outcome.
- Even generalized periodic discharges with a triphasic morphology, historically associated with metabolic disturbances, may commonly have an electroclinical response to escalation of antiseizure medication.
- Electrometabolic status epilepticus is increasingly appreciated as ictal-interictal continuum activity of high frequency in association with exhaustive metabolic crisis measured by cerebral hyperglycolysis during

positron emission tomography, increasing lactate to pyruvate ratio evident from cerebral microdialysis sampling, or brain tissue hypoxia identified during brain tissue oxygenation monitoring.

- Seizure activity is increasingly appreciated as associated with an inflammatory complex of biomarkers in blood and CSF.
- A battery of continuous EEG findings, including decrease in alpha to delta ratio of frequency-band power, one-grade decrease in relative alpha variability, and new or worsening epileptiform activity, have been prospectively validated as a method of predicting subsequent ischemia in patients with subarachnoid hemorrhage.
- Cortical spreading depolarizations are increasingly being monitored in clinical practice as brain activity associated with unexplained coma and poor neurologic outcome.
- Covert consciousness is frequently seen in patients who are critically ill with acute brain injury; wider availability of stimulus-based EEG monitoring (in addition to functional MRI) may not only improve the accuracy of diagnosing patients with disorders of consciousness but also improve the information available to surrogate decision makers.
- Assessment of the EEG background rhythm, including sleep features and continuity, provides prognostic information in addition to the presence of activity on the ictal-interictal continuum.
- Although one randomized study concluded that continuous EEG showed no benefit compared to intermittent EEG, a definitive study would require examining a specific population expected to have a homogeneous pathophysiology, defining a treatment protocol that makes use of neuromonitoring findings, and controlling for changes in life-sustaining treatment resulting from differences in available prognostic information.

ARTICLE 7: NEUROMUSCULAR DISORDERS IN THE INTENSIVE CARE UNIT

Torrey Boland Birch, MD. Continuum (Minneap Minn). October 2021;
27 (5 Neurocritical Care):1344–1364.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses the pathophysiology, presentation, diagnosis, treatment, and prognosis of common neuromuscular disorders seen in the intensive care unit, including Guillain-Barré syndrome, myasthenia gravis, and intensive care unit–acquired weakness.

RECENT FINDINGS:

Guillain-Barré syndrome can have an excellent prognosis if patients are diagnosed early, appropriately treated, and monitored for complications, including respiratory failure and dysautonomia. Intensive care unit–acquired weakness increases overall mortality in patients who are critically ill, and distinguishing between critical illness myopathy and critical illness polyneuropathy may have important prognostic implications.

SUMMARY:

Neuromuscular disorders are not rare in the intensive care unit setting, and precise identification and treatment of these conditions can greatly impact long-term outcomes.

KEY POINTS

- Guillain-Barré syndrome (GBS) has three phenotypical variants: purely demyelinating (acute inflammatory demyelinating polyradiculoneuropathy), purely axonal (acute motor axonal neuropathy), and demyelinating with an axonal component.

- The primary targets in the acute motor axonal neuropathy phenotype of GBS are the neuronal membrane gangliosides, including GM1, GD1a, and GQ1b.
- GBS begins with ascending weakness, typically initially involving the proximal leg muscles, with diminished or absent reflexes.
- Symptoms in GBS typically reach maximal severity within 2 weeks, and progression beyond 4 weeks should raise concern for an alternative diagnosis.
- Autonomic dysfunction occurs in more than one-third of patients with GBS and is related to demyelination of sympathetic nerves and disruption of the baroceptor reflexes.
- The Miller Fisher variant of GBS presents with cranial nerve dysfunction, ocular motor weakness, and bulbar symptoms. It is associated with antibodies against GQ1b and is less likely to progress to respiratory failure than more classic forms of GBS.
- The diagnosis of GBS is clinical, with progressive weakness and decreased reflexes as key features. Supportive features include albuminocytologic dissociation in the CSF and electrophysiologic testing consistent with either demyelination or axonal injury.
- Plasma exchange and IV immunoglobulin are equally effective in the treatment of GBS. No evidence suggests that the combination of the two treatments is more effective than monotherapy. Steroids are not recommended.
- The 20/30/40 rule guides intubation in GBS; forced vital capacity less than 20 mL/kg, maximal inspiratory pressure less than 30 cm H_2O, or maximal expiratory pressure less than 40 cm H_2O suggests the need for mechanical ventilation.
- Patients with GBS have preserved consciousness and should be assessed and treated for pain, anxiety, and depression.
- Most survivors of GBS will regain the ability to walk, although recovery can take more than a year.
- Myasthenia gravis is an autoimmune disorder with antibodies targeting the postsynaptic membrane of the neuromuscular junction, including the acetylcholine receptor, muscle-specific tyrosine kinase, and lipoprotein receptor-related protein 4.
- Twenty percent of patients present in myasthenic crisis as the first manifestation of their disease.
- Myasthenic crisis can be triggered by infection; medications such aminoglycosides, fluoroquinolones, and beta-blockers; and surgery.
- Immune checkpoint inhibitors may induce an immune-related myasthenia gravis in patients without a history of myasthenia gravis.
- Fluctuations in the degree of weakness in myasthenia gravis make respiratory monitoring less helpful in predicting intubation.
- Noninvasive ventilation may be helpful in preventing intubation in patients with respiratory failure and preserved cough and bulbar strength.
- Corticosteroids should be administered either with or shortly after plasma exchange or IV immunoglobulin to prevent worsening of muscle weakness in myasthenic crisis.
- Intensive care unit–acquired weakness includes the diagnoses of critical illness myopathy, critical illness polyneuropathy, and critical illness neuromyopathy.
- Critical illness polyneuropathy typically spares the cranial nerves, and although critical illness myopathy may involve facial muscles, extraocular muscles are spared. Involvement of the cranial nerves should prompt assessment for an alternative cause of weakness.
- Primary treatment strategies for intensive care unit–acquired weakness focus on prevention, with minimization of sedation, avoidance of hyperglycemia, and use of early mobilization strategies.
- Critical illness myopathy carries a significantly better prognosis than critical illness polyneuropathy, with most patients with critical illness myopathy seeing a complete recovery.

ARTICLE 8: ACUTE NEUROLOGIC MANIFESTATIONS OF RESPIRATORY VIRUSES

Michael A. Pizzi, DO, PhD. Continuum (Minneap Minn). October 2021;
27 (5 Neurocritical Care):1365–1381.

ABSTRACT

PURPOSE OF REVIEW:

Understanding the pathophysiology of COVID-19 and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus that causes the disease has demonstrated the complexity of acute respiratory viruses that can cause neurologic manifestations. This article describes the most common respiratory viruses that have neurologic manifestations, with a focus on SARS-CoV-2 and COVID-19.

RECENT FINDINGS:

In vitro and in vivo studies have better elucidated the neurotropism of various respiratory viruses. Understanding host cell receptors that mediate viral binding and entry not only demonstrates how viruses enter host cells but also provides possible mechanisms for therapeutic interventions. Elucidation of SARS-CoV-2 binding and fusion with host cells expressing the angiotensin-converting enzyme 2 (ACE2) receptor may also provide greater insights into its systemic and neurologic sequelae. Respiratory virus neurotropism and collateral injury due to concurrent inflammatory cascades result in various neurologic pathologies, including Guillain-Barré syndrome, encephalopathy, encephalitis, ischemic stroke, intracerebral hemorrhage, and seizures.

SUMMARY:

Numerous respiratory viruses can infect the cells of the peripheral and central nervous systems, elicit inflammatory cascades, and directly and indirectly cause various neurologic manifestations. Patients with neurologic manifestations from respiratory viruses are often critically ill and require mechanical ventilation. Neurologists and neurointensivists should be familiar with the common neurologic manifestations of respiratory viruses and the unique and still-evolving sequelae associated with COVID-19.

KEY POINTS

- Access of virions to the central nervous system can occur by various processes: retrograde transport of viruses in peripheral neurons, anterograde transport of viruses in olfactory neurons, hematogenous spread and infection of central nervous system endothelial cells, infection of leukocytes, or macrophages subsequently undergoing transcellular or paracellular transport across the intact or permeable blood-brain barrier.
- The blood-brain barrier is composed of endothelial cells joined by tight junction proteins, astrocytes, pericytes, and basement membrane.
- The most prevalent respiratory enterovirus genotypes associated with neurologic manifestations are D68 and A71.
- Early administration of IV immunoglobulin may reduce the risk of autonomic dysregulation associated with enterovirus A71 brainstem encephalitis.

- Neurologic manifestations of human respiratory syncytial virus infection occur in approximately 2% cases and include ataxia, central apnea, encephalitis, encephalopathy, and seizures/status epilepticus.
- Influenza types A, B, and C infect humans, with type A often causing more severe symptoms.
- Neurologic manifestations of influenza virus include acute necrotizing encephalitis, Guillain-Barré syndrome, mutism, postencephalitic parkinsonism, Reye syndrome, febrile seizures, and seizures.
- According to Centers for Disease Control and Prevention data from 1990 to 2009, the incidence of Guillain-Barré syndrome was 0.46 cases per million influenza vaccinations, with peak occurrence 2 weeks after vaccination.
- The typical Reye syndrome symptoms of vomiting, encephalopathy, and seizures occur 3 to 5 days after influenza infection.
- The most common neurologic manifestations of human metapneumovirus are seizures and encephalopathy.
- Neurologic manifestations of measles usually present as primary measles encephalitis, acute postinfectious measles encephalomyelitis, measles inclusion body encephalitis, or subacute sclerosing panencephalitis.
- The mechanism of coronaviruses infecting host cells involves the virion's spike protein binding to host cell surface enzymes as receptors, such as angiotensin-converting enzyme 2 in the case of SARS-CoV-2.
- One proposed mechanism underpinning the degradation and permeability of the blood-brain barrier in COVID-19 is elevated inflammatory cytokines (ie, hypercytokinemia or cytokine storm), which occurs in human coronavirus and influenza infections.
- Neurologic manifestations in patients with COVID-19 usually occur within the first 17 days of systemic or respiratory symptoms and are often in proportion to the severity of illness. Approximately 30% of patients who are hospitalized, 45% of patients with severe respiratory illness, and up to 85% of patients with acute respiratory distress syndrome have neurologic manifestations.
- In a review of patients with COVID-19 who developed Guillain-Barré syndrome, the syndrome presented with the typical symptoms of hypoesthesia, paresthesia, and progressive weakness of extremities and bulbar musculature, with an average onset of neurologic symptoms 8 days after systemic symptoms of fever and cough.
- Approximately 1% of patients hospitalized with COVID-19 had acute ischemic stroke. In a review of 46 patients with stroke with COVID-19, four (8.7%) had hemorrhagic stroke.
- Platelets express angiotensin-converting enzyme 2 and transmembrane protease, serine 2, facilitating infection by SARS-CoV-2. Infection of platelets with SARS-CoV-2 results in increased platelet aggregation, release of coagulation factors, and secretion of inflammatory cytokines IL-1β and tumor necrosis factor-α.
- In a study of patients with cerebral venous thrombosis associated with COVID-19, the most common location for cerebral venous thrombosis was the transverse sinus (75%) followed by the sigmoid sinus (50%). One-third of the patients had involvement of the deep venous system.
- Seizures have been described in association with COVID-19 occurring between 3 and 7 days from initial symptom onset.
- Systemic hypoxia can result in anoxic/hypoxic brain injury, which was described in a series of autopsies from 18 consecutive patients with COVID-19 positive for SARS-CoV-2.

ARTICLE 9: NEUROLOGIC COMPLICATIONS IN THE POSTOPERATIVE NEUROSURGERY PATIENT

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ABSTRACT

PURPOSE OF REVIEW:

This article discusses neurologic complications encountered in the postoperative care of neurosurgical patients that are common or key to recognize in the immediate postoperative period. The major neurosurgical subspecialty procedures (cerebrovascular neurosurgery, neuro-oncology, epilepsy neurosurgery, functional neurosurgery, CSF diversion, endovascular neurosurgery, and spinal surgery) are broadly included under craniotomy procedures, endovascular/vascular procedures, and spinal procedures. This article focuses on the range of complications inherent in these approaches with specific scenarios addressed as applicable.

RECENT FINDINGS:

The morbidity and mortality related to neurosurgical procedures remains high, necessitating ongoing research and quality improvement efforts in perioperative screening, intraoperative management, surgical approaches, and postoperative care of these patients. Emerging research continues to investigate safer and newer options for routine neurosurgical approaches, such as coiling over clipping for amenable aneurysms, endoscopic techniques for transsphenoidal hypophysectomy, and minimally invasive spinal procedures; postoperative monitoring and care of patients after these procedures continues to be a key component in the continuum of care for improving outcomes.

SUMMARY:

Postoperative care of patients undergoing major neurosurgical procedures is an integral part of many neurocritical care practices. Neurosurgeons often enlist help from neurologists to assist with evaluation, interpretation, and management of complications in routine inpatient settings. Awareness of the common neurologic complications of various neurosurgical procedures can help guide appropriate clinical monitoring algorithms and quality improvement processes for timely evaluation and management of these patients.

KEY POINTS

- Patients who have had emergent cranial neurosurgical procedures, high-risk elective craniotomies, or multilevel spinal surgeries, especially those involving the cervical spine, and patients with significant cardiopulmonary comorbidities are typically admitted for overnight monitoring in a step-down or neurocritical care unit for their postoperative care.
- Awareness of the expected neurologic deficits in a given neurosurgical procedure and comparison of the patient's postoperative neurologic examination to the preoperative neurologic status are important components of the postoperative evaluation of patients.
- Surgical approaches that minimize the extent of the craniotomy while ensuring appropriate access and anesthesia techniques that decrease the adverse effect of exposure on cerebral hemodynamics have reduced the incidence of cerebral edema.
- Any unexpected focal deficit or impairment of consciousness not explicable by other factors, such as late emergence, sedation, or pain medications, should be evaluated with emergent neuroimaging.
- Intraoperative or postoperative hemorrhage may be extraaxial, intraparenchymal, or subarachnoid and may occur at the surgical site or in a remote location.
- Remote site hemorrhage may occur because of sudden decompression of the intracranial compartment in patients with raised intracranial pressure and can be seen after cranial and, more often, spinal surgeries.
- Unless a high index of suspicion is maintained in surgeries involving intraoperative blood loss or proximity to major cerebral blood vessels, vasospasm of the intracranial vessels may go undetected and present with delayed ischemic neurologic deficits. Patients who are postoperative with persistent unexplained encephalopathy and EEG inconsistent with possible ictal etiology should be assessed for vasospasm.
- Certain surgical approaches may have a high risk of seizures, for example, the superior temporal gyrus approach for middle cerebral artery aneurysm clipping or subdural hematoma evacuation.

- Any encephalopathy or involuntary movement not explained by the patient's neuroimaging and expected structural deficits should be investigated with continuous EEG to assess for the possibility of nonconvulsive seizures.
- The traditional use of antiseizure medications for all craniotomies has fallen out of favor because of the adverse impact of antiseizure medications on cognitive outcomes.
- Proper dural closure is necessary to prevent CSF leaks, which seem to be more common in posterior fossa decompression than in supratentorial craniotomies. If local drainage at surgical sites goes undetected, patients may present with signs and symptoms of CSF hypotension, such as postural headaches, meningismus, and photophobia.
- Pneumocephalus, if persistent or large in volume, can cause neurologic symptoms of encephalopathy, confusion, headaches, and seizures. Tension pneumocephalus may occur because of a one-way entry of air through the craniectomy defect and can cause acute neurologic decline, with coma, seizures, and cerebral herniation.
- Postcraniotomy headaches are one of the most common neurologic complications of craniotomy, occurring in more than two-thirds of patients, and have a multifactorial etiology.
- Compressive neuropathies may develop in patients related to the specific patient positioning used to enhance anatomic access for the surgical approach.
- Patients with shunt obstruction have persistent headache, lethargy, nausea, and vomiting because of persistent hydrocephalus. Such obstruction usually requires shunt revision.
- Although postprocedural headaches are common after cerebral angiograms (occurring in more than one-third to one-half of patients), severe headaches or headaches accompanied by focal deficits are not typically seen after cerebral angiography. New-onset severe headaches after cerebral angiography should trigger investigations via neuroimaging.
- Most intraprocedural aneurysm ruptures can be managed with achieving hemostasis with further coiling or balloon-assisted embolization.
- Perianeurysmal edema occurring de novo after aneurysm coiling has been rarely described in both ruptured and unruptured aneurysms when the aneurysms are embedded in the brain parenchyma.
- Revascularization of the brain of a patient with a chronically stenosed carotid is the proposed mechanism of hyperperfusion injury after carotid endarterectomy and carotid artery stenting; hyperperfusion syndrome can be avoided by careful control of hypertension in the postoperative period for both these procedures.
- Local surgical complications unique to carotid endarterectomy include direct cranial nerve palsies, which may occur in up to 5% of patients and usually involve the hypoglossal and facial nerve.
- Prone positioning is associated with a rare incidence of postoperative visual loss that may be caused by ischemic optic neuropathy, central retinal artery occlusion, or external ocular injury.

ARTICLE 10: NEUROLOGIC OUTCOME PREDICTION IN THE INTENSIVE CARE UNIT

Carolina B. Maciel, MD, MSCR. Continuum (Minneap Minn). October 2021; 27 (5 Neurocritical Care):1405–1429.

ABSTRACT

PURPOSE OF REVIEW:

The burden of severe and disabling neurologic injury on survivors, families, and society can be profound. Neurologic outcome prediction, or neuroprognostication, is a complex undertaking with many important ramifications. It allows patients with good prognoses to be supported

aggressively, survive, and recover; conversely, it avoids inappropriate prolonged and costly care in those with devastating injuries.

RECENT FINDINGS:

Striving to maintain a high prediction performance during prognostic assessments encompasses acknowledging the shortcomings of this task and the challenges created by advances in medicine, which constantly shift the natural history of neurologic conditions. Embracing the unknowns of outcome prediction and the boundaries of knowledge surrounding neurologic recovery and plasticity is a necessary step toward refining neuroprognostication practices and improving the accuracy of prognostic impressions. The pillars of modern neuroprognostication include comprehensive characterization of neurologic injury burden (primary and secondary injuries), gauging cerebral resilience and estimated neurologic reserve, and tying it all together with individual values surrounding the acceptable extent of disability and the difficulties of an arduous convalescence journey.

SUMMARY:

Comprehensive multimodal frameworks of neuroprognostication using different prognostic tools to portray the burden of neurologic injury coupled with the characterization of individual values and the degree of cerebral reserve and resilience are the cornerstone of modern outcome prediction.

KEY POINTS

- Neurologic outcome prediction, or neuroprognostication, may directly impact outcomes, health care costs, and surrogates of patients via its mediation effect on goals-of-care decision making.
- Devastating brain injuries represent conditions that pose an immediate threat to life from a severe neurologic insult in which limitation of disease-targeted interventions is being considered in conjunction with implementation of comfort measures.
- Potentially inappropriate treatments are different from futile interventions. In the former, a reasonable chance exists of accomplishing an effect sought by the patient, but the treatment team may recognize competing ethical considerations that warrant their withholding. The latter refers to the rare event that the desired physiologic effect is not attainable with the treatment.
- It is essential to consider each context when interpreting clinical and outcome evaluations in individual patients, particularly their timing in relation to the injury, medications, and seizures and the progress or lack thereof following therapeutic and rehabilitation trials.
- Many factors modulate the clinical course of severe neurologic injuries, yielding heterogeneous longitudinal trajectories; some patients may experience worsening of functional status after discharge, some will improve, and some will remain unchanged.
- The neuroprognostication literature has been blighted by the self-fulfilling prophecy bias, which overinflates the prediction performance of neuroprognostic tools and leads to overly confident, and often inaccurate, prognostic impressions.
- Modern neuroprognostication studies must attempt to mitigate self-fulfilling prophecy bias by reporting a breakdown of deaths, blinding the treatment team to the studied tool whenever possible, and accounting for the timing of prognostication in relation to injury.
- Most helpful neuroprognostic tools yield objective information linking injury burden with outcomes with very low false-positive rates.
- Bilaterally absent corneal and pupillary light reflexes carry significant prognostic value with very low false-positive rates when predicting poor outcome but are sensitive to the effect of confounders.
- Neuroimaging is helpful in quantifying acute and chronic structural damage and assisting in the estimation of predicted deficits and recovery trajectories.

- The burden of white matter disease and encephalomalacia and degree of atrophy compound on acute structural damage, contributing substantially to a poor cerebral reserve; estimates of cerebral reserve help project individualized expectations of recovery trajectories.
- The characterization of individual values surrounding the acceptable extent of disability and of the difficulties of an arduous convalescence journey is crucial in the process of neuroprognostication.
- When communicating prognostic impressions with surrogates, clinicians should be compassionate but assertive, focus on what is known, avoid medical jargon, and give concrete examples of expected deficits and their potential impact on daily activities.

ARTICLE 11: PALLIATIVE CARE AND SHARED DECISION MAKING IN THE NEUROCRITICAL CARE UNIT

Claire J. Creutzfeldt, MD. Continuum (Minneap Minn). October 2021;
27 (5 Neurocritical Care):1430–1443.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the evidence on integrating palliative care into the care of patients with various types of serious neurologic illness, emphasizes the importance of palliative care in the neurocritical care unit, and suggests tools for clinicians to improve their communication skills and decision making.

RECENT FINDINGS:

Palliative care is a holistic approach to medical care that aims to relieve physical, psychological, social, and spiritual suffering. It is both a medical specialty as young as neurocritical care itself and an approach to patient care by all clinicians who manage patients with serious illness. Patients presenting to the neurocritical care unit and their families have unique palliative care needs that challenge communication and shared decision making.

SUMMARY:

Palliative care, effective communication, and shared decision making require a set of core skills that all neurology clinicians should master.

KEY POINTS

- Patients in the neurocritical care unit face challenging treatment decisions but are themselves typically unable to participate, leaving families and clinicians to make life-and-death decisions on their behalf.
- Palliative care is an approach to medical care that aims to relieve physical, social, psychological, and spiritual suffering and improve communication about end of life and quality of life for patients and their families.
- Most of the evidence showing benefits of palliative care intervention comes from the cancer literature, although some nurse-led support interventions in the general intensive care unit literature are promising.
- Progress in neurocritical care with reduction in morbidity and mortality has brought with it a proliferation of choices that require a compassionate effective team approach to decision making.
- Neurocritical care unit providers should engage in a shared decision-making process with grieving family members who are also surrogate decision makers and integrate medical and prognostic information with their loved one's presumed goals of care.

- Neurocritical care unit providers should master a primary palliative care skill set that includes effective and compassionate communication; elicitation of patient values (goals of care); disease-specific prognostication; assessment and management of pain and other distressing symptoms; and timely identification of social, spiritual, and emotional support needs for patients and their families.
- Prognostic uncertainty is particularly common in the neurocritical care unit. Helpful ways to communicate this uncertainty include describing a best case, worst case, and most likely case; supporting the family in hoping for the best while preparing for the worst; and a mutual agreement on time-limited trials.
- Most patients who die in the neurocritical care unit do so after the withholding or withdrawal of life-sustaining treatment. Providers should provide guidance on timing and symptoms anticipated in the last hours, days, or weeks of life.

ARTICLE 12: BRAIN DEATH/DEATH BY NEUROLOGIC CRITERIA DETERMINATION

Ariane Lewis, MD; Matthew P. Kirschen, MD, PhD. Continuum (Minneap Minn). October 2021; 27 (5 Neurocritical Care):1444–1464.

ABSTRACT

PURPOSE OF REVIEW:

This article describes the prerequisites for brain death/death by neurologic criteria (BD/DNC), clinical evaluation for BD/DNC (including apnea testing), use of ancillary testing, and challenges associated with BD/DNC determination in adult and pediatric patients.

RECENT FINDINGS:

Although death determination should be consistent among physicians and across hospitals, states, and countries to ensure that someone who is declared dead in one place would not be considered alive elsewhere, variability exists in the prerequisites, clinical evaluation, apnea testing, and use of ancillary testing to evaluate for BD/DNC. Confusion also exists about performance of an evaluation for BD/DNC in challenging clinical scenarios, such as for a patient who is on extracorporeal membrane oxygenation or a patient who was treated with therapeutic hypothermia. This prompted the creation of the World Brain Death Project, which published an international consensus statement on BD/DNC that has been endorsed by five world federations and 27 medical societies from across the globe.

SUMMARY:

The World Brain Death Project consensus statement is intended to provide guidance for professional societies and countries to revise or develop their own protocols on BD/DNC, taking into consideration local laws, culture, and resource availability; however, it does not replace local medical standards. To that end, pending publication of an updated guideline on determination of BD/DNC across the lifespan, the currently accepted medical standards for BD/DNC in the United States are the 2010 American Academy of Neurology standard for determination of BD/DNC in adults and the 2011 Society of Critical Care Medicine/American Academy of Pediatrics/Child Neurology Society standard for determination of BD/DNC in infants and children.

KEY POINTS

- The incidence of brain death/death by neurologic criteria declaration worldwide is unknown, but epidemiologic studies have found that 2% to 12% of adult deaths in the United States and Europe and 20% of pediatric deaths in the United States are declared using neurologic criteria.

- The World Brain Death Project standard is not intended to replace local medical standards; rather, it aims to provide guidance for professional societies and countries to revise or develop their own protocols on brain death/death by neurologic criteria, taking into consideration local laws, culture, and resource availability.
- Pending publication of an updated guideline on determination of brain death/death by neurologic criteria across all age groups beginning at birth, the 2010 American Academy of Neurology and 2011 Society of Critical Care Medicine/American Academy of Pediatrics/Child Neurology Society standards remain the current accepted medical standards for brain death/death by neurologic criteria in the United States.
- To prevent false-positive declarations of death, practitioners must take a conservative approach and be scrupulous and attentive to details.
- Examples of etiologies that can lead to brain death/death by neurologic criteria include hypoxic-ischemic brain injury, hemorrhagic stroke, ischemic stroke, traumatic brain injury, bacterial meningitis, viral encephalitis, hepatic encephalopathy, and obstructive hydrocephalus.
- Mimics of brain death/death by neurologic criteria include fulminant Guillain-Barré syndrome, botulism, high cervical cord injuries, snake bites, and rabies.
- Conditions that can preclude completion of the clinical evaluation for brain death/death by neurologic criteria and thus necessitate ancillary testing include, but are not limited to, severe neuromuscular disorders/sensory neuropathies, spinal cord injuries, orbital/facial trauma/swelling/chemosis, ophthalmic surgery, anophthalmia, and a ruptured tympanic membrane.
- Numerous spinally mediated reflexes have been observed in patients who meet clinical criteria for brain death/death by neurologic criteria, including myoclonus, spontaneous extensor posturing, intermittent head turning, slow flexion then extension of the toes (undulating toe), and isolated thumb extension (thumbs-up sign).
- If the complete clinical assessment is performed and found to be consistent with brain death/death by neurologic criteria, the pH and $Paco_2$ thresholds are reached during the apnea test, and the patient does not take any breaths, the patient is declared dead at the time the arterial blood gas results are reported.
- Although EEG was included in the 1968 Harvard standard and is considered an acceptable ancillary test in the 2010 AAN and 2011 SCCM/AAP/CNS standards, the World Brain Death Project standard suggests it only be used if mandated by regional policy or law or if craniovascular impedance is affected by an opening in the skull (such as a skull fracture or open fontanelle), leading to concerns about the accuracy of a blood flow study.
- Clearance of carbon dioxide on extracorporeal membrane oxygenation is influenced by the rate of sweep gas flow through the oxygenator, so the sweep gas flow rate is reduced to 0.5 L/min to 1 L/min during apnea testing to facilitate accumulation of carbon dioxide in the arterial blood.
- When a patient is on venoarterial extracorporeal membrane oxygenation, arterial blood should be sampled simultaneously from both the patient's arterial catheter and the extracorporeal membrane oxygenation circuit postoxygenator to ensure the pH and carbon dioxide in the cerebral circulation exceed the brain death/death by neurologic criteria thresholds.
- Hypothermia can lead to reversible brainstem areflexia and coma, particularly when it is used in conjunction with drugs or medications that depress the central nervous system.
- Practitioners should be empathetic, patient, and culturally sensitive during discussions about brain death/death by neurologic criteria and recognize that public understanding of brain death/death by neurologic criteria is poor because of misinformation promulgated by the media, television, and movies.
- Although practitioners should make reasonable efforts to inform a patient's surrogate/health care proxy about the intent to perform an evaluation for brain death/death by neurologic criteria, the World Brain Death Project standard and guidance published by the American Academy of Neurology in 2019 note that consent is not required to complete a brain death/death by neurologic criteria evaluation, including apnea testing or ancillary testing.

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NEUROINFECTIOUS DISEASES

ARTICLE 1: APPROACH TO NEUROLOGIC INFECTIONS

Aaron L. Berkowitz, MD, PhD. Continuum (Minneap Minn). August 2021; 27 (4 Neuroinfectious Disease):818–835.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of the clinical approach to the diagnosis of neurologic infections, focusing on the symptoms, signs, imaging features, and laboratory findings of the major categories of neuroinfectious diseases.

RECENT FINDINGS:

The increased use of immunosuppressive and immunomodulatory therapy to treat autoimmune diseases has led to an increase in opportunistic neurologic infections. The description of numerous causes of autoimmune antibody–mediated encephalitis over the past decade has expanded the differential diagnosis of encephalitis beyond infection. The emergence of metagenomic next-generation sequencing has led to diagnoses of rare or unexpected causes of neurologic infections and has the potential to enhance diagnostic precision in neuroinfectious diseases.

SUMMARY:

Infections of the nervous system can affect any level of the neuraxis and present over any time course. Neurologic infections may present atypically with respect to clinical, radiologic, and CSF analysis features in immunocompromised patients or older adults. A thorough evaluation including systemic features, past medical history, travel, exposures, detailed examination, neuroimaging, and CSF analysis is often necessary to make a definitive diagnosis. It is important to be aware of the test characteristics and limitations of microbiological tests on CSF for neurologic infections to avoid being misled by false positives or false negatives.

KEY POINTS

- Neurologic infections can affect any level of the neuraxis.
- Neurologic infections can be caused by any category of microbe: viruses, bacteria, fungi, or parasites.
- Infectious agents can cause disease in the nervous system by direct invasion of neural tissue, production of neurotoxins, and/or the immune response incited by the pathogen. Certain infectious pathogens cause a specific clinical syndrome or characteristic radiologic pattern(s), but many can cause a wide variety of different clinical presentations or radiologic abnormalities.

- In general, most viral and bacterial infections of the nervous system present acutely, emerging and evolving over hours to days. In contrast, fungal, mycobacterial, spirochetal, and parasitic infections and neurosyphilis generally present subacutely or chronically. However, many exceptions to these general principles occur.
- Fever is an obvious indication of an infectious etiology of a neurologic presentation but may be absent with localized central nervous system infections (eg, brain abscess), in immunocompromised patients who cannot mount an adequate inflammatory response, and even in immunocompetent patients, particularly infants and older adults.
- Although many neurologic infections can occur in otherwise healthy individuals, a high degree of suspicion for infection must be maintained in patients who are immunocompromised due to human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), congenital immunodeficiency, hematologic malignancy, and patients taking immunosuppressive/immunomodulatory medications (eg, in the setting of autoimmune disease, bone marrow transplantation, or solid organ transplantation).
- In immunocompromised populations, infections may present atypically both clinically and radiologically because of the reduced inflammatory reaction to the infectious pathogen.
- Asking about place of residence, country of origin, and travel history is essential in the evaluation of a patient with a potential neurologic infection.
- Although infection is a primary consideration in the differential diagnosis of meningitis and encephalitis, noninfectious causes must be considered. Although infection is often not a primary consideration in the differential diagnosis of myelopathy, radiculopathy, neuropathy, neuromuscular junction disorder, and myopathy, infections can affect these levels of the neuraxis and must be considered in the differential diagnosis of these conditions.
- While the most common causes of meningitis are infectious, involvement of the meninges can also occur as a result of inflammatory disease (eg, IgG4-related disease, sarcoidosis, Behçet disease, Vogt-Koyanagi-Harada disease), neoplasia (carcinomatous meningitis/leptomeningeal metastases; chemical meningitis due to rupture of epidermoid cyst), and secondary to medications (eg, nonsteroidal anti-inflammatory drugs, IV immunoglobulin [IVIg], trimethoprim-sulfamethoxazole).
- Characteristic symptoms of acute infectious meningitis include fever, headache, neck stiffness, and altered mental status. However, these classic features cannot be relied on because they may be absent, particularly in infants, older adults, immunocompromised patients, and patients on anti-inflammatory analgesics.
- Patients with acute meningitis are often treated empirically for the most likely pathogens in a given patient while awaiting CSF diagnostics to narrow coverage to the microbe ultimately diagnosed.
- In patients with acute meningitis, IV dexamethasone should be initiated with or before starting antibiotics, as it reduces mortality in adults with *Streptococcus pneumoniae* meningitis and decreases the risk of hearing loss in children with *Haemophilus influenzae* meningitis. However, several studies have shown that steroids do not appear to be beneficial in patients with acute meningitis in low-income countries, attributed to the higher likelihood of a delayed presentation and higher burden of HIV and malnutrition.
- The primary differential diagnosis for encephalitis is between infectious and immune-mediated conditions (eg, acute disseminated encephalomyelitis and antibody-mediated autoimmune encephalitis).
- In immunocompromised patients, the differential diagnosis of encephalitis expands to include cytomegalovirus, human herpesvirus 6 (most commonly in patients who have undergone hematopoietic stem cell transplantation), Epstein-Barr virus, and adenovirus.
- The spine can be affected by infection in any of its compartments: vertebrae/discs (osteomyelitis, Pott disease), epidural/subdural spaces (abscess), or the spinal cord parenchyma (infectious myelitis).
- Acute infectious myelitis may be caused by nearly any virus, with the particular pattern of anterior horn cell involvement causing flaccid paralysis associated with enteroviruses (enterovirus 71 [EV71], enterovirus D68 [EVD68], poliovirus) and West Nile virus.
- The most common infectious causes of radiculitis are viral (eg, varicella-zoster virus, herpes simplex virus 2 [Elsberg syndrome], cytomegalovirus [in immunocompromised patients]), Lyme disease, and tuberculous arachnoiditis.
- Infections associated with mononeuropathy multiplex include hepatitis B–associated polyarteritis nodosa,

hepatitis C–associated cryoglobulinemic vasculitic neuropathy, HIV, and leprosy. Infections that can cause polyneuropathy include HIV and diphtheria.

- Infectious myositis can be focal (eg, bacterial pyomyositis) or diffuse (eg, trichinosis [caused by *Trichinella spiralis*], HIV, human T-cell lymphotropic virus type I [HTLV-I]).
- Although definitive diagnosis of a neurologic infection requires microbiological testing of CSF or tissue specimen, neuroimaging is often obtained first because it can provide important clues as to the infectious etiology and may be necessary to exclude contraindications to lumbar puncture.
- Although CT of the brain without contrast may be inadequate to distinguish most infectious lesions from neoplastic, vascular, or inflammatory processes, it can identify the characteristic features of neurocysticercosis in the vesicular or calcified nodular stages (although granular and colloidal stages may be impossible to disambiguate from other hypodense lesions).
- Ring-enhancing lesions most commonly represent abscess or tumor, although subacute stroke may also show a peripheral pattern of enhancement.
- CSF in neurologic infections generally shows elevations in white blood cells and protein.
- Glucose is decreased in bacterial (including mycobacterial) and fungal infections and generally normal in viral infections, but it may be decreased in mumps, herpes simplex virus 2, cytomegalovirus, and Eastern equine encephalitis infection, as well as in non-neurologic causes of meningitis such as leptomeningeal metastases and sarcoidosis.
- A neutrophilic predominance is generally seen in bacterial infections, whereas a lymphocytic predominance is seen in viral, fungal, and mycobacterial infections. However, a neutrophilic predominance may be seen early in the course of viral infections and throughout the course of West Nile virus encephalitis.
- CSF parameters in conjunction with the clinical presentation provide an initial impression of the possible microbiological diagnoses to guide empiric therapy. However, they cannot be relied on because they may change after initiation of antimicrobial therapy and over the course of the illness. In immunocompromised patients, diminished capacity to mount an immune response may also alter the CSF profile.
- Definitive microbiological diagnosis can be made through several different types of laboratory tests. It is, therefore, crucial to be aware of the most sensitive tests when evaluating for particular pathogens.
- CSF cultures are generally the test of choice for gram-positive and gram-negative bacterial CNS infections, but culture is insensitive for viruses, spirochetes, and fungi. Although sensitive for tuberculosis, cultures take weeks to result. Therefore, additional techniques are necessary for diagnosis of these pathogens in the CSF.
- CSF cryptococcal antigen is the most sensitive test for diagnosing cryptococcal meningitis, and antigen tests are also important in the diagnosis of meningitis caused by endemic mycoses.
- CSF serology is considered a more sensitive test than polymerase chain reaction (PCR) for certain viruses (arbovirus IgM; varicella-zoster virus IgG in myelitis and vasculitis), and serology is also the test of choice for Lyme disease (IgG) and neurosyphilis.
- CSF PCR is the most sensitive test for most viral infections of the nervous system, with some notable exceptions (arboviruses, varicella-zoster virus).
- Metagenomic next-generation sequencing of CSF is an emerging unbiased, hypothesis-free technique that evaluates all genetic material in a sample to detect any nonhost sequences and identify them through computational algorithms using bioinformatic libraries. This technique has identified novel or unexpected pathogens in patients with neurologic infections that were unable to be diagnosed with conventional microbiological testing.

ARTICLE 2: MENINGITIS

Allen J. Aksamit Jr, MD, FAAN; Aaron L. Berkowitz, MD, PhD. Continuum (Minneap Minn). August 2021; 27 (4 Neuroinfectious Disease):836–854.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the diagnosis and treatment of infectious meningitis, including updates on newer molecular diagnostic techniques for microbiological diagnosis.

RECENT FINDINGS:

New polymerase chain reaction (PCR)-based molecular diagnostic techniques have improved the timeliness of microbiological diagnosis in meningitis, but clinicians must be aware of the limitations of such tests. Next-generation sequencing can now be applied to CSF, allowing for diagnosis of infections not identifiable by conventional means.

SUMMARY:

Infectious meningitis can be caused by a broad range of organisms. The clinician must be aware of the test characteristics of new molecular techniques for microbiological diagnosis as well as traditional techniques to tailor antimicrobial therapy appropriately in patients with meningitis.

KEY POINTS

- Meningitis is an inflammatory condition of the meninges that can be caused by infections, autoimmune diseases, neoplasia, and medications.
- Signs of meningismus include nuchal rigidity, the Kernig sign (pain and resistance with passive extension of the knee with the hip flexed), and the Brudzinski sign (hip and knee flexion with passive neck flexion). Although highly specific, these signs have very low sensitivity.
- CSF glucose level less than 40% of serum level (or less than 40 mg/dL) is suspicious for infection, most commonly bacterial, tuberculous, and fungal meningitis.
- CSF glucose is normal in most viral meningitides; however, hypoglycorrhachia can occur with some viruses, including mumps, lymphocytic choriomeningitis virus, West Nile virus, enterovirus, and cytomegalovirus (CMV) ventriculitis associated with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS).
- Elevated CSF eosinophils can be seen in parasitic or fungal infections but also in other noninfectious conditions, including hypereosinophilic syndrome, granulomatosis with polyangiitis, Hodgkin disease, and glioblastoma invading the meninges.
- The BioFire FilmArray Meningitis/Encephalitis (ME) Panel is a multiplex polymerase chain reaction (PCR) assay that evaluates for several common meningitis pathogens simultaneously: the bacteria *Escherichia coli* K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus agalactiae* (group B streptococcus), and *Streptococcus pneumoniae*; the viruses including cytomegalovirus, enterovirus, herpes simplex virus 1, herpes simplex virus 2, human herpesvirus 6, human parechovirus, and varicella-zoster virus; and the yeast *Cryptococcus* (both *Cryptococcus neoformans* and *Cryptococcus gattii*).
- The FilmArray ME Panel has an overall percent positive agreement of 97.5% for bacterial pathogens and 90.1% for viruses when compared with stand-alone PCR and/or culture, and only 52% for *Cryptococcus neoformans/Cryptococcus gattii* when compared with cryptococcal antigen.
- The clinical features of bacterial meningitis are fever, headache, stiff neck, and change in mental status. Approximately 45% of patients have all four symptoms, and 95% have at least two of the four.
- Bacterial meningitis is a neurologic emergency and is universally fatal if untreated. Outcomes are worse with

delayed treatment, so empiric antibiotics should be initiated as soon as the diagnosis of bacterial meningitis is considered, guided by age and past medical history.

- The most common bacterial causes of meningitis in adults and children are *S. pneumoniae* and *N. meningitidis*. *H. influenzae* may be seen in children but is now rare because of widespread vaccination. *L. monocytogenes* may be seen in adults older than 50 years and in patients who are immunocompromised. In infants, *E. coli*, *S. agalactiae*, and *L. monocytogenes* are the most common causes of bacterial meningitis.
- *L. monocytogenes* may be seen in adults older than 50 years and in patients who are immunocompromised.
- The monoclonal antibody eculizumab, a complement inhibitor approved for treatment of neuromyelitis optica and myasthenia gravis, is associated with a 1000-fold to 2000-fold increased incidence of meningococcal meningitis. Therefore, administration of the meningococcal vaccine is recommended before beginning eculizumab treatment.
- In infectious bacterial meningitis, postcontrast T1-weighted MRI often reveals enhancement of the leptomeninges within the cerebral sulci.
- Empiric antimicrobial treatment should be initiated immediately if bacterial meningitis is suspected.
- Practice guidelines developed in 2017 for nosocomial ventriculitis and meningitis recommend empiric therapy with vancomycin plus an antipseudomonal beta-lactam (such as cefepime, ceftazidime, or meropenem) with the choice of empiric beta-lactam based on local in vitro susceptibility patterns.
- Although most viruses are diagnosed by PCR, some are more sensitively diagnosed by CSF serology, such as arboviruses.
- The FilmArray ME Panel evaluates for enterovirus, herpes simplex virus type 2, and varicella-zoster virus but is less sensitive for herpes simplex virus than stand-alone herpes simplex virus PCR.
- Positive serum antibodies confirm exposure to West Nile virus but not necessarily neuroinvasive disease.
- Varicella-zoster virus PCR from spinal fluid is the most sensitive diagnostic test in the acute setting of acute meningitis and myelopathy, but serology (IgG) in spinal fluid is more sensitive in varicella-zoster virus vasculopathy.
- HIV can also cause viral meningitis, most commonly at or around the time of seroconversion. It may be accompanied by a flulike illness. Because the patient may not yet have formed antibodies, HIV antibody testing may be negative, requiring viral load for confirmation.
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been rarely associated with viral meningitis and is usually associated with the typical respiratory and systemic manifestations of the disease.
- Chronic meningitis is defined as meningitis lasting longer than 1 month without improvement. The most common causes are chronic bacterial and fungal infections and inflammatory disorders (eg, sarcoidosis, IgG4-related disease).
- TB meningitis can occur with or without evidence of systemic TB.
- Diagnosis of Lyme meningitis is established by CSF to serum serology antibody index in the setting of CSF pleocytosis.
- Meningovascular syphilis causes a subacute meningitis syndrome and should be considered in patients with HIV or history of other sexually transmitted diseases who develop chronic meningitis.
- The CSF VDRL test is specific for neurosyphilis but is only 30% to 70% sensitive; if the test is negative in cases with a high index of suspicion, CSF fluorescent treponemal antibody absorption should be performed, although positive results can occur in previously treated patients.
- Fungal organisms are common causes of subacute to chronic meningitis. The fungi to consider depend on geography, exposure history, and immune status.
- Most cases of cryptococcal meningitis are caused by *Cryptococcus neoformans*, but *Cryptococcus gattii,* endemic in the Pacific northwest region of the United States and Canada, can cause meningitis in patients who are immunocompetent.
- CSF cryptococcal antigen is the most sensitive test for diagnosis of cryptococcal meningitis.
- Elevated intracranial pressure is a common complication of cryptococcal meningitis, often requiring serial lumbar punctures or temporary external ventricular drain for CSF decompression.

- Histoplasmosis is endemic in the Mississippi and Ohio River valleys. When meningitis occurs, it is often accompanied by active pulmonary disease.
- Blastomycosis is endemic in the Mississippi and Ohio River valleys, as is histoplasmosis, but it is also found in the Great Lakes region. Involvement of the nervous system can be as chronic meningitis or as a focal mass with or without meningitis. CNS disease is usually accompanied by pulmonary infection, although pulmonary disease may be subclinical.
- Diagnosis of *Candida* meningitis is made by CSF culture, and CSF 1,3-β-D-glucan is frequently positive.
- The most common neuroimaging findings in fungal meningitis are thick, nodular leptomeningeal enhancement (most commonly in the basilar cisterns and subarachnoid space), hydrocephalus, and deep stroke(s) (due to infectious vasculitis of small perforating arteries).

ARTICLE 3: ENCEPHALITIS AND BRAIN ABSCESS

Arun Venkatesan, MD, PhD. Continuum (Minneap Minn). August 2021;
27 (4 Neuroinfectious Disease):855–886.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews infections of the brain parenchyma and includes an overview of the epidemiology, pathogenesis, diagnostic approach, and management of infectious encephalitis and brain abscess.

RECENT FINDINGS:

The epidemiology of infectious encephalitis and brain abscess has changed in recent years. Vaccination has reduced the incidence of certain viruses associated with encephalitis, while a decrease in fulminant otogenic infections has led to fewer brain abscesses associated with otitis media. However, changes in climate and human population density and distribution have enabled the emergence of newer pathogens and expanded the geographic range of others, and greater adoption of intensive immunosuppressive regimens for autoimmune conditions has increased the risk of opportunistic infections of the brain. The widespread use of early neuroimaging, along with improved diagnostic methodologies for pathogen detection, newer antimicrobial therapies with better brain penetration, and less invasive neurosurgical techniques, has resulted in better outcomes for patients with infectious encephalitis and brain abscess. Novel technologies including metagenomic next-generation sequencing are increasingly being applied to these conditions in an effort to improve diagnosis. Nevertheless, both infectious encephalitis and brain abscess continue to be associated with substantial mortality.

SUMMARY:

Infectious encephalitis and brain abscess can present as neurologic emergencies and require rapid assessment, thorough and appropriate diagnostic testing, and early initiation of empiric therapies directed against infectious agents. Close clinical follow-up, proper interpretation of diagnostic results, and appropriate tailoring of therapeutic agents are essential to optimizing outcomes. Diagnosis and management of parenchymal brain infections are complex and often best achieved with a multidisciplinary care team involving neurologists, neurosurgeons, neuroradiologists, infectious disease physicians, and pathologists.

KEY POINTS

- Encephalitis refers to inflammation of the brain parenchyma and is caused by a wide range of infectious and autoimmune conditions.
- Because a broad range of pathologic processes can cause altered mental status, including metabolic derangements, toxins, and cerebrovascular disease, patients with suspected encephalitis must be thoroughly evaluated for alternative conditions.
- Infections account for up to half of all cases of encephalitis; autoimmune causes are identified in 20% to 30%, and in the remaining 20% to 30% of cases, a specific cause is not ascertained.
- Changes in climate, human population growth and migration, and farming practices have resulted in the emergence and spread of arthropod-borne viruses (arboviruses), such as West Nile virus, chikungunya virus, and tick-borne encephalitis virus.
- Herpes simplex virus (HSV) most often affects the temporal lobes and other limbic areas.
- The deep gray matter is commonly affected in flaviviral infections such as West Nile virus and Japanese encephalitis virus.
- Many patients with HSV-1 encephalitis present with prodromal symptoms suggesting upper respiratory tract or other systemic infection.
- Early in the course, some patients with encephalitis may have fever and headaches without encephalopathy or focal neurologic deficits, even when parenchymal brain involvement is demonstrated by neuroimaging or EEG.
- Early in the disease course of HSV-1 encephalitis, findings are often unilateral; when bilateral, asymmetry may help to distinguish HSV-1 encephalitis from autoimmune causes of limbic encephalitis, which more commonly cause symmetrical changes.
- False-negative polymerase chain reaction (PCR) may occur early in the course of HSV-1 encephalitis. Notably, in children and people who are immunocompromised, the clinical manifestations and MRI findings are broader and can include a more diffuse encephalitis or meningoencephalitis with or without temporal lobe involvement.
- Rash may be absent in up to one-third of cases of varicella-zoster virus (VZV) encephalitis.
- In contrast to HSV-1 encephalitis, the primary pathologic process associated with VZV in the central nervous system (CNS) may be vasculopathy.
- Human herpesvirus 6 (HHV-6) can cause encephalitis in adults who are immunocompromised, most commonly in patients who have undergone hematopoietic stem cell transplantation.
- HHV-6 causes a limbic encephalitis that develops weeks to months after hematopoietic stem cell transplantation.
- Cytomegalovirus encephalitis is an important consideration in patients with acquired immunodeficiency syndrome (AIDS) (particularly when CD4+ count is less than 50 cells/mm^3) and may be accompanied by retinitis, polyradiculitis, and ventriculitis; a neutrophilic pleocytosis may be seen on CSF analysis, in contrast to the more common viral pattern of lymphocytic pleocytosis.
- In arboviral encephalitis, involvement of the deep gray matter is commonly seen on MRI and often accompanied clinically by movement disorders.
- As a result of the insensitivity of CSF PCR, laboratory diagnosis of arboviral encephalitis often rests on detection of virus-specific IgM in CSF and blood.
- Less than 1% of people infected with West Nile virus will develop West Nile neuroinvasive disease in the form of meningitis, encephalitis, or acute flaccid myelitis.
- West Nile virus IgM may persist for prolonged periods, with detectable IgM titers for longer than 1year, and thus, in some cases, the finding of West Nile virus IgM may reflect previous exposure rather than current illness.
- Japanese encephalitis virus is the most important cause of encephalitis in South and Southeast Asia, typically affecting children younger than 10.
- In addition to causing meningitis, *Listeria monocytogenes* can cause rhombencephalitis. Although *Listeria* infections occur more commonly in individuals who are immunocompromised, immunocompetent individuals

may also be affected; according to one review of previously reported cases, the majority of patients who developed rhombencephalitis were immunocompetent.

- Thrombocytopenia and vascular involvement are common in Rocky Mountain spotted fever, likely accounting for the petechiae and the brain MRI findings of scattered punctate areas of restricted diffusion and T2 hyperintensity in the deep gray and white matter in affected children.
- *Balamuthia mandrillaris* can affect individuals who are immunocompetent. Mortality is high, and many cases have been identified only postmortem; however, increased recognition and earlier identification have resulted in rapid initiation of multidrug treatments with associated survival.
- In recent years, it has been recognized that contaminated tap water is a potential source of transmission of *Naegleria fowleri*, as underscored by several cases associated with the use of neti pots.
- Encephalitis can present as a systemic and neurologic emergency, and thus, initial management is focused on stabilizing patients who are acutely ill while concurrently initiating a diagnostic evaluation.
- A comprehensive history encompassing travel, ill contacts, occupational exposures, vector and animal exposures, outdoor activities, ingestions, and recent illnesses should be ascertained.
- Neuroimaging, preferably MRI because of its higher sensitivity for early or subtle findings of encephalitis than CT, should be performed urgently and is helpful in not only suggesting potential etiologies of encephalitis but also excluding some mimics.
- To assess for common and treatable infectious conditions, important studies to obtain in all adults with suspected encephalitis include opening pressure; protein; glucose; cell count and differential; Gram stain; bacterial cultures; PCRs for HSV-1, HSV-2, VZV, and enterovirus; cryptococcal antigen; and testing for syphilis.
- Autoimmune causes are particularly suspected in the setting of limbic encephalitis and marked personality or behavioral changes or when brain MRI is normal.
- In patients in whom the clinical picture is suggestive of HSV or VZV, acyclovir should be started as soon as possible.
- If testing from the first lumbar puncture does not reveal a specific cause and HSV-1 encephalitis is still suspected (eg, limbic encephalitis, temporal lobe involvement), acyclovir should be continued and a second lumbar puncture should be performed in several days because the HSV PCR can be falsely negative, particularly early in the course of illness and in children.
- Patients who are immunocompromised and have VZV infection may develop a relapsing or refractory course.
- Advanced age, immunosuppression, and other major medical comorbidities are typically reported as poor prognostic factors in patients with encephalitis.
- Sources of infection that lead to brain abscess include direct extension from a focus adjacent to the CNS (eg, sinusitis, otitis media, mastoiditis, or dental infection), hematogenous spread from a distant site (eg, endocarditis, pulmonary infection, skin), or direct inoculation (eg, penetrating head trauma, neurosurgical procedure).
- The most common pathogens in brain abscesses in individuals who are immunocompetent are streptococcal species, including aerobic streptococci (eg, *Streptococcus anginosus* group, also known as the *Streptococcus milleri* group) and anaerobic streptococci, which are identified in more than half of cases and are frequently associated with sinus infections.
- Brain abscesses arising from hematogenous dissemination are most commonly of pulmonary origin, and, in addition to streptococcal and staphylococcal species, may be caused by *Actinomyces* species, *Fusibacterium* species, and *Nocardia* species.
- Opportunistic filamentous bacteria such as *Nocardia* species, and to a lesser extent *Actinomyces* species, are notable causes of brain abscess in the immunocompromised host and can be challenging to distinguish histologically because of their resemblance to fungi on histopathologic examination.
- Although aggressive management of otitis media has led to a decrease in otogenic-related brain abscess in many countries, it remains a prominent source of brain abscess in low- and middle-income countries.
- Penetrating head trauma and neurosurgical procedures account for an increasing proportion of brain abscesses.

- Headache is the most frequent manifestation of brain abscesses, occurring about 70% of the time, and focal neurologic deficits occur in about half of all cases. Fever may be absent in half of all cases.
- MRI is preferred over CT because it is more sensitive during early stages of abscess formation, can more precisely demonstrate complications of abscess, and can help better distinguish abscess from other mimics.
- The combination of rim enhancement and intense central restriction of diffusion is highly suggestive of brain abscess but does not exclude other conditions.
- Blood cultures should routinely be collected. Although they are positive in only about one-quarter of patients with brain abscesses, the yield is higher in those with hematogenous dissemination. In addition, positive blood cultures may eliminate the need to directly sample the brain abscess.
- In about one-quarter of cases of brain abscess, cultures of the abscess fluid are negative, and the yield decreases further in patients in whom empiric antimicrobial therapy is initiated before sample acquisition. However, empiric antibiotics should never be withheld or delayed in those who are critically ill in an attempt to improve the diagnostic yield of sampling.
- Broad-based molecular techniques typically identify multiple bacterial taxa, underscoring the complex and polymicrobial nature of brain abscesses.
- Even when the causative pathogen has already been identified, neurosurgical approaches often still play an important role in management by reducing the size of the abscess.
- Minimally invasive stereotactic aspiration has largely replaced surgical excision of brain abscesses because of lower rates of intracranial hemorrhage and mortality.
- In recognition of the polymicrobial composition of many abscesses, empiric regimens typically provide broad aerobic and anaerobic coverage. Regimens have historically consisted of penicillin, chloramphenicol, and metronidazole but have largely been replaced by third-generation cephalosporins (eg, cefotaxime or ceftriaxone) and metronidazole over the past several decades.
- The identification of an aerobic organism does not preclude the concomitant presence of an anaerobic organism, the latter of which can be difficult to isolate and culture. Thus, anaerobic coverage may be maintained for the duration of therapy, particularly in the setting of contiguous infections.
- Some bacterial abscesses, such as those associated with *Nocardia* species, along with mycobacterial and fungal infections, require a longer duration of therapy than the typical 6- to 8-week course.
- Mortality due to brain abscess is associated with advanced age, comorbid conditions (eg, diabetes, congenital heart disease or congestive heart failure, immunodeficiency), and hematogenous dissemination of infection.
- The presence of intraventricular rupture is strongly associated with in-hospital mortality; the majority of adult and pediatric patients with ventricular rupture die.
- In-hospital outcomes from brain abscess have improved over the past several decades, likely attributable to better general medical care, more widespread and earlier adoption of neuroimaging, improved microbial diagnostics, adoption of minimally invasive neurosurgical procedures, and increased effectiveness of CNS penetrating antimicrobial agents.

ARTICLE 4: INFECTIONS OF THE SPINE AND SPINAL CORD

Shamik Bhattacharyya, MD, MS; Michael J. Bradshaw, MD. Continuum (Minneap Minn). August 2021; 27 (4 Neuroinfectious Disease):887–920.

ABSTRACT

PURPOSE OF REVIEW:

Infections of the spine and spinal cord are associated with a high risk of morbidity and mortality and, therefore, require prompt clinical recognition, efficient diagnostic evaluation, and interdisciplinary treatment. This article reviews the pathophysiology, epidemiology, clinical manifestations, diagnosis, and treatment of infections of the spine and spinal cord to help practicing clinicians recognize, evaluate, and manage patients with such infections.

RECENT FINDINGS:

Aging of the population, increasing use of immunosuppressive medications, and other factors have contributed to increasing rates of spinal infections. Although the most common agents responsible for spinal infections remain bacteria and viruses, fungal infections occur in individuals who are immunocompromised, and parasitic infections are common in endemic regions, but patterns are in evolution with migration and climate change. Recent outbreaks of acute flaccid myelitis in children have been associated with enteroviruses A71 and D68.

SUMMARY:

Infections of the spine and spinal cord can be challenging to diagnose, requiring a thorough history and neurologic examination, laboratory studies of serum and CSF, neuroimaging (particularly MRI), and, in some instances, biopsy, to establish a diagnosis and treatment regimen. Interdisciplinary management including collaboration with experts in internal medicine, infectious disease, and neurosurgery is important to improve clinical outcomes.

KEY POINTS

- Spondylodiscitis is most often caused by pyogenic bacteria, which can infect spinal structures via hematogenous spread from distant sites, direct inoculation by instrumentation, or contiguous spread from adjacent infection.
- Fever is present only in roughly half of patients with spondylodiscitis; is less likely to develop in patients with *Brucella*, mycobacterial, or fungal infections; and may be absent in patients taking antipyretic analgesics and those who are immunosuppressed.
- Spondylodiscitis should be suspected in patients with new or worsening back pain particularly with fever, new neurologic deficits, recent bacteremia, endocarditis, hemodialysis, IV access, or IV drug use.
- Erythrocyte sedimentation rate and C-reactive protein should be included as screening studies when spondylodiscitis is a possibility; they are valuable as screening studies with sensitivities in the range of 94% to 100%.
- The most common initial manifestations of brucellosis include fever, arthralgias, malaise, and night sweats.
- The risk of extrapulmonary tuberculosis is especially high in patients with human immunodeficiency virus (HIV) co-infection, who are up to 5 times more likely to develop central nervous system involvement than those without HIV.
- The spine is the most common site of osteoarticular tuberculosis, and tuberculous spondylitis is the most common mechanism of myelopathy associated with tuberculosis.
- The most common neurologic manifestation of tuberculosis is meningitis, although tuberculous granulomas

or abscesses can affect the spine, and tuberculosis can also cause syringomyelia, arachnoiditis, and myelitis often accompanied by radiculitis.

- Tuberculous spondylitis typically presents with insidious back pain that worsens over weeks to months, may be accompanied by muscle spasms, and is less often associated with fever than bacterial spondylitis.
- Precise diagnosis of tuberculous spondylitis is primarily based on microscopy and culture data obtained from biopsy or surgical specimens.
- Patients with coccidioidomycosis spondylodiscitis present most often with back pain, radiculopathy, and sensory disturbances and less often with weakness and/or myelopathy; fever is uncommon.
- Prognosis in spinal epidural abscess depends on the degree and duration of neurologic deficits before decompression and antimicrobial therapy; therefore, early diagnosis and management are critical, and clinicians should maintain a high index of suspicion to avoid potentially devastating consequences.
- The classic triad of epidural abscess including fever, back pain, and focal neurologic deficits is observed in only 2% to 33% of patients at presentation, which, therefore, has inadequate sensitivity to be considered a useful clinical marker.
- Epidural abscess is a neurologic emergency and requires urgent evaluation and treatment to decrease the risk of permanent neurologic injury.
- Clinically, most patients with spinal meningitis often have symptoms of polyradiculitis manifesting as shooting, sharp pain along dermatomal distributions accompanied by focal numbness or weakness in radicular distributions.
- Early neuroborreliosis often involves the peripheral nervous system, and frequently encountered manifestations include cranial neuritis (most commonly unilateral or bilateral facial nerve palsy), radiculoneuritis, and lymphocytic meningitis.
- Myelitis is inflammation of the spinal cord parenchyma and can be caused by infectious or immune-mediated etiologies.
- The anterior horn syndrome consists of a lower motor neuron pattern flaccid weakness with decreased or absent reflexes and preservation of sensory modalities (often referred to as *acute flaccid myelitis*).
- In enteroviral myelitis, enterovirus was detected in only 20% of CSF samples compared with 94% of rectal and 79% of oropharyngeal samples, highlighting the greater sensitivity of peripheral over CSF sampling in neurologic disease associated with enteroviral infection.
- Human infection with West Nile virus typically occurs in the late spring, summer, or early fall, when mosquitos are most active in the environment.
- West Nile neuroinvasive disease most often presents with meningitis or meningoencephalitis, which may co-occur with myelitis as well.
- Myelitis develops in an estimated 5% to 10% of cases of West Nile neuroinvasive disease and most often presents as an acute flaccid paralysis.
- For West Nile neuroinvasive disease, CSF IgM is more sensitive than CSF polymerase chain reaction (PCR), and the detection of West Nile virus IgM in the CSF in the appropriate clinical context strongly indicates West Nile neuroinvasive disease.
- The anterior cord syndrome is characterized by weakness and loss of spinothalamic tract sensory modalities below the level of the lesion with preservation of the dorsal column sensory modalities and is most often caused by a vascular injury to the cord.
- Although myelitis is an infrequent manifestation, varicella-zoster virus (VZV) is one of the most common causes of infectious myelitis and is important to recognize given the availability of specific antiviral therapy.
- CSF VZV PCR should be obtained when CNS zoster is suspected, although it is also prudent to test CSF VZV IgM/IgG, which may be more sensitive than PCR and can also be used to confirm the diagnosis.
- Small, centrally located lesions in the spinal cord may only affect the spinothalamic tract as they decussate via the anterior commissure and produce a suspended level of decreased pain and temperature sensation roughly two spinal levels below the level of the lesion.
- The dorsal column syndrome is characterized by decreased or absent vibration and proprioception below the level of the lesion with preserved strength, pain, and temperature sensation.

- Human T-cell lymphotropic virus type I–associated myelopathy and HIV vacuolar myelopathy often affect the dorsal and lateral columns producing a syndrome marked by spastic paraparesis and impaired vibration and joint position sense.
- Elsberg syndrome is a presumed infectious syndrome defined by acute or subacute progressive bilateral lumbosacral radiculitis or myeloradiculitis of the caudal spinal cord and lumbosacral nerve roots.
- In toxoplasmosis, involvement of the spinal cord rarely occurs and is most often concomitant with brain involvement.

ARTICLE 5: INFECTIONS OF THE PERIPHERAL NERVOUS SYSTEM

Samantha LoRusso, MD. Continuum (Minneap Minn). August 2021; 27 (4 Neuroinfectious Disease):921–942.

ABSTRACT

PURPOSE OF REVIEW:

This article describes infections that affect the peripheral nervous system, including their clinical features, differential diagnoses, and treatments.

RECENT FINDINGS:

Rates of pyomyositis have increased recently in the United States, possibly because of an increase in risk factors such as IV drug use, obesity, and diabetes. Other peripheral nervous system infections, such as diphtheria, have become more common in older patients secondary to a lack of revaccination or waning immunity. Although recommended treatment regimens for most infections remain unchanged over recent years, debate over the ideal dosing and route of administration continues for some infections such as tetanus and leprosy (Hansen disease).

SUMMARY:

Infections of the peripheral nervous system are varied in terms of the type of infection, localization, and potential treatment. Nerve conduction studies and EMG can help determine localization, which is key to determining an initial differential diagnosis. It is important to recognize infections quickly to minimize diagnostic delays that could lead to patient morbidity and mortality.

KEY POINTS

- Although infections of the peripheral nervous system are rare, it is important for neurologists to be able to recognize their clinical manifestations because many are treatable.
- West Nile virus is now the most common viral cause of acute flaccid paralysis in adults in the United States.
- One of the most common infectious causes of radiculopathy is Lyme disease.
- If the presentation is a mononeuropathy or multiple mononeuropathies, then leprosy, hepatitis B and C viruses, Lyme disease, human immunodeficiency virus (HIV), and cytomegalovirus should be considered.
- Leprosy is predominantly a disease of the peripheral nerves and skin and is still a common cause of neuropathy in Southeast Asia, South America, and Africa.
- Common sites of mononeuropathy in leprosy include the greater auricular nerve, the ulnar nerve at the elbow, the median nerve proximal to the carpal tunnel, the superficial radial nerve at the wrist or radial nerve at the spiral groove, the fibular (peroneal) nerve at the fibular head, the facial nerve, and the sural nerve.
- Peripheral neuropathy is thought to occur in about 10% of patients with hepatitis C virus and may be the presenting symptom.

- A length-dependent sensory or sensorimotor axonal neuropathy is the most common peripheral nervous system manifestation of HIV.
- Diphtheritic neuropathy is the prototypical infection leading to a demyelinating neuropathy with a presentation that resembles Guillain-Barré Syndrome.
- Chagas disease, caused by the parasite *Trypanosoma cruzi*, can cause autonomic neuropathy, particularly affecting cardiac and gastrointestinal function.
- A positive "spatula test," in which attempting to elicit the gag reflex results in the patient biting down, is both sensitive and specific for tetanus.
- Wound botulism can occur after trauma but is more commonly seen in relation to recreational drug use, especially IV drugs and subcutaneous heroin.
- Nerve conduction studies/EMG is important in aiding the clinical diagnosis of botulism because it can help confirm the diagnosis before laboratory testing results and make other diagnoses less likely.
- An acute, self-limited myositis may occur secondary to viral infections, particularly influenza.
- Pyomyositis classically occurs in otherwise healthy young men in tropical regions but has become more common in the United States.

ARTICLE 6: PARASITIC INFECTIONS OF THE NERVOUS SYSTEM

Hector H. Garcia, MD, PhD. Continuum (Minneap Minn). August 2021;
27 (4 Neuroinfectious Disease):943–962.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews how parasites affect the human nervous system, with a focus on four parasitic infections of major public health importance worldwide, two caused by protozoa (malaria and toxoplasmosis) and two by helminths (neurocysticercosis and schistosomiasis).

RECENT FINDINGS:

Parasitic infections in humans are common, and many can affect the central nervous system where they may survive unnoticed or may cause significant pathology that can even lead to the death of the host. Neuroparasitoses should be considered in the differential diagnosis of neurologic lesions, particularly in individuals from endemic regions or those with a history of travel to endemic regions.

SUMMARY:

Cerebral malaria is a significant cause of mortality, particularly in African children, in whom infected red blood cells affect the cerebral vessels, causing severe encephalopathy. Neurocysticercosis is the most common cause of acquired epilepsy worldwide and has varied clinical presentations, depending on the number, size, and location of the parasites in the nervous system as well as on the host's inflammatory response. Toxoplasmosis is distributed worldwide, affecting a significant proportion of the population, and may reactivate in patients who are immunosuppressed, causing encephalitis and focal abscesses. Schistosomiasis causes granulomatous lesions in the brain or the spinal cord.

KEY POINTS

- The human nervous system can be invaded by multiple parasite species, which, in some cases, cause a significant burden of morbidity and mortality.

- Parasites use multiple mechanisms to overcome the physical and immunologic barriers that vertebrates have evolved to protect their nervous systems.
- Malaria is the most common parasitic disease of humans and the most common parasitic cause of mortality and morbidity worldwide. Annually, malaria causes more than 400,000 deaths in endemic regions, mostly in African children.
- Untreated cerebral malaria is lethal in all cases. Even under appropriate care, short-term mortality may approach 15% to 30%.
- Up to one-third of the world's population is infected with latent toxoplasmosis (usually asymptomatic), and disease occurs when latent brain infections are reactivated in patients who become immunocompromised.
- The clinical manifestations of cerebral toxoplasmosis are usually subacute and depend on the topography and number of lesions. The main symptoms are fever, headache, seizures, focal deficits, confusion, lethargy, and visual alterations related to retinal toxoplasmosis.
- Therapy with pyrimethamine-based treatment or trimethoprim-sulfamethoxazole is usually effective for neurotoxoplasmosis, with clinical and radiologic improvement in 80% to 90% of patients receiving one of these regimens.
- Neurocysticercosis represents a significant source of morbidity and mortality, causing approximately 30% of cases of epilepsy in endemic regions, making it the most common preventable risk factor in the world for adult acquired epilepsy.
- Neurocysticercosis varies in clinical and radiologic presentation depending on the location, size, and number of lesions and host immune response.
- The enzyme-linked immunoelectrotransfer blot assay using lentil-lectin purified glycoprotein parasitic antigens in serum is the assay of choice for antibody detection of neurocysticercosis.
- For a single parenchymal cyst in neurocysticercosis, albendazole at 15 mg/kg/d for 7 to 15 days is the regimen of choice. In cases with multiple viable cysts, the combination of albendazole plus praziquantel at 50 mg/kg/d for 10 days has demonstrated superior efficacy.
- Schistosomal infection of the central nervous system (neuroschistosomiasis) is a rare complication of schistosomiasis presenting with myelopathy or encephalopathy; it can present months to years after exposure.
- Transverse myelitis is the most common presentation of spinal neuroschistosomiasis and is related to granulomatous lesions with inflammatory necrosis of the spinal cord.
- A variety of parasitic infections may affect the human central nervous system less frequently. Epidemiologic suspicion, particularly in the settings of atypical clinical presentations of neurologic disease, should help to detect parasitic infections of the central nervous system.

ARTICLE 7: NEUROLOGIC COMPLICATIONS OF HUMAN IMMUNODEFICIENCY VIRUS

Marie F. Grill, MD. Continuum (Minneap Minn). August 2021;
27 (4 Neuroinfectious Disease):963–991.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the neurologic complications associated with human immunodeficiency virus (HIV) infection.

RECENT FINDINGS:

Neurologic complications of HIV may be caused by direct virally mediated pathology, immune-mediated phenomena in response to viral infection, or opportunistic infections secondary to depletion of lymphocytes. These neurologic disorders may be influenced by the degree of immunosuppression (ie, CD4+ T-cell lymphocyte count) and stage of infection (early versus late), as well as use of antiretroviral therapy, and may manifest as a variety of central and peripheral neurologic syndromes, including the more commonly encountered HIV-associated cognitive disorders and length-dependent sensorimotor polyneuropathy, respectively. Immune dysregulation underlies the majority of these neurologic phenomena, as well as other HIV-associated conditions including immune reconstitution inflammatory syndrome (IRIS), CD8 lymphocytosis, and potentially the development of compartmentalized infection within the CSF, also referred to as *CSF escape*.

SUMMARY:

This article reviews a spectrum of clinical syndromes and related neuropathologic states associated with HIV infection.

KEY POINTS

- Evidence of human immunodeficiency virus (HIV) RNA and inflammation in the CSF has been identified from the time of acute infection through the entire course of the disease, correlating with the clinical observation that nervous system manifestations of HIV can occur throughout the course of infection.
- Neurologic complications of HIV may result from direct viral complications, immune-mediated complications, opportunistic infections, and antiretroviral therapy (ART)-associated toxicities.
- Early in HIV infection, acute seroconversion syndrome and other autoimmune-mediated phenomena are most likely to be seen, whereas in middle to late HIV infection, opportunistic infections, malignancies, and long-term complications of HIV are more frequently encountered.
- Patients with acute HIV seroconversion have also presented with Guillain-Barré type syndrome/acute inflammatory demyelinating polyradiculoneuropathy. Other rarely observed neurologic conditions that may be seen at the time of seroconversion include transverse myelitis, acute disseminated encephalomyelitis (ADEM), a multiple sclerosis–like illness, and bilateral brachial plexus neuritis.
- HIV-associated neurocognitive disorders include asymptomatic neurocognitive impairment, minor or mild neurocognitive disorder, and HIV-associated dementia, distinguished by the degree of symptomatology and functional impairment, as well as neuropsychologic test performance.
- Asymptomatic neurocognitive impairment is asymptomatic/subclinical, identified only with neuropsychologic testing and used in research settings. Minor or mild neurocognitive disorder and HIV-associated dementia exist on a spectrum of clinically manifest neuropsychological impairment of varying severity, primarily affecting executive functioning, memory, learning, and attention.
- *CSF escape* refers to the presence of ongoing viral replication within the central nervous system compartment despite relative virologic suppression in the blood with antiretroviral therapy use.
- Perhaps the most common clinically encountered HIV-related neurologic complication is distal symmetric polyneuropathy. ART has both decreased the incidence of this condition and slowed disease progression in patients with distal symmetric polyneuropathy, although asymptomatic peripheral neuropathy (as defined by mild impairment in vibratory sensation in the great toes or diminished ankle reflexes bilaterally on examination in the absence of clinical symptoms) may be present despite virologic control.
- Immune reconstitution inflammatory syndrome (IRIS) is a worsening of symptoms when the immune system rebuilds (ie, when the CD4+ T-cell lymphocyte count increases and HIV plasma viral load decreases) after initiation of ART therein reflecting an inflammatory rebound phenomenon.
- Worsening of neurologic impairment, as well as new-onset neurologic decline, may be seen in neuro-IRIS, which is most frequently associated with cryptococcal meningitis and progressive multifocal

leukoencephalopathy, although it may also be seen with toxoplasmosis encephalitis and other opportunistic infections.

- CD8+ encephalitis is a rare, recently recognized cause of encephalopathy seen in patients who are HIV positive and have a normal CD4+ count stable on ART (although on occasion may be seen briefly after initiation of ART). Patients present with acute to subacute encephalopathy that may be accompanied by seizures and headaches.
- Although they are uncommon, immune-mediated acute and chronic inflammatory demyelinating polyradiculoneuropathies occur more frequently in individuals who are HIV positive compared with those who are HIV negative.
- Risk factors for ischemic stroke include accelerated atherosclerotic disease and other microangiopathic changes, altered vascular reactivity/endothelial changes secondary to HIV-induced inflammatory changes, HIV-associated hyperviscosity and coagulopathy (eg, antiphospholipid antibody syndrome), effects of combination ART, comorbid substance use (including tobacco use and stimulants), and cardioembolic phenomena (including both bacterial and marantic endocarditis, as well as cardiac dysfunction).
- Comorbid opportunistic infections such as varicella-zoster virus–associated vasculitis, meningovascular syphilis, and tuberculous and cryptococcal meningitis are additional specific risk factors for stroke in HIV, as is intravascular lymphoma albeit less commonly. HIV-associated thrombocytopenia, vasculopathy, and mycotic aneurysms are associated with an increased risk of hemorrhagic stroke.
- Timely recognition, diagnosis, and treatment are key to decreasing morbidity and mortality risk associated with opportunistic infections. Restoration of immune function with combination ART is also of critical importance, although the risk of IRIS must be considered and may influence the timing of ART initiation.
- Toxoplasmosis is the most common cause of intracranial mass lesions in patients with HIV, typically with a CD4+ count less than 200 cells/mm^3, most often with less than 100 cells/mm^3.
- Clinically, patients with toxoplasmosis often present with subacute focal neurologic signs (eg, hemiparesis, unilateral movement disorder, gait disturbance, or speech abnormalities) and with headache, fever, and altered mental status.
- Nuclear imaging modalities such as positron emission tomography (PET) may be helpful in making the distinction (ie, no increase in metabolic activity of lesions in toxoplasmosis whereas increased metabolic activity is suggestive of primary CNS lymphoma).
- Progressive multifocal leukoencephalopathy is one of the opportunistic infections more commonly associated with IRIS, which can appear on imaging as edema, mass effect, and contrast enhancement.
- Other novel JC virus–associated CNS disorders are caused by JC virus variants and include granule cell neuronopathy in which cerebellar granule cell neurons are infected, as well as JC virus encephalopathy in which cortical gray matter pyramidal neurons are infected.
- Patients with cryptococcal meningitis typically present with subacute progressive headache and fever. Other symptoms may manifest from complications relating to meningitis including altered mental status, blurred vision, and cranial nerve palsies secondary to elevated intracranial pressure with or without accompanying hydrocephalus.
- Formation of gelatinous cysts may develop in increasingly dilated perivascular spaces, referred to as a *soap bubble appearance* on brain MRI, and is more commonly seen in patients with cryptococcal disease infected with HIV in contrast to patients who are not infected with HIV.
- Cytomegalovirus infection is seen almost exclusively in individuals who are immunocompromised; in patients infected with HIV, this is typically seen when CD4+ counts are less than 50 cells/mm^3. It may be associated with meningitis, encephalitis, myelitis, and radiculitis.
- The Centers for Disease Control and Prevention recommends delaying the initiation of ART for 8 weeks after initiation of antituberculosis treatment to decrease the risk of tuberculosis CNS IRIS.
- CSF varicella-zoster (VZV) IgG is considered more sensitive than PCR, particularly in those with a latency of weeks to months since rash or in cases of zoster sin herpete. Treatment consists of IV acyclovir, as well as steroids in the setting of VZV-associated vasculitis.
- Neurosyphilis should be considered in all individuals infected with HIV who have neurologic symptoms.

Serum rapid plasma reagin (RPR) titer of at least 1:32 is associated with an increased likelihood of neurosyphilis, both in patients who are not infected with HIV and in those who are, with an even higher risk in the latter group.

- Nucleoside reverse transcriptase inhibitors such as didanosine and zalcitabine, as well as stavudine, can cause peripheral neuropathy with mitochondrial toxicity postulated to be the underlying mechanism.

ARTICLE 8: NEUROLOGIC COMPLICATIONS OF TUBERCULOSIS

Deanna Saylor, MD, MHS. Continuum (Minneap Minn). August 2021;
27 (4 Neuroinfectious Disease):992–1017.

ABSTRACT

PURPOSE OF REVIEW:

This article describes the current epidemiology, common clinical characteristics, and up-to-date evidence-based approaches to the diagnosis and management of the most common neurologic complications of tuberculosis (TB): tuberculous meningitis, intracranial tuberculoma, and spinal TB.

RECENT FINDINGS:

Central nervous system (CNS) TB remains common and associated with significant mortality and neurologic sequelae worldwide. Human immunodeficiency virus (HIV) co-infection is strongly associated with both the development of and mortality due to CNS TB. *Strongyloides* co-infection is associated with reduced CNS inflammation and improved outcomes in the setting of tuberculous meningitis. Stroke remains a common complication of tuberculous meningitis, and emerging evidence suggests aspirin may be used in this context. Although a recent nucleic acid amplification test has demonstrated suboptimal sensitivity in the diagnosis of CNS TB, emerging diagnostic techniques include cell-free DNA, peripheral blood microRNA, metagenomic next-generation sequencing, and advanced imaging techniques, but these are not yet well validated. CNS TB is associated with high mortality even with current treatment regimens, although novel, promising strategies for treatment are under investigation, including a combination of IV isoniazid and ethambutol and high-dose rifampicin.

SUMMARY:

TB can affect the nervous system in various ways and is associated with high mortality. Diagnosis remains challenging in endemic settings, with empiric treatment often initiated without a definitive diagnosis. Furthermore, optimal treatment regimens remain uncertain because current treatment for all forms of CNS TB is extrapolated from trials of tuberculous meningitis whereas the role of steroids in people with HIV and tuberculous meningitis remains controversial.

KEY POINTS

- Tuberculosis (TB) is the leading cause of death from an infectious etiology and remains in the top 10 causes of death globally. In 2019, TB accounted for 10 million new symptomatic infections (1.2 million symptomatic infections in children) and 1.4 million deaths globally, and 25% of the world's population is thought to be infected with TB.
- Central nervous system (CNS) TB is one of the most severe forms of TB and is associated with high mortality, especially among people with human immunodeficiency virus (HIV).
- The most common form of CNS TB is tuberculous meningitis, which can present either as an insidious chronic

meningitis or as an acute fulminant meningitis with the most common symptoms being fever, headache, and alterations in consciousness.

- Stroke, usually in the basal ganglia, is one of the most common complications of tuberculous meningitis, occurring in approximately 30% to 60% of cases.
- Seizures are common in tuberculous meningitis, occurring in approximately one-third of individuals and most often occurring more than 1 month after the onset of meningitis symptoms.
- Immune reconstitution inflammatory syndrome is paradoxical worsening of an individual's clinical and radiographic presentations that occurs in people with HIV initiating antiretroviral therapy.
- The primary microbiological tools for CNS diagnosis include acid-fast bacilli stain, *Mycobacterium* culture, and nucleic acid amplification tests. All of these modalities are limited in their sensitivity, which results in higher than acceptable rates of false-negative results.
- Novel and adjunctive assays have been developed in hopes of improving the ability to accurately diagnose CNS TB but, thus far, continue to demonstrate suboptimal sensitivity or have not been widely validated.
- Investigating combinations of diagnostic tests may lead to the highest utility for diagnosing tuberculous meningitis.
- Given the difficulty of obtaining a microbiologically confirmed diagnosis of tuberculous meningitis, clinical case definitions such as the Uniform Case Definition and the Thwaites Score are often used in high-TB-burden regions to make presumptive diagnoses to initiate empiric treatment.
- The World Health Organization recommends treatment of tuberculous meningitis in two stages, which are (1) the intensive phase: rifampicin, isoniazid, pyrazinamide, and ethambutol for 2 months and (2) the continuation phase: rifampicin and isoniazid for 9 to 12 months.
- Concomitant steroids in addition to antitubercular therapy tapered over 6 to 8 weeks have also been shown to reduce mortality, severe disability, and disease relapse.
- A systematic review found that the addition of aspirin to standard treatment regimens for tuberculous meningitis reduced the risk of stroke and was safe but had no effect on overall mortality.
- A systematic review of tuberculous meningitis among adults worldwide identified a 23% mortality risk and 29% risk of neurologic sequelae. However, outcomes vary widely with mortality rates as high as 60% in lower-resource settings and less than 20% in higher-resource settings with greater access to critical care facilities.
- Approximately 10% of individuals with tuberculous meningitis have concomitant tuberculomas, but tuberculomas can also occur in the absence of meningitis and without evidence of TB infection outside of the CNS.
- In the absence of meningitis, CSF is usually normal in patients with tuberculoma, and the only definitive diagnostic test is a brain biopsy. As such, a presumptive diagnosis based on clinical and radiographic characteristics is often made to facilitate the initiation of empiric TB treatment.
- Tuberculoma treatment largely mirrors recommendations for tuberculous meningitis with most guidelines recommending 9 to 12 months of standard TB treatment along with adjuvant corticosteroids.
- Tuberculous spondylitis presents insidiously over the course of months to more than 1 year, first with nonspecific back pain that is then followed by kyphosis, sensory symptoms, bowel and bladder symptoms, and, finally, paraparesis.
- Intradural tuberculous spinal infections, including radiculomyelitis, spinal arachnoiditis, intramedullary tuberculomas, and myelitis, are seen most commonly in the setting of tuberculous meningitis because of the spread of inflammatory exudates from the cranial to the spinal compartment.

ARTICLE 9: NEUROSYPHILIS

Felicia Chow, MD, MAS. Continuum (Minneap Minn). August 2021;
27 (4 Neuroinfectious Disease):1018–1039.

ABSTRACT

PURPOSE OF REVIEW:

This article focuses on the epidemiology, clinical presentation, diagnosis, and management of neurosyphilis, with an emphasis on clinically relevant issues faced by the practicing neurologist.

RECENT FINDINGS:

The incidence of primary and secondary syphilis, the sexually transmissible stages of infection, has been on the rise for the past 2 decades. A concerning recent trend is the surge in cases of syphilis in women and of congenital syphilis. Neurosyphilis remains a relatively common complication that can occur at any stage of syphilis. Along with meningitis, meningovascular syphilis, which has been historically described as a late presentation of neurosyphilis, now frequently occurs as a manifestation of early infection. Late forms of neurosyphilis, including tabes dorsalis and general paresis, are less prevalent in the era of widespread penicillin use. As more laboratories adopt the reverse-sequence algorithm for syphilis testing, patients with serodiscordant results (ie, a reactive serum treponemal test with a nonreactive nontreponemal test) may present an increasingly encountered diagnostic challenge for neurologists. Although the CSF Venereal Disease Research Laboratory (VDRL) remains a mainstay of diagnostic testing for neurosyphilis, using a higher titer cutoff (greater than 1:320) for the *Treponema pallidum* particle agglutination assay (TPPA) from the CSF may improve the utility of the TPPA as a supporting criterion for the diagnosis of neurosyphilis. Penicillin G is the treatment of choice for neurosyphilis, although ceftriaxone may be a reasonable alternative therapy.

SUMMARY:

A high index of suspicion and awareness of the variable clinical presentations of neurosyphilis are essential to the approach to this treatable infection. Neurologists should be mindful of the limitations of serologic testing in the diagnosis of neurosyphilis and exercise clinical judgment to determine the likelihood of the diagnosis.

KEY POINTS

- Symptomatic neurosyphilis can occur at any stage of syphilis and, in fact, is now diagnosed most commonly in early syphilis.
- Although the syphilis epidemic in the United States is centered on young men who have sex with men, syphilis rates are on the rise in women and newborns.
- The prevalence of neurosyphilis is higher in men, particularly men who have sex with men, along with people with HIV infection.
- In early neurosyphilis, the CSF, meninges, and cerebral blood vessels are typically affected, leading to syphilitic meningitis and meningovascular disease, whereas late forms of neurosyphilis tend to cause injury to the brain and spinal cord parenchyma.
- Patients with symptomatic early neurosyphilis typically present with signs and symptoms of a meningitis (eg, headache, photophobia, neck stiffness, confusion) with or without cranial nerve involvement.
- Red flags that should raise the suspicion for meningovascular syphilis include stroke with concurrent or preceding symptoms of meningitis or encephalitis and stroke in young, sexually active individuals, especially in the absence of traditional cerebrovascular risk factors.

- Late forms of neurosyphilis (eg, tabes dorsalis and general paresis) are much less common in the era of penicillin.
- The classic presentation of tabes dorsalis, which usually occurs decades after primary infection, is a sensory gait ataxia with profoundly impaired proprioception, diminished reflexes, bowel and bladder dysfunction, and lancinating pains in the abdomen and extremities.
- General paresis is a chronic encephalitic form of neurosyphilis that presents with neuropsychiatric symptoms years to decades after primary infection.
- All patients with neurosyphilis should have evidence of current or previous syphilis with a reactive serum treponemal test.
- Serologic testing for syphilis is divided into nontreponemal and treponemal tests. Both types of tests, one as an initial screen followed by the other as a confirmatory test, are required to make a presumptive diagnosis of syphilis.
- The sensitivity of nontreponemal and treponemal testing varies by stage of syphilis.
- Serum false-positive nontreponemal tests, which are usually low titer (less than 1:8) can be seen in a variety of clinical situations, including in HIV infection, autoimmune disorders, pregnancy, and injection drug use.
- Nontreponemal test results are reported as a titer that correlates with disease activity. A minimum fourfold decrease in titer, which represents a change of two dilutions (eg, from 1:32 to 1:8), is one criterion used to demonstrate a successful response to treatment.
- Treponemal tests typically remain positive for life, even after appropriate treatment, making them less specific for active infection.
- The probability of neurosyphilis in people with serodiscordant serologies (ie, reactive serum treponemal test with a nonreactive RPR) is thought to be low overall.
- The CSF pleocytosis in early neurosyphilis tends to be more robust than in late neurosyphilis.
- Although reports of "burned out" tabes dorsalis with normal CSF have been described, as has normal CSF in a relatively high proportion of patients with general paresis in modern case series, this clinical scenario should be viewed as atypical for neurosyphilis.
- The high specificity but variable sensitivity of the CSF Venereal Disease Research Laboratory (VDRL) makes it a clinically informative test when reactive, whereas a nonreactive test does not exclude the diagnosis of neurosyphilis.
- CSF treponemal tests are less specific than the VDRL and do not distinguish between previously treated neurosyphilis and active infection.
- If the CSF VDRL is nonreactive in a patient for whom the clinical suspicion for neurosyphilis is high, obtaining a CSF treponemal assay is a reasonable next step.
- High-dose IV penicillin G for 10 to 14 days is the treatment of choice for neurosyphilis. IV ceftriaxone 2 grams daily may be an acceptable alternative therapy, especially for those with a penicillin allergy.
- Patients with early neurosyphilis are more likely to respond to treatment than those with late neurosyphilis, both in terms of clinical recovery and resolution of CSF abnormalities.

ARTICLE 10: NEUROLOGIC COMPLICATIONS OF LYME DISEASE

Karen L. Roos, MD, FAAN. Continuum (Minneap Minn). August 2021;
27 (4 Neuroinfectious Disease):1040–1050.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the symptomatology, diagnosis, and treatment of neuroborreliosis.

RECENT FINDINGS:

The most recent guidelines for the diagnosis and treatment of Lyme disease were published in 2020 by the Infectious Diseases Society of America, the American Academy of Neurology, and the American College of Rheumatology.

SUMMARY:

The most common neurologic complications of Lyme disease are cranial neuritis (most often a unilateral or bilateral facial nerve palsy), meningitis, and radiculoneuritis/mononeuropathy multiplex. Testing for Lyme disease begins with an enzyme-linked immunosorbent assay (ELISA). If the ELISA is positive or borderline, Western blots should be performed for both IgM and IgG antibodies. As a general rule, in infectious diseases, an IgM antibody response is followed by an IgG antibody response. A central nervous system infection has either a CSF pleocytosis or pathogen-specific intrathecal antibody production. Lyme meningitis, cranial neuropathy, radiculoneuropathy, or other peripheral nervous system manifestations are treated with oral doxycycline or IV ceftriaxone, cefotaxime, or penicillin G. No additional antibiotic therapy is indicated for patients with posttreatment Lyme disease syndrome or patients with concern for chronic Lyme disease with no evidence of previous or current Lyme infection.

KEY POINTS

- In North America, only one spirochete in the genus *Borrelia* causes Lyme disease, *Borrelia burgdorferi.*
- The most common neurologic complications of Lyme disease are cranial neuritis (most often cranial nerve VII), meningitis, and radiculoneuritis.
- An *Ixodes* tick typically must remain attached for 24 to 48 hours to transmit *Borrelia* to the host.
- The initial sign of infection with *Borrelia burgdorferi* is a nonpruritic targetoid skin lesion called *erythema migrans* that develops at the site of the tick bite.
- The Centers for Disease Control and Prevention recommends a two-step serologic testing procedure for Lyme disease. First, an enzyme-linked immunosorbent assay (ELISA) for antibodies to *B. burgdorferi* should be obtained. If the ELISA is negative, the patient does not have Lyme disease. If the ELISA is positive or borderline, a Western blot for both IgM and IgG antibodies is performed.
- The CSF to serum antibody index is used to determine if intrathecal production of antibodies to *Borrelia* has occurred.
- Doxycycline is not recommended in pregnant women, women who are breast-feeding, and children younger than 8 years of age, although a short course of doxycycline is not likely to stain teeth.
- No rationale exists for managing posttreatment Lyme disease syndrome with long-term antibiotic therapy; convincing biological and clinical evidence is lacking for the existence of chronic *B. burgdorferi* infection after the recommended treatment regimens for Lyme disease are completed.
- Lyme disease IgM Western blots have a high false-positive rate and must be followed by IgG testing.

ARTICLE 11: NEUROLOGIC MANIFESTATIONS OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 INFECTION

Avindra Nath, MD. Continuum (Minneap Minn). August 2021;
27 (4 Neuroinfectious Disease):1051–1065.

ABSTRACT

PURPOSE OF REVIEW:

This article describes the spectrum of neurologic complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, their underlying pathology and pathogenic mechanisms, gaps in knowledge, and current therapeutic strategies.

RECENT FINDINGS:

COVID-19 is the clinical syndrome caused by the novel coronavirus SARS-CoV-2. It can affect the entire neuraxis, and presentations in the acute phase are variable, although anosmia is a common manifestation. Encephalopathy is common in patients who are hospitalized and is often associated with multiorgan involvement. Immune-mediated encephalitis is probably underrecognized; however, viral encephalitis is rare. Other manifestations include stroke, seizures, myelitis, and peripheral neuropathies, including Guillain-Barré syndrome, which sometimes has atypical manifestations. Treatment is symptomatic, and immunotherapies have been used successfully in some patients. Long-term complications include dysautonomia, exercise intolerance, malaise, sleep disturbances, cognitive impairment, and mood disorders.

SUMMARY:

Neurologic manifestations of COVID-19 may occur in the acute setting and may be independent of respiratory manifestations. Immune-mediated syndromes and cerebrovascular complications are common. Large populations of patients are expected to have long-term neurologic complications of COVID-19, many of which may emerge only after recovery from the acute illness.

KEY POINTS

- Coronaviruses are enveloped viruses with a positive-sense single-stranded RNA genome.
- Although effective vaccines have been developed for COVID-19 and are being distributed, millions of people will have long-term complications from the infection, some of which will be neurologic.
- Myalgia and fatigue are seen in about 50% of patients with COVID-19 and may persist even after recovery from the other symptoms. Headache occurs in 8% of patients.
- Anosmia and ageusia may be heralding manifestations of COVID-19.
- Mortality in COVID-19 is higher with advanced age and underlying comorbidities, including diabetes, cardiac and respiratory disorders, and immunosuppressed states.
- The neurologic manifestations of COVID-19 can be broadly divided into two categories: those that occur during the acute phase of the infection (parainfectious complications) and the postviral manifestations that occur following the acute phase (post–acute phase complications).
- Anosmia and ageusia are the most common early symptoms of COVID-19 infection. Nearly 40% to 60% of patients develop loss of smell, and, upon testing, nearly 90% have alteration of smell.
- Encephalopathy is the most common neurologic manifestation in patients who are hospitalized with COVID-19, with nearly one-third of patients who are hospitalized developing encephalopathic symptoms ranging from alteration in consciousness to delirium and seizures.
- Direct viral invasion of the brain in COVID-19 is rare.
- Acute necrotizing hemorrhagic encephalopathy is a feared complication of several viruses, most notably influenza. It is thought to result from cytokine release syndrome rather than direct viral invasion of brain parenchyma, which is especially salient given the propensity of SARS-CoV-2 for causing similar cytokine storms in the lungs.
- Acute disseminated encephalomyelitis is a rare demyelinating disease; it is often postviral and is more common in children than adults. However, in patients with COVID-19, it has been described mainly in adults.
- Patients with COVID-19 develop a hypercoagulable syndrome causing both arterial and venous occlusions in the brain vasculature. Ischemic stroke, hemorrhagic stroke, and cerebral venous sinus thrombosis have all been reported.

- Cerebrovascular complications of COVID-19 are likely due to altered coagulation pathways as demonstrated by observations of elevated D-dimer, increased prothrombin time and activated partial thromboplastin time, and disseminated intravascular coagulation.
- Variants of Guillain-Barré syndrome seem to be more common when associated with preceding COVID-19 infection.
- Myositis can occur at any time during the course of COVID-19; it can be quite extensive and associated with myalgia and muscle weakness that can persist after recovery of the other symptoms.
- Long-haul COVID is a distinct postviral syndrome that is independent of the severity of the acute phase of the illness. This syndrome can emerge even in patients who have relatively mild symptoms during the acute phase.
- A distinction needs to be made between patients with long-haul COVID and patients who were hospitalized, who often have a large number of lingering symptoms from respiratory disease, other organ damage, and prolonged hospitalization.

ARTICLE 12: NEUROLOGIC INFECTIONS IN PATIENTS ON IMMUNOMODULATORY AND IMMUNOSUPPRESSIVE THERAPIES

Pria Anand, MD. Continuum (Minneap Minn). August 2021;
27 (4 Neuroinfectious Disease):1066–1104.

ABSTRACT

PURPOSE OF REVIEW:

Both broadly immunosuppressive medications and selective immunomodulatory agents that act on particular components of the immune system are increasingly used in the treatment of neurologic and non-neurologic diseases. These therapies predispose patients to particular infections, some of which may affect the nervous system. Therefore, familiarity with the clinical and radiologic features of neurologic infections associated with specific immunomodulatory therapies is of importance for the practicing neurologist. This article reviews these neuroinfectious conditions, as well as other neurologic complications unique to transplant recipients and other patients who are immunocompromised.

RECENT FINDINGS:

Diagnosis of infectious pathogens in patients who are immunocompromised may be particularly challenging because a decreased immune response can lead to atypical imaging or laboratory findings. Next-generation sequencing and other novel diagnostic modalities may improve the rate of early identification of neurologic infections in patients who are immunocompromised and ultimately ameliorate outcomes in this vulnerable population.

SUMMARY:

A broad range of bacterial, viral, fungal, and parasitic infections of the nervous system can complicate solid organ and hematopoietic cell transplantation as well as other forms of immunocompromise. In addition to neurologic infections, such patients are at risk of neurotoxic and neuroinflammatory complications related to immunomodulatory and immunosuppressive therapies. Early recognition of infectious and noninfectious complications of immunocompromise is essential to guide appropriate treatment, which can include antimicrobial

therapy and, in some cases, withdrawal of the predisposing medication with a transition to an alternative regimen.

KEY POINTS

- The term *immunocompromise* spans the effects of both broadly immunosuppressive therapies used to treat autoimmune and neoplastic conditions (eg, cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, and tacrolimus) and immunomodulatory therapies such as natalizumab or fingolimod, which act selectively on part of the immune system.
- Although immunosuppressive therapies predispose patients to a wide range of opportunistic infectious pathogens, the risk profile in patients on immunomodulatory therapies may be limited to specific pathogens or infectious syndromes.
- The immunosuppressive or immunomodulatory effects of a medication may persist for weeks or even months after it is discontinued.
- When neurologic infections that can also affect immunocompetent hosts occur in patients who are immunocompromised, atypical clinical presentations, imaging, and laboratory findings may be seen.
- Early recognition of infectious and noninfectious complications of immunocompromise is essential to guide appropriate treatment, which can include antimicrobial therapy and, in some cases, withdrawal of the predisposing medication with a transition to an alternative regimen.
- Neurologic complications after transplantation affect as many as 11% to 19% of hematopoietic stem cell transplant recipients and approximately one-third of solid organ transplant recipients.
- Among solid organ transplant recipients, liver transplant recipients, particularly those with fulminant hepatic failure, often have serious medical problems at the time of their transplant and may be at higher risk of early central nervous system infections, whereas heart, intestinal, and pancreas transplant recipients are chronically immunosuppressed and may be most prone to late infectious complications.
- Immune reconstitution inflammatory syndrome, an exuberant and dysfunctional host inflammatory response to a recent infection triggered by immune recovery, can involve the central nervous system in both solid organ and hematopoietic cell transplant recipients. In the latter population, central nervous system immune reconstitution inflammatory syndrome may occur during engraftment, but it has also been reported later after transplant and even several months after discontinuation of immunosuppression.
- On MRI, large, confluent T2-hyperintense lesions and deep gray matter lesions were more frequent in patients with progressive multifocal leukoencephalopathy (PML) than in patients with multiple sclerosis, whereas crescentic cerebellar lesions were seen only in patients with PML.
- Ocrelizumab, a humanized anti-CD20 monoclonal antibody used in the treatment of multiple sclerosis, has also been associated with PML, primarily in patients previously treated with rituximab, fingolimod, or natalizumab, although a case of ocrelizumab-associated PML was described in 2020 in the setting of lymphopenia in a patient with primary progressive multiple sclerosis who had not received previous immunomodulatory or immunosuppressive medication.
- Risk factors for the development of PML in patients on natalizumab include elevated serum levels of anti–JC virus antibodies, the use of immunosuppressant or immunomodulatory therapies before natalizumab initiation, and the duration of natalizumab treatment, with a median time from treatment initiation to onset of PML symptoms of 25 months.
- In patients who have an anti–JC virus antibody index of 0.9 or greater, natalizumab should be discontinued in favor of an alternative disease-modifying therapy at 24 months because of the increasing risk of PML.
- Although meningococcal vaccination is recommended for all patients before initiating eculizumab, infections with nontypable strains not included in the vaccine have been reported in vaccinated patients, and antibiotic prophylaxis with penicillin or a macrolide is warranted for the duration of therapy.
- Treatment with alemtuzumab carries a risk of both autoimmune conditions and opportunistic central nervous system infections with herpesviruses, *Listeria*, and *Nocardia*.
- Patients who are immunocompromised represent one-fourth of patients with *Streptococcus pneumoniae*

bacterial meningitis, and transplant recipients and others with impaired cell-mediated immunity are at risk of fungal and mycobacterial meningitis.

- India ink staining has been largely supplanted by serum and CSF cryptococcal antigen, which has sensitivity and specificity greater than 97%.
- Ischemic strokes are a significant cause of long-term morbidity in tuberculous meningitis and affect 25% to 50% of infected patients.
- Infectious etiologies of encephalitis unique to patients who are immunosuppressed include viruses such as cytomegalovirus, human herpesvirus 6, BK virus, and varicella-zoster virus.
- In patients who do not respond to antiviral therapy, transplant guidelines regarding general management of cytomegalovirus infection suggest that dose reduction of immunosuppressive therapies may be beneficial.
- Although the incidence of CMV encephalitis in patients who are immunocompromised has been reduced in the setting of ganciclovir prophylaxis, the mortality remains high because of antiviral drug resistance and reduced efficacy of antiviral therapy due to poor CSF penetration.
- Human herpesvirus 6 reactivation in the posttransplant population may present with a classic limbic encephalitis, also sometimes called *posttransplant acute limbic encephalitis*.
- Given the involvement of the limbic system and the possibility of electrolyte depletion secondary to foscarnet therapy, patients with posttransplant acute limbic encephalitis are at high risk of seizures, and clinicians should maintain a low threshold for EEG monitoring.
- Clinical presentations of varicella-zoster virus encephalitis are heterogeneous, and the syndrome may present with concomitant cerebellitis, cranial neuropathies, meningitis, myelitis, or vasculopathy.
- In patients who are immunocompromised, varicella-zoster virus vasculopathy more often affects small vessels, whereas in older patients who are immunocompetent, it typically causes a large vessel vasculopathy several weeks after trigeminal zoster.
- Varicella-zoster virus DNA in the CSF is highly specific and helpful if positive, but it has only 30% sensitivity in patients with isolated vasculopathy.
- Visual processing deficits including homonymous hemianopia, visual agnosia, visual hallucinations, hemineglect, and other visuospatial deficits may be the presenting symptom in 20% of patients with PML and occur at some point during the disease in up to half of patients.
- In some patients who are immunocompromised, JC virus may cause a granule cell neuronopathy, characterized by infection of the granule cells of the cerebellum and presenting with slowly progressive cerebellar atrophy without white matter lesions.
- Patients who discontinue or reduce immunosuppressive medications are at risk of developing progressive multifocal leukoencephalopathy–immune reconstitution inflammatory syndrome, particularly patients on natalizumab, who can develop the syndrome weeks or even months after discontinuing natalizumab.
- Early, small reports have suggested favorable outcomes in patients with PML treated with immune checkpoint inhibitors such as pembrolizumab or nivolumab and in those treated with virus-specific cytotoxic T cells.
- *Toxoplasma gondii* has a predilection for the basal ganglia and may cause hyperkinetic movement disorders.
- The majority of patients with toxoplasmosis have radiographic and clinical improvement after 2 weeks of empiric treatment; in patients who show no improvement, biopsy may be necessary to evaluate for primary central nervous system lymphoma.
- In a study of patients who are immunocompetent and have primary central nervous system lymphoma, immunoglobulin heavy chain gene rearrangement studies and cytology were frequently found to be discordant, suggesting that the two tests may be complementary in making a diagnosis of primary central nervous system lymphoma.
- Primary central nervous system posttransplant lymphoproliferative disorder may occur as early as 6 weeks after transplantation but more typically develops several years after transplantation, with a median time to occurrence of 4 to 5 years.
- Patients who are immunocompromised are at particular risk of fungal brain abscesses, with 86% of abscesses in solid organ transplant recipients and 92% of brain abscesses in bone marrow transplant recipients

resulting from fungal pathogens including *Aspergillus*, *Mucor, Candida*, *Nocardia*, and *Cryptococcus* (cryptococcomas).

- Clinical findings of central nervous system aspergillosis in several large series included nonspecific manifestations such as fever, altered mental status, hemiplegia, and seizures, whereas headache, nausea, vomiting, and meningismus occurred more rarely.
- Early tissue diagnosis followed by surgical excision of the necrotic tissue and aggressive antifungal therapy with amphotericin B can reduce morbidity and mortality from cerebral mucormycosis.
- Neuroimaging in patients with *Nocardia* infection shows either single or multiple ring-enhancing lesions consistent with cerebral abscesses in the vast majority of cases, and rare cases may show meningeal enhancement as well.
- Prognosis for patients with granulomatous amebic encephalitis remains poor and the disease is fatal in more than 90% of cases.
- Varicella-zoster virus may cause a myelopathy in patients on natalizumab and other immunomodulatory agents through several mechanisms, including varicella-zoster virus vasculopathy causing spinal cord infarction, direct viral infection of the spinal cord, or a postinfectious inflammatory process.
- Cytomegalovirus polyradiculitis or polyradiculomyelitis occurs in patients who are severely immunocompromised, including hematopoietic cell and solid organ transplant recipients, typically more than 100 days after transplant.
- MRI in patients with Elsberg syndrome (herpes simplex virus-2 myeloradiculitis) typically shows T2 hyperintensities of the cord and contrast enhancement of both the spinal cord and nerve roots, sometimes with cervicothoracic extension.
- Next-generation sequencing of the CSF is a promising approach for unbiased diagnostic evaluation and organism identification in central nervous system infections and may be used more commonly in clinical practice in the coming years.

ARTICLE 13: CONGENITAL INFECTIONS OF THE NERVOUS SYSTEM

Payal Patel, MD. Continuum (Minneap Minn). August 2021;
27 (4 Neuroinfectious Disease):1105–1126.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of congenital infections affecting the central nervous system (CNS), discussing the epidemiology, clinical features, diagnostic tools, and preventive and treatment measures for a variety of pathogens with the potential to infect the developing fetal brain.

RECENT FINDINGS:

Contrary to popular belief, many congenital CNS infections are preventable and treatable. Treatment options exist for congenital cytomegalovirus, human immunodeficiency virus (HIV), herpes simplex virus, toxoplasmosis, and syphilis, although the efficacy of these treatments and the populations that may benefit from treatment are variable. Zika virus has recently emerged as a pathogen affecting the fetal brain, and new data suggest that the pathogenesis of Zika virus involves direct infection of neuronal progenitor cells leading to destruction of CNS tissue. The incidence of congenital syphilis has been increasing in the United States over the past

decade as a direct result of new syphilis cases among adults and poor access to adequate maternal health care.

SUMMARY:

Congenital CNS infections often result in significant neurologic morbidity in pediatric patients. Therefore, early identification of maternal illness and implementation of preventive measures are important in improving developmental outcomes and quality of life.

KEY POINTS

- Many congenital infections affecting the central nervous system (CNS) are preventable and treatable. Therefore, anticipatory guidance regarding preventive measures and early detection are important.
- Transmission of congenital acquisition of infections most often occurs transplacentally but may also occur as infants pass through the birth canal or may be acquired through breast-feeding.
- CNS involvement is common in congenital toxoplasmosis infection presenting as macrocephaly, cerebral calcifications, hearing loss, and seizures.
- If in utero toxoplasmosis exposure is suspected, spiramycin can be administered in the first or early second trimester, or pyrimethamine/sulfadiazine or leucovorin can be given in the late second or third trimester. Treatment with antimicrobial therapy should be continued for 1 year after delivery and has been shown to improve neurologic outcomes in neonates born with congenital toxoplasmosis.
- Positive cytomegalovirus (CMV) titers do not indicate protection against acquisition of the virus by pregnant women, and transmission to their fetus, given that multiple strains of CMV exist globally, and reactivation of latent disease can occur.
- Cerebral manifestations of congenital CMV infection include intracranial calcifications, hydranencephaly, atrophy, schizencephaly, and cerebellar hypoplasia. Of the 10% of infants who present with symptomatic CMV disease at birth, one-third will experience sensorineural hearing loss and two-thirds will have persistent neurologic deficits.
- Valganciclovir has been shown to improve neurologic outcomes in infants born with symptomatic congenital CMV infection.
- Cognitive impairment in children with human immunodeficiency virus (HIV) usually encompasses multiple domains and is more severe in children with a history of acquired immunodeficiency syndrome (AIDS)-defining illnesses.
- Early identification and initiation of treatment for children living with perinatally acquired HIV may be neuroprotective, particularly for the prevention of opportunistic CNS infections.
- Classically, herpes simplex virus (HSV) encephalitis affects the temporal lobe, but neonates often present with diffuse cerebral involvement.
- In neonates with HSV encephalitis, CSF HSV polymerase chain reaction (PCR) has a 75% positive predictive rate with most false negatives occurring early (within 24 hours of onset) in the disease process. Therefore, if HSV infection is suspected based on clinical suspicion, acyclovir should be started immediately, and repeat CSF testing should be performed within the next 24 to 48 hours.
- The rate of CNS morbidity after HSV encephalitis remains high (two-thirds of infants with a history of HSV encephalitis experience developmental delay) despite adequate treatment.
- Five features are considered characteristic of congenital Zika syndrome and distinguish congenital Zika syndrome from other congenital CNS infections: (1) severe microcephaly with partially collapsed skull, (2) thin cerebral cortex with subcortical calcifications, (3) macular scarring and focal pigmentary retinal mottling, (4) congenital contractures, and (5) marked early hypertonia.
- False-positive rates are high for serum Zika titers given cross-reactivity with other flaviviruses. These viruses often coexist in the same geographic area. Therefore, accurate prevalence data are difficult to ascertain after endemic outbreaks.
- Neurologic manifestations of congenital syphilis present late after decades of untreated infection and include meningitis, infarcts, hydrocephalus, and hearing loss.

- **Congenital syphilis is diagnosed if one or more of the following are true in infants with reactive serum rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL): (1) clinical signs characteristic of congenital syphilis, (2) serum quantitative nontreponemal titers that are fourfold higher than maternal titers, and (3) a positive dark field test or PCR of lesions, placenta, or infant bodily fluids.**

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NEUROLOGY OF PREGNANCY

ARTICLE 1: PREGNANCY MANAGEMENT IN MULTIPLE SCLEROSIS AND OTHER DEMYELINATING DISEASES

Riley M. Bove, MD; Maria K. Houtchens, MD. Continuum (Minneap Minn). February 2022; 28 (1 Neurology of Pregnancy):12–33.

ABSTRACT

PURPOSE OF REVIEW:

Multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSDs) are chronic autoimmune demyelinating conditions of the central nervous system often diagnosed in women of childbearing age. Therefore, safe family planning, pregnancy, and postpartum management are important considerations for many patients with MS or NMOSD.

RECENT FINDINGS:

Many patients with MS can safely become pregnant and remain well throughout pregnancy and the postpartum period with guidance from specialists on treatment planning. During pregnancy, women with NMOSD may face some increased risk of both neurologic and obstetric complications. Recent attention has focused on evaluating the safety of pharmacologic agents during pregnancy and breastfeeding. Unfortunately, care disparities remain common in both MS and NMOSD, and recovery of function is often not optimally managed in the postpartum period.

SUMMARY:

This article reviews the current state of knowledge on peripartum management in these neurologic conditions and offers practical considerations and case studies. When caring for women with MS and NMOSD of childbearing potential, treatment planning is important to optimize outcomes in both patient and newborn.

KEY POINTS

- Many patients with multiple sclerosis (MS) can safely go through pregnancy and the postpartum period.
- In patients with more serious and active neurologic disease and patients who experience health care disparities with poor access to neurologic or obstetric care, maternal pregnancy and postpartum outcomes are at risk.
- In MS, postpartum MRI may reveal elevated inflammatory activity even in women deemed clinically stable and is a useful evaluation tool to decide on treatment selection.

- Women with neuromyelitis optica spectrum disorder (NMOSD) face elevated risk of inflammatory activity both during and after pregnancy relative to prepartum and potentially greater pregnancy complications than the general population.
- For both MS and NMOSD, there is a trend to use anti-CD20 therapies before pregnancy, which can provide clinical stability before conception, during pregnancy, and, potentially, postpartum.
- Intrapartum and postpartum outcomes in patients with MS or NMOSD are linked to disease stability for a year preceding pregnancy.
- Asking patients "Would you like to become pregnant in the next year?" allows for a screening assessment of the patient's family planning needs to help guide the health care provider's treatment and care plan.
- Any form of contraception is safe for patients with MS or NMOSD.
- In patients with demyelinating diseases, if pregnancy is not achieved after 3 to 6 months of optimal conception attempts, referral to a fertility clinic should be considered.
- Many disease-modifying therapies are used in MS. A thorough understanding of prepregnancy washout and safety in pregnancy exposure recommendations is needed to optimize MS management.
- To ensure complete elimination of products before conception, typically waiting at least 5 maximal half-lives is recommended (with the exception of teriflunomide, for which an accelerated washout protocol is recommended).
- If natalizumab is continued into the mid to late third trimester, hematologic screening of the newborn is necessary because of an increased risk of transient thrombocytopenia and anemia in some newborns.
- MRI without gadolinium can be obtained and compared to the preconception MRI in cases of new neurologic symptoms in pregnancy.
- Methylprednisolone, prednisone, and prednisolone are preferred in pregnancy as they are inactivated by placental 11-β-hydroxysteroid dehydrogenase and therefore do not enter the fetal circulation.
- Surveillance neuroimaging should be considered within the first few months postpartum to establish a new baseline.
- Comprehensive evaluation of women with MS and NMOSD is recommended early postpartum and should include gait, balance, bladder, bowel, mood, fatigue, cognition, strength, pain, social supports, and neuroimaging review.
- In MS, exclusive breastfeeding is protective against postpartum inflammatory activity.
- Safety data suggest that both first-line self-injectable therapies (glatiramer and interferon beta) and IgG monoclonal antibodies (such as ocrelizumab and rituximab) are reasonable to consider during breastfeeding.
- Women with MS and women with NMOSD may face disparities in their obstetric and neurologic care and outcomes. Care coordination between the two specialists is important.

ARTICLE 2: EPILEPSY AND PREGNANCY

Yi Li, MD, PhD; Kimford J. Meador, MD, FAAN, FAES, FRCPE. Continuum (Minneap Minn). February 2022; 28 (1 Neurology of Pregnancy):34–54.

ABSTRACT

PURPOSE OF REVIEW:

Seizure disorders are the most frequent major neurologic complication in pregnancy, affecting 0.3% to 0.8% of all gestations. Women of childbearing age with epilepsy require special care related to pregnancy. This article provides up-to-date information to guide practitioners in the management of epilepsy in pregnancy.

RECENT FINDINGS:

Ongoing multicenter pregnancy registries and studies continue to provide important information on issues related to pregnancy in women with epilepsy. Valproate poses a special risk for malformations and cognitive/behavioral impairments. A few antiseizure medications pose low risks (eg, lamotrigine, levetiracetam), but the risks for many antiseizure medications remain uncertain. Although pregnancy rates differ, a prospective study found no difference in fertility rates between women with epilepsy who were attempting to get pregnant and healthy controls. During pregnancy, folic acid supplementation is important, and a dose greater than 400 mcg/d during early pregnancy (ie, first 12 weeks) is associated with better neurodevelopmental outcome in children of women with epilepsy. Breastfeeding is not harmful and should be encouraged in women with epilepsy even when they are on antiseizure medication treatment.

SUMMARY:

Women with epilepsy should be counseled early and regularly about reproductive health. Practitioners should discuss the risks of various obstetric complications; potential anatomic teratogenicity and neurodevelopmental dysfunction related to fetal antiseizure medication exposure; and a plan of care during pregnancy, delivery, and postpartum. Women with epilepsy should also be reassured that the majority of pregnancies are uneventful.

KEY POINTS

- Although pregnancy rates differ, no difference in fertility rate is seen between women with epilepsy who are attempting to get pregnant and healthy controls (60.7% compared to 60.2%).
- Certain medications, including valproate and phenobarbital, have been linked to lower fertility, but these findings require further validation in a larger cohort.
- Patients treated with CYP3A4 enzyme-inducing antiseizure medications should consider alternative methods of contraception.
- Lamotrigine may require substantial titration when it is used in combination with oral hormonal contraceptives.
- Knowledge is limited regarding the interaction of oral contraceptives and some of the new antiseizure medications.
- Most women with epilepsy will not experience seizure frequency changes during pregnancy.
- The diagnosis of epilepsy alone should not be considered as an indication for cesarean delivery.
- The risk of gestational hypertension and preeclampsia may be slightly increased in women with epilepsy.
- The majority of women with epilepsy have uneventful pregnancies, and 90% of children born to women with epilepsy are healthy.
- The risk of major congenital malformations has been associated with first trimester antiseizure medication exposure, the dose and type of antiseizure medication (especially valproate), polytherapy, low folate concentrations, and low maternal level of education.
- The teratogenic risks for many antiseizure medications are uncertain. Valproate is the poorest choice of antiseizure medication based on the higher risk profile of both anatomic and behavioral teratogenicity. If used, the dose should be as low as possible.
- The impact of neuromodulation therapy on pregnancy outcomes is limited.
- Children born to women with epilepsy may have impaired cognitive development; the contributing factors include antenatal antiseizure medication exposure, frequent tonic-clonic seizures in pregnancy, low maternal IQ, and maternal education level.
- Women with epilepsy of childbearing potential should be taking folic acid 0.4 mg/d to 4 mg/d.
- Monitoring of antiseizure medication levels during pregnancy should be considered.
- The most marked decline in serum concentration of antiseizure medications in pregnancy is seen with lamotrigine, levetiracetam, and oxcarbazepine (decrease ranging from 40% to 70%). Carbamazepine and valproate have minimal decreases in serum concentration, usually 10% to 20%.
- Breastfeeding while taking antiseizure medication appears to be safe.

ARTICLE 3: NEUROMUSCULAR DISORDERS AND PREGNANCY

Janice M. Massey, MD, FAAN; Karissa L. Gable, MD. Continuum (Minneap Minn). February 2022; 28 (1 Neurology of Pregnancy):55–71.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of neuromuscular disorders in pregnancy, with a focus on diagnosis and management.

RECENT FINDINGS:

Neuromuscular disorders with issues that occur in pregnancy include conditions that are acquired (including autoimmune) or genetic; each requires a unique approach to management and treatment prepartum, peripartum, and postpartum. Guidance in the literature regarding management and treatment options is predominantly from case series and retrospective reviews. Treatment can be complex, particularly in autoimmune neuromuscular diseases, because of the risks of side effects of the treatments that may affect the patient and fetus.

SUMMARY:

This article summarizes expectations, diagnosis, and management for a wide range of neuromuscular disorders in pregnancy.

KEY POINTS

- Treatment of Guillain-Barré syndrome in pregnant women is similar to treatment in nonpregnant patients. Both IV immunoglobulin (IVIg) and plasma exchange are considered to be safe.
- Accurate diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy relies on clinical history, examination findings, and electrodiagnostic testing meeting European Federation of Neurological Societies/Peripheral Nerve Society criteria.
- IVIg, plasma exchange, or corticosteroids can be used in treatment of chronic inflammatory demyelinating polyradiculoneuropathy during pregnancy, and IVIg is most effective for multifocal motor neuropathy.
- If thiamine deficiency is suspected in pregnant women, treatment with vitamin repletion is recommended even while awaiting laboratory results for serum levels of vitamins as no significant harm exists in treatment. Treatment can be stopped if levels are found to be within normal limits.
- Pregnancy outcomes in women with Charcot-Marie-Tooth disease have been found to be similar to women without the disease.
- Supportive care is often all that is necessary for carpal tunnel syndrome in pregnancy. Resolution has variable timing.
- Recovery from idiopathic brachial plexopathy may be partial and can take months to years.
- Focal neuropathies associated with pregnancy often improve over time with supportive care.
- Recurrence of facial nerve palsy in future pregnancies is rare.
- Exacerbations of myasthenia gravis occur more often in the first trimester and postpartum.
- Preconception counseling is very important to select the appropriate medications for treatment of myasthenia gravis.
- It is typically advised not to initiate or stop steroid-sparing agents during pregnancy, except in unique circumstances, because of the potential risk of myasthenic exacerbations.
- It is recommended to use antiseizure medications rather than magnesium in the treatment of eclampsia in women with myasthenia gravis.

- It is recommended that women do not breastfeed while taking methotrexate or mycophenolate mofetil.
- Women with muscular dystrophies generally have good pregnancy outcomes.
- Rhabdomyolysis has not been reported during labor in patients with McArdle disease.
- Neonatal outcomes for babies born to women with spinal muscular atrophy are generally good.

ARTICLE 4: HEADACHE IN PREGNANCY AND LACTATION

Melissa Rayhill, MD, FAHS. Continuum (Minneap Minn). February 2022;
28 (1 Neurology of Pregnancy):72–92.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses the many tools available for the treatment of pregnant and postpartum patients with headache. Adequate treatment of headache is an essential part of good prenatal and postnatal care.

RECENT FINDINGS:

New therapies such as the calcitonin gene-related peptide monoclonal antibodies, lasmiditan, direct calcitonin gene-related peptide antagonists, and neuromodulation devices are available for the treatment of headache. This article contextualizes these new therapies in practice as they relate to the treatment of migraine in pregnancy and lactation.

SUMMARY:

Headache is common in pregnancy, and neurologists should be prepared to care for pregnant patients with headache. Preconception counseling is an important part of providing safe care to patients of childbearing potential with headache. Identifying potentially dangerous secondary headache syndromes during pregnancy and the puerperium is also essential. The repertoire of available acute and preventive headache treatments is expanding. It is important to discuss the effectiveness and safety of these therapies in the context of individual patient circumstances during pregnancy and lactation in coordination with the patient's obstetric team.

KEY POINTS

- In women between the ages of 30 and 39, the prevalence of migraine can be as high as 27%, which is about 3 times higher than the prevalence in men in the same age range.
- It is prudent to discuss any potential teratogenicity of medications at the time they are prescribed, regardless of the patient's current reproductive plan, as plans may unexpectedly change with time.
- Patients taking monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) activity should be advised to stop injections approximately 5 to 6 months before conception.
- The diagnosis of headache is guided by the *International Classification of Headache Disorders, Third Edition.*
- Women with migraine with aura may be less likely to improve in pregnancy, and aura can present for the first time during pregnancy.
- One study showed that the most common secondary headache syndromes in patients who presented to acute care with severe headache were caused by hypertensive disorders of pregnancy. In this study, a lack of headache history was associated with a nearly fivefold risk of secondary headache, and elevated blood pressure was associated with a 17-fold risk of secondary headache.
- Warning signs for secondary headache include fever, papilledema or other abnormal neurologic examination findings, thunderclap headache onset, postural provocation, and a history of immunosuppression.

- Compared to women without a history of migraine, women with a history of migraine are more likely to have a secondary cause of headache, such as cerebral venous thrombosis, pregnancy-associated stroke, or preeclampsia.
- Preeclampsia is quite common, occurring in 3% to 5% of pregnancies.
- Pituitary apoplexy characteristically presents with acute or thunderclap headache, and it can lead to bitemporal hemianopia and hypotension.
- Intracranial hypotension usually presents with postpartum headache that progressively worsens throughout the day and usually worsens with upright posture.
- The US Food and Drug Administration previously categorized medications based on a hierarchical scale from A (safest) to X (contraindicated in pregnancy), but these categories were discontinued in 2015.
- To make an accurate assessment of headache burden, it is essential to ask patients about days of complete headache freedom.
- Given the natural improvement in headache that many patients experience with pregnancy, it may be reasonable to monitor their headaches without preventive therapy early on to see if preventive therapy is indeed required.
- All patients with headache may benefit from a discussion of lifestyle modifications, such as sleep optimization, stress management, adequate hydration, and regular healthy meals.
- Given the lower levels of CGRP in patients with preeclampsia compared to normotensive individuals, most headache specialists believe avoidance of CGRP monoclonal antibodies in pregnancy is warranted.
- Despite its efficacy, topiramate should be avoided during pregnancy given the known risks of cleft palate and lip, intrauterine growth restriction, and metabolic acidosis.
- Feverfew is contraindicated for migraine prevention in pregnancy as it can provoke uterine contractions and spontaneous miscarriage.
- Reviewing prescription medications for safety in pregnancy is routine, but clinicians must not forget to specifically ask about over-the-counter medication and supplement use.
- The goal of acute therapy for headache is to restore function and resolve pain and other associated symptoms within 2 hours. If a treatment does not reliably help within 2 hours, other options should be explored.
- Butalbital-containing medications and opiates are not recommended for the treatment of migraine in the general population; this applies to both pregnant and nonpregnant patients.
- The new direct CGRP receptor antagonists ubrogepant and rimegepant and the new serotonin-1F agonist lasmiditan should be avoided in pregnancy given the paucity of available evidence about their safety in pregnancy.
- Neuromodulation devices should be theoretically safe to use in pregnant women with migraine or cluster headache, but data are limited.
- If headache improved during pregnancy, some women enjoy a continued improvement during lactation and may not require immediate resumption of their prior preventive therapies.
- Eletriptan has the lowest milk to plasma ratio of the triptans, and sumatriptan has the most safety data available for breastfeeding.
- Ubrogepant, rimegepant, and lasmiditan should be avoided during lactation given the absence of available data.
- The CGRP monoclonal antibodies have not been studied in lactation. However, given their large size, it is unlikely that they will pass through into breast milk, and some headache specialists are now considering their use when treating particularly disabling and intractable migraine.

ARTICLE 5: MATERNAL STROKE ASSOCIATED WITH PREGNANCY

Eliza C. Miller, MD, MS. Continuum (Minneap Minn). February 2022;
28 (1 Neurology of Pregnancy):93–121.

ABSTRACT

PURPOSE OF REVIEW:

This article summarizes current knowledge of the epidemiology, pathophysiology, prevention, and treatment of cerebrovascular disease in pregnant and postpartum women.

RECENT FINDINGS:

Stroke is a leading cause of maternal morbidity and mortality, and most fatal strokes are preventable. Adaptive physiologic changes of pregnancy, including hemodynamic changes, venous stasis, hypercoagulability, and immunomodulation, contribute to increased maternal stroke risk. The highest-risk time period for maternal stroke is the immediate postpartum period. Migraine and hypertensive disorders of pregnancy, including gestational hypertension and preeclampsia, are major risk factors for maternal stroke. Adverse pregnancy outcomes, including gestational hypertension, preeclampsia, preterm delivery, and fetal growth restriction, are important risk factors for cerebrovascular disease later in life.

SUMMARY:

Many catastrophic maternal strokes could be avoided with targeted prevention efforts, early recognition of warning signs, and rapid evaluation of neurologic symptoms. Neurologists play a central role in the care of pregnant patients with cerebrovascular disease, whether acute or chronic, and should be familiar with the unique and complex physiology of pregnancy and its complications, particularly hypertensive disorders of pregnancy.

KEY POINTS

- The incidence of stroke in women during pregnancy and the postpartum period is approximately triple the incidence of stroke in nonpregnant women of similar age.
- The majority of maternal strokes occur postpartum, often after discharge home following delivery, and up to half are hemorrhagic.
- Migraine and hypertensive disorders of pregnancy, including gestational hypertension and preeclampsia, are important risk factors for maternal stroke.
- The adaptive physiologic changes of pregnancy, including hemodynamic changes, venous stasis, hypercoagulability, and immunomodulation, can contribute to increased stroke risk.
- Common pregnancy-associated stroke mechanisms include cardioembolism, cervical artery dissection, cerebral venous thrombosis, cerebral vasospasm or subarachnoid hemorrhage due to reversible cerebral vasoconstriction syndrome, and hypertensive intracerebral hemorrhage, often in association with posterior reversible encephalopathy syndrome.
- Despite the term *reversible* in their names, reversible cerebral vasoconstriction syndrome and posterior reversible encephalopathy syndrome can lead to severe disability or death if complicated by ischemic stroke or intracerebral hemorrhage.
- Pregnant or postpartum women who develop cerebral venous thrombosis should be evaluated for underlying hypercoagulable disorders; pregnancy should not be assumed as the sole cause.
- Migraine is associated with increased risk of preeclampsia and a 15-fold increase in risk of maternal stroke.

- Proteinuria is no longer required for the diagnosis of preeclampsia; new severe headache or neurologic symptoms are considered disease-defining in the presence of new or worsening hypertension.
- Hypertensive disorders of pregnancy, including gestational hypertension, preeclampsia, and chronic hypertension with superimposed preeclampsia, affect up to 1 in 10 pregnancies.
- Intracerebral hemorrhage is a leading cause of maternal mortality in patients with preeclampsia, and frequently, no underlying vascular lesion is identified.
- No evidence shows that cesarean delivery decreases the risk of rupture of cerebrovascular lesions in pregnancy.
- In selected patients with moyamoya, particularly those with recurrent transient ischemic attacks or decreased regional flow on brain imaging, surgical revascularization before pregnancy may decrease the risk of peripartum neurologic complications.
- Women with elevated risk for maternal stroke should be counseled on stroke signs and symptoms and warned that the postpartum period is the highest-risk time point for stroke.
- A history of stroke or cerebrovascular disease is not, in itself, an indication for cesarean delivery. Delivery planning should be based on obstetric considerations in most cases.
- Red flag headache features in a pregnant or postpartum woman, such as lack of headache history, elevated blood pressure, very severe pain, or focal neurologic deficits, should prompt urgent neurologic evaluation.
- When a pregnant woman presents with acute disabling neurologic deficits, CT is usually the fastest and most accessible imaging modality and thus is preferred. CT angiography should be performed in pregnant patients with symptoms concerning for large vessel occlusion.
- Current guidelines for acute ischemic stroke do not consider pregnancy to be a contraindication to IV thrombolysis if the deficits are disabling and the bleeding risks are acceptable.
- Poststroke depression may be exacerbated by the pregnant or postpartum state, particularly if the pregnancy had an adverse outcome, and early involvement of psychiatry is recommended.
- Adverse pregnancy outcomes, including hypertensive disorders of pregnancy, preterm delivery, and fetal growth restriction, are associated with higher risk for future cerebrovascular disease, including stroke and vascular cognitive impairment.
- Neurologists who treat young women should screen them for a history of pregnancy complications; for women who have experienced pregnancy complications, how to reduce future stroke risk and optimize brain health should be discussed.

ARTICLE 6: MANAGING CENTRAL NERVOUS SYSTEM TUMORS DURING PREGNANCY

Na Tosha N. Gatson, MD, PhD, FAAN. Continuum (Minneap Minn). February 2022; 28 (1 Neurology of Pregnancy):122–146.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses current recommendations and special considerations for the management of central nervous system (CNS) tumors in pregnant women and provides case vignettes to emphasize important clinical concepts.

RECENT FINDINGS:

Given that nearly 60% of all intracranial and spinal cord tumors, including both primary and metastatic tumor types, malignant or benign, are diagnosed in women, it is equitable to bring attention to the unique management considerations that pertain to women during specific phases of their lifespan, such as pregnancy. The pregnancy phase is marked by changes in hormonal, immunologic, and other physiologic responses. Although substantial evidence supports a pregnancy influence on tumor oncogenicity, the cumulative effect of the pregnancy state on brain tumor biology remains elusive. Furthermore, as innovative cancer treatments and surveillance technologies expand, providers must consider potential new risks to safe pregnancy maintenance. This article reviews pregnancy considerations in CNS tumor care and offers best practice approaches and considerations.

SUMMARY:

Informed neuro-oncology practices on safer surgical, radiation, medical, device, and imaging techniques is of critical importance to pregnancy and fertility maintenance in cancer survivors. Expanding this knowledge relies on advocacy and a commitment to develop equitable and multidisciplinary research within the field. This also requires a focus on patient-reported outcomes and patient-centered conversations to best care for pregnant women with CNS tumors.

KEY POINTS

- Nearly 60% of all intracranial and spinal cord tumors, including both primary and metastatic tumor types, malignant or benign, are diagnosed in women.
- Brain cancer is among the rarest malignancies found during pregnancy, with a reported incidence comparable to the incidence in nonpregnant age-matched females.
- Meningiomas account for almost 55% of all nonmalignant primary brain tumors and make up about 38% of all central nervous system tumors.
- In adults, glioblastoma (World Health Organization grade 4) is the deadliest and most common primary brain malignancy (49%), comprising 14.5% of all primary brain tumors.
- Overall, schwannomas do not have a known sex predilection; however, vestibular schwannomas are more common in women.
- Prolactinomas are the most common hormone-secreting pituitary tumor and are 4.5 times more likely to occur in women.
- Breast cancer brain metastases have increased in incidence secondary to improved diagnostic and surveillance technologies as well as to innovative cancer therapies that extend patient survival.
- Breast cancer is the most reported cancer concurrent with pregnancy.
- Multiple patient case series have reported that although pregnancy does not confer a higher risk for incidence of brain tumor, pregnancy is associated with worsening aggressive tumor behavior.
- Vascular endothelial growth factor is highly expressed by specific brain tumors and regulates neoangiogenesis and vascular permeability; it is often targeted to limit brain tumor growth and complications such as vasogenic edema.
- Follicle-stimulating hormone and luteinizing hormone are tumor inhibitory hormones, whereas progesterone has been implicated in worsening oncogenicity of several cancer types based on its role in regulating cell apoptosis, proliferation, and tumor metastasis.
- The human immune response is more specialized in four vital compartments within the human body: the eyeball, the testis, the brain, and the gravid uterus.
- Tolerance of neoantigens is a hallmark characteristic of immune-specialized compartments.
- The maternal-fetal interface becomes a site for reeducation of immune cells to the new foreign fetal antigens.

- Routine hemodynamic and cardiac monitoring of the mother and fetus over the course of the pregnancy may help prevent adverse pregnancy outcomes.
- Noncontrast MRI with a lower than 3T magnet is the best modality for brain tumor imaging in pregnant women.
- Head CT for brain tumor imaging during pregnancy is contraindicated as it uses ionizing radiation, a carcinogen, and is reserved for emergent scenarios (eg, hemorrhage or acute stroke) in which the benefit to the mother outweighs the risk to the fetus.
- Tumor grade, anatomic location, and tumor rate of growth are important for neuroclinical prognostication.
- When considering neurosurgery for pregnant patients with central nervous system tumors, it is important to involve multidisciplinary experts to discuss the patients options for pregnancy maintenance or termination as well as any risks for future fertility.
- The risk of neurocognitive dysfunction resulting from radiation therapy was higher in fetal exposures between 100 mGy and 500 mGy during the first trimester (6%) as compared to the second trimester (2%).
- Targeted therapies and standard chemotherapies cross the placenta and may result in spontaneous abortion or other risks to the developing fetus, especially during the first trimester.
- Tumor treating fields therapy has been demonstrated to be effective in extending patient survival when used in combination with standard chemotherapy and has received US Food and Drug Administration clearance for both recurrent and newly diagnosed glioblastoma.
- Supportive care issues often arise in patients with brain tumors secondary to tumor treatment or tumor progression.
- Steroids may be used during pregnancy for a variety of reasons, ranging from facilitation of fetal lung maturity in high-risk pregnancies to providing a safer alternative to anti-inflammatory or immunosuppressive therapies during pregnancy.
- Newly diagnosed and recurrent brain tumors are frequently associated with vasogenic edema causing significant morbidity and require steroids as a temporary supportive care measure.
- Although pregnancy is not specifically addressed in the guideline by the Congress of Neurological Surgeons, the recommending body, in general, does not recommend prophylactic use of antiseizure medications in patients with brain tumors.

ARTICLE 7: NEURO-OPHTHALMOLOGY AND PREGNANCY

Heather E. Moss, MD, PhD, FAAN. Continuum (Minneap Minn). February 2022; 28 (1 Neurology of Pregnancy):147–161.

ABSTRACT

PURPOSE OF REVIEW:

This article summarizes the impact of pregnancy on neuro-ophthalmic pathways and presents an approach to the evaluation of pregnant women who have neuro-ophthalmic symptoms or signs.

RECENT FINDINGS:

Advances in noninvasive ophthalmic imaging have increased knowledge of the impact of pregnancy on ocular blood flow, which may have relevance for understanding the impact of preeclampsia and eclampsia on the eye.

SUMMARY:

The framework for approaching neuro-ophthalmic symptoms and signs in pregnant women is similar to the general approach for people who are not pregnant. Visual symptoms are common

in preeclampsia and eclampsia. Some diseases that impact the neuro-ophthalmic pathways are more common in pregnant women. Pregnancy should be considered when recommending the workup and treatment for neuro-ophthalmic symptoms and signs.

KEY POINTS

- Ocular surface and cornea changes in pregnancy can cause blur, eye pain, refractive shift, and contact lens discomfort.
- Branch retinal vein occlusions, branch retinal artery occlusions, and central serous chorioretinopathy are retinal causes of acute partial vision loss in pregnancy.
- Visual symptoms occur in more than one-fourth of patients with preeclampsia and almost half of patients with eclampsia.
- The approach to visual symptoms in pregnant patients is similar to the approach to visual symptoms in other patients.
- Dilating the pupils with eye drops is regarded to be safe during pregnancy.
- Optic neuritis related to multiple sclerosis, neuromyelitis optica, or myelin oligodendrocyte glycoprotein–associated disorder is less common during pregnancy and has increased frequency postpartum.
- Bilateral optic disc edema from increased intracranial pressure does not cause visual symptoms in up to half of affected patients.
- Regular formal perimetry to monitor visual fields of patients with papilledema from primary or secondary high intracranial pressure is important to detect vision loss so that intracranial pressure–lowering therapy can be advanced to prevent further worsening.
- Sixth nerve palsies in pregnancy can result from intracranial hypertension (eg, due to cerebral venous sinus thrombosis) and hypotension (eg, due to dural puncture during anesthesia).
- Growth of sellar and suprasellar structures during pregnancy can cause vision loss, diplopia, facial numbness, and Horner syndrome.
- Eye movement abnormalities can be caused by thiamine deficiency provoked by hyperemesis gravidarum, which requires urgent treatment.
- Facial nerve palsy is the most common cranial nerve palsy in pregnancy.
- Artificial tears are the first-line treatment for management of eye pain and blur due to dry eye.

ARTICLE 8: NEUROLOGIC COMPLICATIONS OF OBSTETRIC ANESTHESIA

Janet F. R. Waters, MD, MBA, FAAN. Continuum (Minneap Minn). February 2022; 28 (1 Neurology of Pregnancy):162–179.

ABSTRACT

PURPOSE OF REVIEW:

The advantages of neuraxial anesthesia over general anesthesia in the obstetric population are well established. Some neurologic conditions have the potential to lower the safety threshold for administration of neuraxial anesthesia, whereas others require special consideration before using general anesthesia. The aim of this article is to help neurologists determine when neuraxial anesthesia can be safely administered and when it is inadvisable.

RECENT FINDINGS:

Neuraxial anesthesia can usually be given safely in most pregnant patients with neurologic disease. Patients with mass lesions causing increased intracranial pressure or spinal tumors at the site of neuraxial needle placement and patients on anticoagulant medication are the exceptions. Post–dural puncture headaches and obstetric nerve injuries are the most common complications of neuraxial anesthesia and resolve in most patients. Other complications, including epidural hematoma, meningitis, and epidural abscess, are rare but devastating.

SUMMARY:

This article provides a review of neurologic diseases that may affect the decision-making process for anesthesia during delivery. It discusses the neurologic complications that can occur because of obstetric anesthesia and how to recognize them and describes obstetric nerve injuries and how to distinguish these relatively benign injuries from more serious complications.

KEY POINTS

- Women with multiple sclerosis who are pregnant often have less frequent exacerbations than women with multiple sclerosis who are not pregnant. Flare-ups increase in the postpartum period.
- Neuraxial anesthesia may be given safely in women with multiple sclerosis.
- Studies show that the use of neuraxial anesthesia poses no risk to women with Chiari malformation type I in the absence of increased intracranial pressure. Spinal and epidural anesthesia may be given safely in pregnant women with syringomyelia.
- Although elevated intracranial hypertension due to a mass lesion is a contraindication to neuraxial anesthesia because of the risk of herniation, it is safe in patients with idiopathic intracranial hypertension and may be therapeutic in these patients.
- General anesthesia should be avoided, if possible, in patients with idiopathic intracranial hypertension because of the risk of increased intracranial pressure during intubation. Obesity puts these patients at increased risk for difficult intubation and aspiration.
- Epidural and spinal anesthesia is preferable in pregnant women with myasthenia gravis. When general anesthesia is used, extubation can be challenging. If general anesthesia is used, depolarizing agents (including succinylcholine) should be avoided because of the risk of neuromuscular blockade.
- Meningiomas, schwannomas, and gliomas may all have accelerated growth in pregnancy. If increased intracranial pressure is demonstrated, neuraxial anesthesia should be avoided because of the risk of herniation.
- General anesthesia presents risk in pregnant women with brain tumors. An increase in intracranial pressure can occur during induction and intubation.
- In most pregnant women with brain tumors without mass effect and increased intracranial pressure, neuraxial anesthesia can be safely administered. A case-by-case assessment of these patients is indicated.
- In patients with neurofibromatosis, the presence of lumbar tumors can increase the risk of epidural hematoma during spinal and epidural needle placement. Pregnant women with neurofibromatosis should undergo noncontrast MRI of the lumbar spine before undergoing neuraxial anesthesia.
- Patients with Guillain-Barré syndrome are at no increased risk with the use of neuraxial anesthesia but should be monitored carefully for the development of hypotension due to autonomic dysfunction and exaggerated vasovagal response. If general anesthesia is used, succinylcholine is contraindicated because of the potential for life-threatening hyperkalemia.
- Most women with lumboperitoneal shunts are able to undergo neuraxial anesthesia; however, imaging may be needed before delivery to ascertain the position of the shunt. Spinal anesthesia may be unpredictable and of shorter duration if local anesthetic leaks via the shunt into the peritoneal cavity, which can lead to an inadequate block.

- In pregnant women with myotonic dystrophy, delivery may be difficult because of uterine smooth muscle abnormality, which can affect all stages of labor. The second stage of labor may be prolonged because of skeletal muscle weakness.
- General anesthesia should be avoided in patients with myotonic dystrophy, if possible, as they are at high risk for aspiration because of pharyngeal muscle weakness and gastric immotility. Triggers for myotonia should be avoided, including hypothermia and shivering. Respiratory complications can occur in the postoperative period, and opioid use should be minimized.
- Intubation may be difficult in patients with spinal muscular atrophy as many have limited jaw opening because of mandibular joint ankylosis and cervical immobility. Depolarizing neuromuscular blockers have a prolonged effect on patients with spinal muscular atrophy even after reversal and should be avoided. Neuraxial anesthesia is preferable to general anesthesia but may not be feasible in some patients with severe scoliosis. Imaging before placement of epidural or spinal anesthesia can be helpful.
- Post–dural puncture headache is the most common complication of neuraxial anesthesia. It may be associated with hyperacusis, double vision, photophobia, and nausea. It can be distinguished from migraine and other types of headaches by its postural nature.
- Treatment of post–dural puncture headache starts with conservative management, including bed rest, adequate hydration, and analgesics. Although some clinicians advocate the use of caffeine, this has not been supported by the literature.
- If conservative management of post–dural puncture headache fails, an epidural blood patch can be placed. A blood patch done less than 24 hours after the dural puncture has a high failure rate. An epidural blood patch performed after 24 hours after dural puncture has a success rate of 70% to 97%.
- A rare consequence of intracranial hypotension from dural puncture is the development of a subdural hematoma.
- Spinal epidural hematoma should be suspected in patients who experience anesthesia persisting for greater than the expected duration, unusual back pain, persistent motor weakness, sensory loss, and sphincter dysfunction.
- Risk factors for spinal epidural hematoma include intrinsic or iatrogenic clotting dysfunction and spinal tumors.
- Early diagnosis and management of a spinal epidural hematoma is essential to prevent permanent neurologic injury.
- Direct conus and cord injury can result if the lower end of the spinal cord is not accurately determined before needle placement. Placement of neuraxial block, especially spinal anesthesia, at the level below the second lumbar vertebra reduces the risk.
- Cauda equina syndrome manifests as burning low back pain, sphincter dysfunction, lower extremity weakness, and saddle anesthesia. It can develop because of neurotoxicity caused by pooling of local anesthetic.
- Skin flora is the most common source of infection in women who develop spinal epidural abscess, and *Staphylococcus aureus* is the most common underlying organism. The risk of developing an abscess increases with prolonged duration of epidural catheterization. Urgent MRI with gadolinium should be done to confirm the diagnosis.
- Microbial contamination from the mouth and nose of the practitioner are the most common source of meningitis as a complication of neuraxial anesthesia. The most common causative organism is *Streptococcus viridans*. Confirmation is obtained with CSF analysis, and treatment is aggressive antimicrobial therapy.
- A total spinal block will occur if a large volume of local anesthetic intended for the epidural space is injected into the subarachnoid space. It can produce anesthesia involving the entire spinal cord, nerve roots, and brainstem. Cranial nerve findings, including pupillary dilatation, may occur. It can lead to respiratory insufficiency and profound hypotension and bradycardia. Treatment is supportive.
- Seizures may occur when local anesthetic is accidentally injected intravascularly. Systemic toxicity is more likely to occur after obstetric epidural anesthesia than spinal anesthesia because larger volumes of local anesthetics are used.

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Neurology of Systemic Disease

Article 1: Cardiac and Pulmonary Disorders and the Nervous System

Natalie R. Weathered, MD, MS. Continuum (Minneap Minn). June 2020; 26 (3 Neurology of Systemic Disease):556–576.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the neurologic complications encountered with cardiac and pulmonary disorders, specifically focusing on endocarditis, cardiac arrest, heart failure, hypercapnia, hypoxia, and cystic fibrosis. As neurologic dysfunction is one of the most frequent complications of these diseases and may even be the presenting symptom, it is important to be familiar with these complications to foster early recognition and intervention.

RECENT FINDINGS:

Advances have been made in the identification of which patients can safely undergo valvular surgery for treatment of infective endocarditis in the setting of stroke, which, ideally, will minimize the risk of recurrent stroke in these patients. Additionally, technologic advances are improving our ability to use a multimodal approach for prognostication after cardiac arrest.

SUMMARY:

The neurologic complications from the described disorders range from cerebrovascular complications to encephalitis, cognitive impairment, sleep-disordered breathing, headache, and increased intracranial pressure leading to coma or even death. Given the severity of these symptoms, it is paramount that neurologists be closely involved in the care of patients with neurologic complications from cardiac and pulmonary disorders.

KEY POINTS

- **Antiplatelets, anticoagulants, and recombinant tissue plasminogen activator should not be used in the acute phase of an ischemic stroke due to infective endocarditis without strong clinical indication.**
- **Infectious intracranial aneurysms tend to be distal, and often multiple aneurysms are present.**
- **Most infectious aneurysms remain clinically silent, and if they are small, they may fully resolve with antimicrobial therapy.**
- **In the setting of clinically silent infarcts or transient ischemic attack, valvular surgery has been shown to be safe.**
- **Current American Heart Association Guidelines recommend targeted temperature management for all patients who are comatose after a cardiac arrest without regard to initial rhythm or whether they were**

outpatient or inpatient at the time of arrest, with a goal temperature between 32°C (89.6°F) and 36°C (96.8°F) for at least 24 hours.

- Prognostication in patients who are comatose after cardiac arrest should be done no earlier than postarrest day 3 if the patient was not cooled or 72 hours after reaching normothermia if cooled.
- It is imperative to ensure that all sedating medications and paralytics have been cleared from the system of patients who are comatose before proceeding with the prognostication examination to minimize confounding effects.
- A multimodal approach is often ideal for prognostication in patients who are comatose after cardiac arrest, combining the clinical examination with supportive studies.
- Anticoagulation lowers the risk of ischemic stroke due to low cardiac ejection fraction; however, that effect is counterbalanced by the increased risk of hemorrhage.
- The use of anticoagulation for the primary prevention of stroke in the setting of heart failure with reduced ejection fraction should be decided on a case-by-case basis, weighing the risk of hemorrhage if anticoagulation is started.
- The cognitive impairment associated with heart failure ranges from delirium to mild cognitive impairment and dementia.
- The neurologic sequelae of hypercapnia include inattention, memory deficits, confusion, lethargy, asterixis, tremor, headache, papilledema, and seizures. These symptoms occur as a consequence of cerebral edema and increased intracranial pressure.
- Most of the neurologic complications of cystic fibrosis are due to deficiencies of the fat-soluble vitamins.
- Vitamin E deficiency in cystic fibrosis causes cognitive impairment, microcephaly, dysmetria, ataxia, and spinal cord demyelination.
- Vitamin K deficiency in cystic fibrosis can result in spontaneous intracerebral hemorrhage.

Article 2: Gastrointestinal Disorders and the Nervous System

Halina White, BM BCh, MA, MRCP. Continuum (Minneap Minn). June 2020; 26 (3 Neurology of Systemic Disease):577–590.

ABSTRACT

PURPOSE OF REVIEW:

This article describes the neurologic sequelae of various nutritional micronutrient deficiencies, celiac disease, inflammatory bowel disease, and liver disease. Where relevant, appropriate treatments for these conditions are also discussed. The developing field of the microbiome and nervous system interaction is also outlined.

RECENT FINDINGS:

Pathology in the gastrointestinal system can affect the nervous system when it causes micronutrient deficiency, when immune responses created by the gastrointestinal system affect the nervous system, when toxins caused by gastrointestinal organ failure harm the nervous system, and when treatments aimed at a gastrointestinal medical condition cause damage to the nervous system as a side effect.

SUMMARY:

This article addresses familiar concepts and new developments in the treatment and understanding of diseases that affect the gut and nervous system simultaneously.

KEY POINTS

- The neurologic complications of celiac disease include headaches, mood disorders, seizures, white matter lesions, impaired cognition, gluten ataxia (ataxia of arms, legs, and gait; dysarthria; myoclonus), myelopathy, myopathy, peripheral neuropathy (usually sensorimotor axonal), mononeuritis multiplex, and autonomic neuropathy.
- Peripheral neuropathy is one of the most common neurologic complications of celiac disease.
- The neurologic complications of inflammatory bowel disease include peripheral neuropathy, cranial neuropathies, myelopathy, myopathy, ischemic stroke, cerebral venous sinus thrombosis, cerebral vasculitis, and posterior reversible encephalopathy syndrome.
- Crohn disease is sometimes associated with Melkersson-Rosenthal syndrome, a triad of recurrent facial nerve palsy, intermittent orofacial swelling, and fissuring of the tongue (lingua plicata).
- The neurologic complications of acute liver failure include encephalopathy, cerebral edema, intracranial hypertension, seizures, coma, and herniation.
- The neurologic complications of cirrhosis include cognitive decline, encephalopathy, parkinsonism, cerebellar dysfunction, basal ganglia dysfunction, hepatic myelopathy, and hepatic neuropathy.
- The neurologic complications of Wilson disease include dysarthria, dystonia, intentional and postural tremor, parkinsonism, cognitive impairment with a frontal syndrome or subcortical dementia, seizures, hyperreflexia, myoclonus, and autonomic dysfunction.
- Dysfunction of the microbiome, called *dysbiosis*, may contribute to the pathogenesis of many diseases, including some that were previously considered to be strictly neurologic, such as Parkinson disease, Alzheimer disease, and multiple sclerosis.
- Lewy bodies and α-synuclein, the neuropathologic hallmarks of Parkinson disease, appear in the enteric nervous system and parasympathetic nerves leading to the gut in the early stages of Parkinson disease, before they appear in the central nervous system.
- Periodontal disease and poor dental hygiene are associated with the development of mild cognitive impairment and Alzheimer disease, but no causal relationship between these two conditions has ever been established in humans.

Article 3: Rheumatologic Disorders and the Nervous System

Pantelis P. Pavlakis, MD, PhD. Continuum (Minneap Minn). June 2020; 26 (3 Neurology of Systemic Disease):591–610.

ABSTRACT

PURPOSE:

This article describes the neurologic manifestations of systemic autoimmune diseases.

RECENT FINDINGS:

Systemic autoimmune diseases can be associated with a wide spectrum of neurologic comorbidities involving the central and peripheral nervous systems. Systemic lupus erythematosus (SLE) can be associated with a number of manifestations predominantly affecting the central nervous system (CNS), whereas peripheral neuropathy is less common. Sjögren syndrome can be associated with peripheral neuropathy in 10% of cases and CNS disease in 2% to 5% of cases. The risk of stroke is increased in SLE, rheumatoid arthritis, temporal arteritis, psoriatic arthritis, and ankylosing spondylitis. Systemic vasculitides present most commonly with mononeuritis multiplex but can also affect the CNS. Cognitive dysfunction is a common

symptom among patients with systemic autoimmune diseases, most commonly seen in patients with SLE or Sjögren syndrome.

SUMMARY:

Neurologic manifestations of systemic autoimmune disease are important to recognize, as they may often be the presenting manifestation leading to diagnosis of the systemic disease or may be associated with increased morbidity, other complications, or mortality. Timely diagnosis and institution of appropriate treatment, often requiring multidisciplinary care, is essential to minimize morbidity and decrease the risk of permanent neurologic deficits.

KEY POINTS

- Patients with systemic lupus erythematosus, rheumatoid arthritis, temporal arteritis, psoriatic arthritis, and ankylosing spondylitis have increased risk of stroke.
- Patients with systemic lupus erythematosus have increased risk of developing posterior reversible encephalopathy syndrome.
- Neuromyelitis optica spectrum disorders can overlap with systemic lupus erythematosus or Sjögren syndrome.
- Small fiber neuropathy is the most common peripheral neuropathy in Sjögren syndrome. It may present with length-dependent or non–length-dependent distribution of symptoms and tends to be associated with fewer extraglandular manifestations than large fiber neuropathy.
- Patients with Sjögren syndrome and small fiber neuropathy are less frequently seropositive for anti-Ro and anti-La antibodies. Therefore, their absence should not preclude the diagnosis of Sjögren syndrome in an otherwise appropriate clinical setting.
- Sensory ataxic neuropathy (neuronopathy) can be seen in patients with Sjögren syndrome due to lymphocyte infiltration of dorsal root ganglia. The differential diagnosis includes paraneoplastic syndromes (usually in cases of small cell lung carcinoma) human immunodeficiency virus infection, platinum-based chemotherapy, or vitamin B_6 toxicity.
- Neuromyelitis optica spectrum disorders can overlap with systemic lupus erythematosus or Sjögren syndrome.
- Patients with rheumatoid arthritis have increased risk of cervical spinal stenosis, particularly at the atlantooccipital, atlantoaxial, or subaxial level.
- Pannus formation is a mechanism by which patients with rheumatoid arthritis can develop cervical spinal stenosis. The imaging modality of choice to detect it is MRI.
- Mononeuritis multiplex is the most common peripheral neuropathy associated with vasculitis. Over time, confluent neurologic deficits can mimic a distal symmetric polyneuropathy.
- Combined nerve and muscle biopsy increases the sensitivity for vasculitis diagnosis.
- In a patient with known or suspected systemic autoimmune disease or constitutional symptoms, coexisting deficits of subacute onset that localize to the central and peripheral nervous systems should raise the suspicion of vasculitis.
- Peripheral neuropathy is present in more than 50% of patients with polyarteritis nodosa and is often a presenting manifestation.
- Pituitary involvement can be seen in granulomatosis with polyangiitis.
- Cerebral venous sinus thrombosis is associated with Behçet disease and is often of insidious onset.
- Cognitive symptoms are common among patients with systemic autoimmune diseases, ranging from mild subjective cognitive symptoms to more severe cognitive dysfunction.
- Patients with rapidly progressing cognitive decline should be evaluated for other central nervous system processes, such as vasculitis, infections, aseptic meningitis, autoimmune encephalitis, or prion diseases.
- Cognitive dysfunction is seen more frequently in systemic lupus erythematosus and Sjögren syndrome, followed by rheumatoid arthritis.
- Tumor necrosis factor-α inhibitors can cause central demyelination or demyelinating neuropathies.

- Demyelinating neuropathy associated with tumor necrosis factor-α inhibitors persists after their cessation and requires treatment with IV immunoglobulin.

Article 4: Obstetric and Gynecologic Disorders and the Nervous System

Mary Angela O'Neal, MD. Continuum (Minneap Minn). June 2020; 26 (3 Neurology of Systemic Disease):611–631.

ABSTRACT

PURPOSE OF REVIEW:

This article highlights the multiple intersections between obstetric/gynecologic issues and neurologic disorders.

RECENT FINDINGS:

Neurologic issues can arise related to contraceptive medications, infertility treatments, pregnancy, and menopause. This article explores these areas in chronologic order, beginning with women's neurologic conditions that overlap their reproductive years and those that may occur during pregnancy and continuing through menopause. For each disorder, the epidemiology, pathophysiology, complications, and best sex-based treatment are described. Recent findings and treatments are highlighted.

SUMMARY:

Obstetric and gynecologic disorders may present with neurologic symptoms, so it is important for neurologists to understand these intersections to deliver the best care for our female patients.

KEY POINTS

- Migraine is more prevalent in women because of the effects of estrogen on the condition.
- Migraine without aura is more hormonally driven than migraine with aura.
- Migraine with aura conveys a small increased risk for stroke, which is further magnified by combined hormonal contraception.
- The risk of stroke in women who have migraine with aura is significantly increased when combined with other traditional stroke risk factors.
- Ovarian hyperstimulation syndrome is a rare iatrogenic condition that increases the risk of thrombotic events.
- Rising levels of human chorionic gonadotropin given for follicular maturation to trigger ovulation or related to pregnancy are pivotal in the development of the increased vascular permeability that is the core feature of ovarian hyperstimulation syndrome.
- Pregnancy causes major changes in clotting factors, resulting in a hypercoagulable state.
- The hypercoagulable changes that occur in pregnancy are most prominent in the last trimester and persist up to 12 weeks in the postpartum period.
- Migraine frequency (especially migraine without aura) generally improves during pregnancy.
- Women with a history of migraine have almost double the risk of preeclampsia than those without migraine.
- Preeclampsia/eclampsia is a major risk factor for stroke in pregnancy and remains a stroke risk factor even decades later.
- Posterior reversible encephalopathy syndrome is the radiographic correlate of preeclampsia/eclampsia.
- The causes of stroke in pregnancy and the postpartum period are diverse.

- Pregnant women with an ischemic stroke who meet criteria for either recombinant tissue plasminogen activator or endovascular therapy should be offered these therapies.
- Reversible cerebral vasoconstriction syndrome and posterior reversible encephalopathy syndrome should be thought of as occurring on a continuum, with similar etiologies and treatment during pregnancy and postpartum.
- Dissection of the carotid or vertebral arteries in pregnancy is most commonly related to trauma associated with labor.
- Cerebral venous thrombosis is treated with anticoagulation even in the presence of a venous hemorrhage.
- Pituitary apoplexy can be a neuroendocrine emergency due to acute adrenal insufficiency.
- Postpartum neuropathies/plexopathies are usually related to a traumatic or compressive injury during labor and delivery and are seldom related to neuraxial anesthesia.
- Bell's palsy is 2 to 4 times more prevalent in pregnancy, usually occurring in the last trimester and the first week postpartum.
- Migraines may worsen due to the hormonal fluctuations during the menopause transition.
- Sleep disturbances are common during the menopausal transition.

Article 5: Electrolyte Disorders and the Nervous System

Nuri Jacoby, MD. Continuum (Minneap Minn). June 2020; 26 (3 Neurology of Systemic Disease):632–658.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of the major electrolyte disorders and discusses in detail the homeostasis, etiologies, neurologic manifestations, and treatment of these disorders.

RECENT FINDINGS:

The diagnosis and management of hyponatremia continue to evolve. Diagnostic accuracy is improved by assessing serum and urine osmolality as well as urinary sodium. Avoiding overcorrection of hyponatremia is crucial to avoid osmotic demyelination syndrome, although even careful correction can cause osmotic demyelination syndrome in patients who have other risk factors. The clinical presentation of osmotic demyelination syndrome has expanded, with many patients presenting with extrapontine myelinolysis in addition to central pontine myelinolysis.

SUMMARY:

Electrolyte disorders often present with neurologic manifestations. Whereas disorders of some electrolytes, such as sodium, preferentially affect the central nervous system, disorders of others, such as potassium and calcium, have significant neuromuscular manifestations. An understanding of the pathophysiology of these disorders and recognition of these manifestations are crucial for the practicing neurologist as the symptoms are reversible with correct management.

KEY POINTS

- Water homeostasis is regulated by thirst and antidiuretic hormone, with antidiuretic hormone playing a larger role.

- The etiologies of hypoosmolar hyponatremia can be separated into three categories based on volume status: hypovolemia, euvolemia, and hypervolemia.
- The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) can be due to neurologic or pulmonary etiologies, drugs, or malignancy.
- Medications that cause SIADH include selective serotonin reuptake inhibitors; serotonin norepinephrine reuptake inhibitors; tricyclic antidepressants; and antiepileptic drugs such as carbamazepine, oxcarbazepine, and eslicarbazepine acetate.
- SIADH, which is the most common cause of hyponatremia and occurs in patients who are euvolemic, must be differentiated from cerebral salt wasting, which occurs in the setting of hypovolemia. In SIADH, the treatment is fluid restriction, whereas in cerebral salt wasting, the treatment is fluid resuscitation.
- Low osmolality due to hyponatremia produces a shift in the osmotic gradient, causing water to flow into the intracellular compartment, with resultant intracellular edema and rupture of cell membranes.
- Hyponatremia is more likely to cause symptoms if it occurs rapidly (ie, within hours). When levels decrease rapidly to lower than 115 mmol/L to 120 mmol/L, a risk of brain herniation and respiratory arrest exists.
- For acute hyponatremia or symptomatic hyponatremia regardless of duration, guidelines recommend a bolus of 3% sodium chloride (100 mL over 10 minutes, up to 3 times as needed).
- For chronic hyponatremia, guidelines recommend increasing plasma sodium concentration by ≤8 mmol/L/d, with consideration of slower correction if a high risk of osmotic demyelination syndrome is present. First-line treatment for chronic nonhypovolemic hyponatremia is to reduce free water intake (<1 L/d).
- Risk factors for the development of osmotic demyelination syndrome in the setting of correction of hyponatremia are alcohol use disorder, malnutrition, concurrent hypokalemia, and liver transplantation.
- Patients with central pontine myelinolysis present with a flaccid quadriparesis that later becomes spastic, dysarthria, dysphagia, and, potentially, ocular motor abnormalities.
- Osmotic demyelination syndrome that occurs outside the pons is called *extrapontine myelinolysis*, which can occur concurrently with central pontine myelinolysis or alone. Extrapontine myelinolysis often presents with parkinsonism and other movement disorder symptoms.
- Although seizures can be seen in hypernatremia, they are less common than in hyponatremia.
- Treatment of hypernatremia is with hypotonic fluids. In acute hypernatremia (<2 days), hypotonic saline can be given to decrease plasma sodium concentration by 2 mmol/L per hour until plasma sodium concentration is 145 mmol/L. In chronic hypernatremia or if timeline is unknown, a slower correction of up to 10 mmol/L per day is recommended.
- Neurologic symptoms of hypokalemia generally occur at levels lower than 3.0 mmol/L and include generalized proximal greater than distal weakness, leg cramps, paresthesia, irritability, and rhabdomyolysis.
- The most dangerous manifestations of hyperkalemia are cardiac arrhythmias, which typically develop before neurologic manifestations.
- The periodic paralyses are rare autosomal disorders due to mutations in skeletal muscle sodium, calcium, and potassium channels. They are characterized by episodes of flaccid muscle paralysis typically associated with hypokalemia or hyperkalemia.
- Diagnosis of all periodic paralysis disorders can be done through genetic testing, which identifies 60% to 70% of all cases. Electrodiagnostic testing and clinical features can be helpful in cases in which genetic testing is negative.
- Treatment of the periodic paralyses includes behavioral changes to minimize triggers, potassium treatment (either supplementation or avoidance), and medications.
- Calcium and phosphorus levels are regulated by parathyroid hormone, calcitonin, and vitamin D metabolites.
- The neurologic manifestations of hypercalcemia are primarily neuropsychiatric and neuromuscular and include subtle personality changes, difficulty concentrating, confusion, dementia, and proximal muscle weakness.
- Neurologic symptoms can be seen in hypocalcemia if levels are reduced quickly or are lower than 7.5 mg/dL. Neurologic signs and symptoms include neuromuscular manifestations, including the Trousseau sign and Chvostek sign, seizures, confusion, and psychosis.

- Treatment of acute symptomatic hypocalcemia is IV calcium, typically calcium gluconate diluted in 5% dextrose infused over 10 minutes.
- Mildly reduced levels of phosphate are generally asymptomatic, although in severe cases, encephalopathy, hallucinations, coma, and cerebellar and extrapyramidal signs such as ataxia, tremor, and nystagmus can be seen.
- As hypomagnesemia often causes both hypocalcemia and hypokalemia, it is difficult to determine which neurologic symptoms are due to which electrolyte abnormality.
- Hypermagnesemia can worsen disorders of the neuromuscular junction such as myasthenia gravis and Lambert-Eaton myasthenic syndrome; thus, magnesium should be used with caution in patients with those disorders.
- In acid-base disorders, a change in the partial pressure of carbon dioxide ($Paco_2$) causes a compensatory change in the bicarbonate concentration (HCO_3^-), whereas changes in bicarbonate cause a compensatory response in the $Paco_2$.
- Metabolic disorders (either acidosis or alkalosis) occur when the primary change is in the bicarbonate level, and respiratory disorders (either acidosis or alkalosis) occur when the primary change is in the $Paco_2$ level.
- In respiratory acidosis, cerebral vasodilation occurs at $Paco_2$ levels higher than 50 mm Hg, which can lead to increased intracranial pressure.
- Respiratory alkalosis can be due to any etiology that causes hyperventilation and presents with dizziness, paresthesia of the limbs and perioral area, headaches, muscle cramps, blurry vision, and seizures.
- Metabolic acidosis can be classified as high anion gap and normal anion gap disorders, with the distinction important for determining the underlying etiology.
- Neurologic symptoms of metabolic acidosis are nonspecific and can include headache, lethargy, stupor, and coma.

Article 6: Blood Cell Disorders and the Nervous System

Alexander E. Merkler, MD. Continuum (Minneap Minn). June 2020; 26 (3 Neurology of Systemic Disease):659–674.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses the epidemiology, diagnosis, treatment, and prevention of neurologic complications of common and rare blood cell disorders.

RECENT FINDINGS:

A growing number of preventive treatment options are available for stroke in sickle cell disease. Paroxysmal nocturnal hemoglobinuria and immune thrombocytopenia can lead to stroke. Thrombotic thrombocytopenic purpura frequently causes neurologic symptoms and should be considered in the differential diagnosis of a patient with neurologic symptoms, thrombocytopenia, and hemolytic anemia. Polycythemia vera and essential thrombocythemia are rare causes of stroke.

SUMMARY:

This article discusses sickle cell disease and the most recent advances in stroke preventive therapy as well as neurologic complications of paroxysmal nocturnal hemoglobinuria, immune thrombocytopenia, thrombotic thrombocytopenic purpura, polycythemia vera, and essential thrombocythemia.

KEY POINTS

- Sickle cell disease is a multisystem disease that causes myriad acute and chronic medical complications. Stroke affects 1 in 10 children with sickle cell disease and is one of the most devastating consequences because of its propensity to lead to physical and cognitive impairment and a decreased quality of life.
- Patients with sickle cell disease are at risk for all types of stroke, including cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage.
- In patients with sickle cell disease, strokes due to moyamoya syndrome are typically found in either the distribution of a large intracranial artery or at the watershed zone between the large arteries.
- Cerebral infarction occurs in approximately 11% of patients with sickle cell disease by age 20, 15% by age 30, and 24% by age 45.
- Red blood cell transfusion is the mainstay of primary and secondary stroke prevention in children with sickle cell disease.
- Guidelines recommend that children 2 to 16 years of age undergo annual TCD to monitor velocities; in patients with mean velocities greater than 200 cm/s, transfusion therapy should be initiated to reduce sickle hemoglobin to less than 30% and hydroxyurea should be considered.
- Cerebral venous sinus thrombosis or thrombosis of an intracranial vein is the most frequent neurologic complication of paroxysmal nocturnal hemoglobinuria and occurs in 2% to 8% of patients.
- In patients with a cerebral venous thrombosis of unknown etiology, a diagnosis of paroxysmal nocturnal hemoglobinuria should be considered when patients are young, have evidence of hemolysis, or have any cytopenia.
- Intracranial hemorrhage is a feared complication of immune thrombocytopenia given its association with severe long-term morbidity and high mortality.
- Based on a large meta-analysis, the frequency of intracranial hemorrhage is approximately 1% in patients with immune thrombocytopenia.
- Predictors of bleeding in immune thrombocytopenia include the presence of severe thrombocytopenia, previous bleeding, and advanced age.
- Patients with immune thrombocytopenia and intracranial hemorrhage should receive immediate therapy with platelet transfusion/continuous infusion and concomitantly be treated with high-dose corticosteroids with consideration of IV immunoglobulin as an adjunctive therapy.
- Thrombotic thrombocytopenic purpura is due to a severe deficiency in ADAMTS13, which is a metalloproteinase that is responsible for the breakdown of von Willebrand factor.
- Overall, more than 90% of patients with thrombotic thrombocytopenic purpura have neurologic involvement, including ischemic stroke, hemorrhagic stroke, and posterior reversible encephalopathy syndrome.
- Diagnosis of thrombotic thrombocytopenic purpura requires demonstration of a severe deficiency in ADAMTS13, defined as activity of less than 10%.
- Plasma exchange is the first-line therapy for treatment of thrombotic thrombocytopenic purpura.

Article 7: Critical Medical Illness and the Nervous System

Matthew B. Maas, MD, MS, FAAN. Continuum (Minneap Minn). June 2020; 26 (3 Neurology of Systemic Disease):675–694.

ABSTRACT

PURPOSE OF REVIEW:

Nervous system tissues have high metabolic demands and other unique vulnerabilities that place them at high risk of injury in the context of critical medical illness. This article describes the

neurologic complications that are commonly encountered in patients who are critically ill from medical diseases and presents strategies for their diagnosis, prevention, and treatment.

RECENT FINDINGS:

Chronic neurologic disability is common after critical medical illness and is a major factor in the quality of life for survivors of critical illness. Studies that carefully assessed groups of patients with general critical illness have identified a substantial rate of covert seizures, brain infarcts, muscle wasting, peripheral nerve injuries, and other neurologic sequelae that are strong predictors of poor neurologic outcomes. As the population ages and intensive care survivorship increases, critical illness–related neurologic impairments represent a large and growing proportion of the overall burden of neurologic disease.

SUMMARY:

Improving critical illness outcomes requires identifying and managing the underlying cause of comorbid neurologic symptoms.

KEY POINTS

- Nervous system tissues have high metabolic demands and other unique vulnerabilities that place them at high risk of injury in the context of critical illness. Approximately 20% of circulation and energy consumption occurs in the brain, which accounts for less than 2% of body mass.
- Patients with chronic neurologic disease have increased susceptibility to neurologic dysfunction from systemic causes.
- Patients with resolved focal deficits may experience a reemergence of those deficits during critical illness, a phenomenon called *recrudescence*.
- Specific chronic neurologic diseases may pose unique complications in the context of new medical complications.
- Medications, monitoring equipment, invasive devices, and impaired mental status can complicate safe examination of patients. High situational awareness, attention to the effects of medications, and assistance from nursing colleagues will maximize safety.
- Ischemic and hemorrhagic strokes are the principle causes of acute focal brain injuries during critical illness.
- Encephalopathy is the clinical syndrome of generalized brain failure. It can be caused by a single etiology or a combination of many factors. Etiology is often hard to distinguish by clinical examination findings alone.
- Delirium is a syndrome of decreased arousal and attention with incoherent thought and speech that may occur due to any process that provokes encephalopathy. The incidence of delirium during critical illness is associated with hospital complications, increased mortality, and worse long-term cognitive outcomes.
- Delirium is best prevented and treated by care bundles to address multiple factors that variably contribute to delirium risk in many patients. Care bundles are most effective when implemented uniformly for entire patient care areas.
- Encephalopathy in the context of sepsis is associated with microvascular brain injuries (infarcts, hemorrhages, and microabscesses). Therefore, recovery of encephalopathy often lags resolution of systemic disease.
- Neuropharmacology becomes very complicated in patients who are critically ill because of polypharmacy and dynamic changes in liver and kidney function that affect drug metabolism and clearance. The potential for medication toxicity should be considered for every patient who is encephalopathic.
- Many critical illnesses can cause diffuse microvascular injuries in the brain and peripheral nerves. Unlike large vascular lesions, focal symptoms are relatively uncommon, and, in many cases, damage occurs in lesions below the resolution of standard neuroimaging studies.
- Withdrawal syndromes caused by alcohol, opiate, or benzodiazepine dependence are relatively common in patients who are critically ill.
- Critical illness and multiorgan failure alone are sufficient to trigger seizures, although a history of epilepsy or focal brain lesions increase risk. Many seizures in patients who are critically ill are nonconvulsive. EEG monitoring should be considered in patients who are critically ill with unexplained alteration of mental status.

- Polyneuropathy and myopathy are widespread in patients who are critically ill and frequently go unrecognized. Strict glycemic control, maximizing nutrition, and mobilizing patients as early as possible may reduce the risk of these complications.
- Post–intensive care syndrome, a constellation of cognitive, psychological, and physical disability seen as sequelae of acute neurologic comorbidities of critical illness, occurs in more than half of critical illness survivors and is a major cause of chronic disability.

Article 8: Sarcoidosis and the Nervous System

Siddharama Pawate, MD. Continuum (Minneap Minn). June 2020; 26 (3 Neurology of Systemic Disease):695–715.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview and update on the neurologic manifestations of sarcoidosis.

RECENT FINDINGS:

The 2018 Neurosarcoidosis Consortium diagnostic criteria emphasize that biopsy is key for diagnosis and determines the level of diagnostic certainty. Thus, *definite neurosarcoidosis* requires nervous system biopsy and *probable neurosarcoidosis* requires biopsy from extraneural tissue. Without biopsy, *possible neurosarcoidosis* can be diagnosed if the clinical, imaging, and laboratory picture is compatible and other causes are ruled out. Recent large retrospective studies from the United States and France established that infliximab appears to be efficacious when other treatments are inadequate.

SUMMARY:

Sarcoidosis is a multisystem noninfectious granulomatous disorder that is immune mediated, reflecting the response to an as-yet unidentified antigen or antigens. Neurosarcoidosis refers to neurologic involvement due to sarcoidosis that clinically manifests in 5% of cases of sarcoidosis, with asymptomatic involvement in as many as another one in five patients with sarcoidosis. Sarcoid granulomas can occur in any anatomic substrate in the nervous system, causing protean manifestations that have earned neurosarcoidosis the sobriquet *the great mimic*. Nevertheless, central nervous system sarcoidosis occurs in well-defined presentations that can be classified as cranial neuropathies, meningeal disease, brain parenchymal (including pituitary-hypothalamic) disease, and spinal cord disease. In addition, the peripheral nervous system is affected in the form of peripheral neuropathy and myopathy. Glucocorticoids are the cornerstone of treatment, especially in the acute stage, whereas steroid-sparing agents such as methotrexate, mycophenolate mofetil, and azathioprine are used for prolonged therapy to minimize steroid toxicity. Anti–tumor necrosis factor agents may help in refractory cases.

KEY POINTS

- Sarcoidosis is a multisystem noninfectious immune-mediated inflammatory granulomatous disease. The histopathologic hallmark of sarcoidosis is the noncaseating granuloma.
- African Americans in the United States are 10 times more likely to have sarcoidosis than whites, and African American women have the highest incidence.
- Neurosarcoidosis has acquired the reputation of being a challenging disease to diagnose because of its protean manifestations, earning it the nickname *the great mimic*. However, it is helpful to recognize that

neurosarcoidosis occurs as well-defined neurologic manifestations: cranial neuropathies, meningitis, parenchymal disease, spinal cord disease, peripheral neuropathy, and myopathy.

- The facial nerve and optic nerve are the most commonly affected cranial nerves in neurosarcoidosis.
- In the brain parenchyma, hypothalamic-pituitary involvement is common and causes a variety of neuroendocrine manifestations.
- Seizures and focal neurologic deficits can result from parenchymal neurosarcoidosis. The specific manifestations depend on the size, location, and speed of development of the inflammatory process.
- Both the leptomeninges and the dura can be affected in neurosarcoidosis. Headache is a common presentation in these cases. Hydrocephalus can develop as a secondary complication of meningitis.
- A longitudinally extensive transverse myelitis can be seen in neurosarcoidosis and can be difficult to differentiate from neuromyelitis optica spectrum disorders and other causes.
- The neuropathy of neurosarcoidosis cannot be distinguished from other immune-mediated neuropathies clinically, by nerve conduction studies and EMG, or by response to immunotherapies.
- Small fiber neuropathy in sarcoidosis is termed a *paraneurosarcoidosis*, reflecting that it is not due to direct granulomatous invasion of small fibers but a distant effect due to circulating inflammatory mediators.
- CSF studies are sensitive to demonstrate intrathecal inflammation but lack specificity for neurosarcoidosis. CSF findings in neurosarcoidosis include pleocytosis, increased protein, decreased glucose, elevated IgG index, and the presence of oligoclonal bands.
- The Neurosarcoidosis Consortium Consensus Group criteria for neurosarcoidosis seek to standardize the definition of neurosarcoidosis encompassing both central nervous system and peripheral nervous system involvement. They affirm the vital role of biopsy in the diagnosis.
- A biopsy of the nervous system lesion is required for the diagnosis of definite neurosarcoidosis. Extraneural biopsy consistent with sarcoidosis, in conjunction with central nervous system inflammation suggestive of sarcoidosis, allows the diagnosis of probable neurosarcoidosis. In the absence of histopathologic confirmation, possible neurosarcoidosis can be diagnosed in the presence of appropriate clinical, imaging, and laboratory findings.
- As with CSF, MRI is sensitive to the presence of inflammation but is not specific for neurosarcoidosis.
- Chest imaging is a vital initial study in the investigation of neurosarcoidosis because 90% of patients with sarcoidosis will have intrathoracic involvement. A chest CT can pick up additional cases missed by chest x-ray.
- If clinical suspicion is high and chest imaging is negative, positron emission tomography can show extrathoracic systemic sarcoidosis and provide targets for biopsy.
- Corticosteroids are the first-line agents in therapy of neurosarcoidosis, but their long-term use is fraught with adverse effects. The goal should be to minimize their use to the shortest possible duration.
- Steroid-sparing agents have been used in patients requiring long-term immunotherapy to minimize steroid adverse effects; they include methotrexate, mycophenolate mofetil, and azathioprine.
- Infliximab has emerged as a cornerstone in the treatment of refractory or severe cases of neurosarcoidosis.

Article 9: Commonly Used Drugs for Medical Illness and the Nervous System

Mary L. Vo, MD, PharmD. Continuum (Minneap Minn). June 2020; 26 (3 Neurology of Systemic Disease):716–731.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of the neurologic side effects of commonly prescribed medications, some of which can result in significant impairment if not addressed. This article

aims to help clinicians recognize neurologic adverse drug reactions of a range of medication classes.

RECENT FINDINGS:

Adverse drug reactions are a source of significant morbidity and rising health care costs. Failure to recognize neurologic adverse drug reactions may prompt unnecessary testing to identify a primary neurologic condition and expose the patient to continued adverse effects of a medication. Familiarity with the side effect profiles of newer medications, timing of side effects, pattern of reaction, medication rechallenge, and concurrent medical issues and awareness of significant medication interactions may aid in the identification of a medication side effect.

SUMMARY:

Early recognition of neurologic adverse medication reactions can be challenging but is essential to prompt discontinuation of the offending medication or administration of specific symptomatic treatments in select cases. A high index of suspicion is needed to arrive at the correct diagnosis promptly, initiate a treatment plan, limit unnecessary testing, and reduce overall health care cost burden.

KEY POINTS

- All beta-lactam antibiotics can potentially cause encephalopathy and seizure by reducing γ-aminobutyric acid A activity, leading to neuronal excitotoxicity. Imipenem and cefepime carry the highest risk of seizure.
- Prolonged metronidazole treatment can precipitate a subacute cerebellar syndrome that can start several weeks following treatment discontinuation. MRI shows T2-hyperintense lesions in the dentate nuclei.
- Metronidazole, fluoroquinolones, linezolid, and chloramphenicol can cause peripheral neuropathy. Symptoms are dose dependent and usually improve after medication withdrawal.
- Fluoroquinolones, macrolides, and aminoglycosides slow neuromuscular transmission by inhibiting presynaptic acetylcholine release and binding postsynaptic acetylcholine receptors. These medications are contraindicated in patients with myasthenic syndromes.
- In contrast to direct sympathomimetic agents, indirect sympathomimetic agents readily penetrate the central nervous system and have widespread neurotoxic effects, including agitation, insomnia, euphoria, delirium, psychosis, seizure, and addiction.
- Patients who are elderly, especially those with neurodegenerative diseases, are vulnerable to anticholinergic side effects. Limiting the use of anticholinergic agents, prescribing the lowest possible doses, and selecting quaternary amines are safer for patients who are elderly.
- The anticholinergic toxidrome is characterized by confusion, mydriasis, hyperthermia, tachycardia, anhidrosis, and urinary retention. Neurologic symptoms can include delirium with hallucinations and seizures. Serotonin syndrome is distinguished from anticholinergic toxicity by the presence of diaphoresis.
- Fluoxetine and other selective serotonin reuptake inhibitors can be very effective in the treatment of steroid-induced depression. Tricyclic antidepressants have been reported to exacerbate symptoms.
- Statin-associated necrotizing autoimmune myopathy is a rare condition characterized by slowly progressive lower extremity weakness, creatine kinase levels from 2000 IU/L to 20,000 IU/L, and antibodies to 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase or signal recognition particle.
- Nucleoside reverse transcriptase inhibitors cause mitochondrial toxicity by blocking mitochondrial DNA synthesis and DNA polymerase inhibition, ultimately leading to myopathy and painful peripheral neuropathy. Symptoms and creatine kinase levels improve within 8 weeks of medication discontinuation.
- Integrase strand transfer inhibitors can cause muscle weakness and creatine kinase elevations, especially when taken with statins and fenofibrates. Mitochondrial myopathy and rhabdomyolysis are rare.
- Metformin treatment can cause cognitive symptoms and myeloneuropathy by depleting vitamin B_{12}. It is important to screen vitamin B_{12} levels in a patient with diabetes mellitus presenting with new-onset neuropathic or cognitive symptoms. Some clinicians routinely monitor vitamin B_{12} levels at least every 4 years.

Article 10: Anticancer Drugs and the Nervous System

Bianca D. Santomasso, MD, PhD. Continuum (Minneap Minn). June 2020; 26 (3 Neurology of Systemic Disease):732–764.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the clinical features, prognosis, and treatment of neurotoxicity from anticancer drugs, including conventional cytotoxic chemotherapy, biologics, and targeted therapies, with a focus on the newer immunotherapies (immune checkpoint inhibitors and chimeric antigen receptor T cells).

RECENT FINDINGS:

Whereas neurologic complications from traditional chemotherapy are widely recognized, newer cancer therapies, in particular immunotherapies, have unique and distinct patterns of neurologic adverse effects. Anticancer drugs may cause central or peripheral nervous system complications. Neurologic complications of therapy are being seen with increasing frequency as patients with cancer are living longer and receiving multiple courses of anticancer regimens, with novel agents, combinations, and longer duration. Neurologists must know how to recognize treatment-related neurologic toxicity since discontinuation of the offending agent or dose adjustment may prevent further or permanent neurologic injury. It is also imperative to differentiate neurologic complications of therapy from cancer progression into the nervous system and from comorbid neurologic disorders that do not require treatment dose reduction or discontinuation.

SUMMARY:

Neurotoxicity from cancer therapy is common, with effects seen on both the central and peripheral nervous systems. Immune checkpoint inhibitor therapy and chimeric antigen receptor T-cell therapy are new cancer treatments with distinct patterns of neurologic complications. Early recognition and appropriate management are essential to help prevent further neurologic injury and optimize oncologic management.

KEY POINTS

- Immunotherapy is associated with new patterns of neurotoxicity that are distinct from those associated with traditional chemotherapy and can affect both the central and peripheral nervous systems.
- Neurologic immune-related adverse events have been reported throughout the course of treatment and even after treatment discontinuation; however, serious events tend to occur days to weeks after treatment initiation.
- Neurologic immune-related adverse events are frequently associated with immune-related adverse events affecting other organ systems; this can be a clue alerting to the possibility of a given neurologic symptom being related to the therapy.
- Early detection of neurologic immune-related adverse events is essential as prompt therapeutic intervention is likely to be associated with better recovery.
- Chimeric antigen receptor (CAR) T-cell therapy induces oncologic responses but is associated with unique toxicities, cytokine release syndrome, and immune effector cell–associated neurotoxicity syndrome.
- Neurotoxicity from anticancer drugs is a diagnosis of exclusion.

- MRI and lumbar puncture for CSF evaluation can be particularly helpful for evaluating possible therapy-associated neurotoxicity by ruling out other causes.
- Recognition of neurotoxicity is important to prevent further neurologic injury or the premature cessation of a necessary anticancer treatment.
- Determination of immune effector cell–associated neurotoxicity syndrome from CAR T-cell therapy is usually more straightforward because classic symptoms are seen that typically follow a stereotyped progression within a defined time window (usually within the first 30 days) after CAR T-cell infusion.
- Chemotherapy-induced peripheral neuropathy is typically dose dependent and cumulative.
- With most chemotherapy drugs, chemotherapy-induced peripheral neuropathy has a symmetric, distal, stocking-glove distribution. Chemotherapy-induced peripheral neuropathy predominantly consists of sensory rather than motor symptoms, although motor symptoms can occur.
- Autonomic neuropathy is rare in chemotherapy-induced peripheral neuropathy with the exception of vinca alkaloids, particularly vincristine. A typical presentation of autonomic neuropathy is constipation.
- Unlike chemotherapy-induced peripheral neuropathy, which is often dose or duration related, neuropathy related to immune checkpoint inhibitors may develop very soon after treatment starts, even within the first one to three doses.
- Neuropathy presentations from immune checkpoint inhibitors may be diverse.
- Unlike chemotherapy-induced peripheral neuropathy, in which holding or discontinuing the drug is the mainstay of management, peripheral neuropathies from immune checkpoint inhibitors are managed by holding therapy plus initiating corticosteroids. For severe cases, other immunosuppressants may be used.
- With several chemotherapies, such as cisplatin and paclitaxel, although initial symptoms usually begin during treatment, they can continue to progress for several months after completion of therapy or may worsen for several months following the discontinuation of therapy (coasting).
- Vincristine primarily affects peripheral nerves but can also cause cranial neuropathies and autonomic nervous system dysfunction. Symptoms such as hoarseness, ptosis, vision loss, facial weakness, and hearing loss are suggestive of cranial neuropathy from vincristine. The major differential diagnosis is tumor recurrence in the central nervous system.
- Unlike classic Guillain-Barré syndrome, in which albuminocytologic dissociation is seen, a lymphocytic pleocytosis is usually seen in the polyradiculoneuropathy resulting from immune checkpoint inhibitor treatment.
- Unlike chemotherapy-induced peripheral neuropathy, immune-related neuropathies are more likely to have an acute or subacute and non–length-dependent presentation.
- Immune-related neuropathies typically occur early in the treatment course but may occur many months after the start of immune checkpoint inhibitor therapy and may persist after the immune checkpoint inhibitor is discontinued.
- Myalgia and muscle cramps are common in patients treated with cisplatin and vincristine but may also occur with several other agents, such as brentuximab, rituximab, imatinib, and the combination of BRAF and MEK inhibitors.
- Myositis is a complication of immune checkpoint inhibitor therapy that usually occurs early in the course of treatment, most often triggered by anti-PD1/PD-L1–containing therapy. It may affect oculobulbar muscles and resemble myasthenia gravis.
- Immune checkpoint inhibitor–induced myositis must be distinguished from immune checkpoint inhibitor–induced myasthenia gravis.
- The diagnostic workup for myositis resulting from immune checkpoint inhibitor therapy often shows elevated creatine kinase or aldolase and a myopathic pattern on EMG. Antistriational antibodies may be present and appear to be associated with a more severe necrotizing myositis.
- In severe cases of myositis, the immune checkpoint inhibitor should be discontinued and patients should be treated with IV corticosteroids with or without IV immunoglobulin or plasma exchange.
- When myasthenia gravis occurs with immune checkpoint inhibitor therapy, it usually occurs within the first 3 months after treatment.

- Since myasthenia gravis may overlap with myositis or myocarditis, immune-related adverse event management guidelines recommend that creatine kinase, antistriational antibodies, and troponin be tested and ECG obtained in cases of immune checkpoint inhibitor–associated myasthenia gravis regardless of cardiac symptoms.
- Headache associated with immune checkpoint inhibitor therapy may suggest aseptic meningitis or hypophysitis.
- Aseptic meningitis from immune checkpoint inhibitor therapy is typically very responsive to oral corticosteroids.
- Immune checkpoint inhibitors may result in encephalitis at an incidence estimated to be 0.1% to 0.2%. Diagnosis is often challenging as patients may present with a wide range of symptoms, including altered mental status, confusion, short-term memory impairment, agitation, aphasia, and seizures.
- Studies found that early treatment with tocilizumab decreased the incidence of severe cytokine release syndrome, but it was not associated with decreased incidence or severity of immune effector cell–associated neurotoxicity syndrome (ICANS); in fact, severe ICANS rates may have been slightly higher. Therefore, tocilizumab is not recommended for management of isolated ICANS.
- ICANS is usually reversible but can be severe or even fatal.
- Many centers use prophylactic levetiracetam or another antiepileptic drug starting on the day of infusion for CAR T-cell agents associated with high incidence of immune effector cell-associated neurotoxicity syndrome (ICANS).
- A variety of inflammatory demyelinating syndromes have been reported following treatment with immune checkpoint inhibitors, including optic neuritis, transverse myelitis, and acute tumefactive demyelinating inflammatory lesions.
- Patients with cancer have an increased risk of stroke and other cerebrovascular disease because of the underlying hypercoagulability of malignancy as well as the treatments they receive.
- The most common chemotherapy to induce a cerebellar syndrome is high-dose cytarabine, usually at high cumulative dose.
- Tremor or myoclonus associated with CAR T-cell therapy is typically mild and transient; it may begin with the onset of cytokine release syndrome and may be the last immune effector cell–associated neurotoxicity syndrome symptom to resolve, usually within a few days of the start of the symptom.
- The risk of myelopathy in patients who have received an intrathecal chemotherapeutic agent is higher in those who have received prior spinal radiation.

Article 11: Drugs of Abuse and the Nervous System

Derek Stitt, MD; Neeraj Kumar, MD. Continuum (Minneap Minn). June 2020; 26 (3 Neurology of Systemic Disease):765-784.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses the neurologic complications of traditional, nontraditional, and emerging drugs of abuse.

RECENT FINDINGS:

The manufacture, distribution, and use of so-called designer drugs are increasing. These agents can induce dramatic neurologic manifestations and can evade identification on conventional drug-screening assays. Additionally, gabapentinoids, drug agents that are very familiar to

neurologists, are being abused in the general population at increasing rates to achieve euphoric highs and potentiate the effects of opiates. Furthermore, even well-known illicit narcotics such as heroin are posing dangers above their baseline because of "lacing" with additives or substitutes such as fentanyl and related compounds. These clandestine agents increase the potency of what are thought to be typical dosages to lethal levels, thus leading to more unintentional overdose deaths.

SUMMARY:

The potential for short- and long-term nervous system injury from drug abuse is well established. However, it is important for the practicing neurologist to possess awareness of the features and observed sequelae of the toxidromes of both traditional and nontraditional drugs of abuse. This is because the use of both is widespread in our society and conventional drug screening can miss detection of some powerful agents, thus forcing us to maintain a high index of suspicion based on recognition of the clinical features.

KEY POINTS

- Severe opioid overdose is characterized by the triad of coma, miosis, and respiratory depression. Treatment is rapid respiratory support and administration of an opioid antagonist (naloxone).
- New synthetic opioid compounds are being used to lace common street drugs, such as heroin, to increase their potency, which leads to more unintentional overdoses.
- Heroin abuse carries the risk of both acute and chronic central nervous system complications, including a toxic spongiform leukoencephalopathy and myelopathy.
- Gabapentin and pregabalin are increasingly becoming abused substances. Their effects serve to potentiate the already dangerous effects of opioids.
- Barbiturates have higher abuse, dependence, and withdrawal potential than benzodiazepines.
- The manifestations of benzodiazepine and barbiturate withdrawal are similar to that of alcohol, with seizures being of highest concern.
- The risk of bizarre behavioral adverse events from zolpidem use is quite low. Its abuse/dependence potential is also low but should not be ignored.
- All psychostimulants have a similar pharmacologic effect of increasing dopaminergic, serotonergic, and noradrenergic neurotransmission.
- Acute intoxication with most psychostimulants carries the risk of serious cardiovascular and cerebrovascular complications, as well as seizures.
- "Bath salts" are synthetic cathinone derivatives and are often marketed as "legal highs." They are not detected on standard drug-screening assays.
- Cerebrovascular complications of stimulant abuse, such as abuse of methamphetamine and cocaine, are well known to include hemorrhagic and ischemic stroke as well as reversible cerebral vasoconstriction syndrome.
- Synthetic cannabinoids are more potent than conventional cannabis and can induce greater stimulantlike effects, including severe agitation and psychosis.
- Seizures are a known and concerning risk with the use of synthetic cannabinoids.
- Marijuana use is not totally benign. Increased risk for neurologic injury exists due to acute cerebral vascular disease; people who use marijuana chronically are at risk for cannabinoid hyperemesis syndrome.
- Hallucinogens cause psychedelic highs marked by distorted sensory perception.
- Hallucinogen overdose is managed supportively. Pharmacologic agitation control may be indicated.
- Withdrawal is a not a standard feature of even repeated psychedelic drug use.
- Lysergic acid diethylamide and other hallucinogens can cause flashbacks of their effects even long after the last usage. Long-term use has been associated with a chronic hallucinogenic persisting perception disorder.
- Phencyclidine is a dissociative drug that produces a syndrome similar to a marked schizophrenic episode.
- Inhalant agents of abuse are volatile hydrocarbons with short euphoric highs lasting a few hours.
- Toluene abuse can cause a chronic white matter dementia from toxic leukoencephalopathy.

- *n*-Hexane is associated with a potentially severe axonal sensorimotor peripheral neuropathy that can persist after discontinuation.
- Nitrous oxide abuse (often in the form of *whip-its*) can lead to a functional vitamin B_{12} deficiency.
- Anticholinergic toxicity manifests with encephalopathy, dilated pupils, tachycardia, dry mouth, constipation, anhidrosis, and urinary retention. Seizures, myoclonus, and coma are risks in severe cases.
- Recreational use of *purple drank* is a means of opioid and anticholinergic toxicity due to the combination of codeine-containing antitussive agents mixed with promethazine.
- IV physostigmine is used as a reversal agent for anticholinergic toxicity because of its central nervous system penetrance.
- A possible link exists between e-cigarette use (*vaping*) and risk of seizures.
- Chronic abuse of alcohol is toxic to the nervous system in many ways, including cerebellar toxicity, peripheral neuropathy (small fiber predominant), and chronic cognitive impairment that may not resolve after cessation.
- People who chronically abuse alcohol are at risk for developing nutritional deficiencies that lead to neurologic injury (thiamine, vitamin B_{12}, and vitamin B_6 deficiency).

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Peripheral Nerve and Motor Neuron Disorders

Article 1: A Structured Approach to the Diagnosis of Peripheral Nervous System Disorders

Zachary N. London, MD, FAAN. Continuum (Minneap Minn). October 2020; 26 (5 Peripheral Nerve and Motor Neuron Disorders):1130–1160.

ABSTRACT

PURPOSE OF REVIEW:

Neuroanatomic localization and pattern recognition can be used to diagnose both focal lesions and generalized disorders of the peripheral nervous system. This article describes the nature and pattern of sensory and motor deficits associated with lesions of specific spinal nerve roots, plexus, or peripheral nerves. It also describes the patterns of sensory and motor deficits that suggest multifocal or generalized disorders of the motor neurons, sensory neurons, and peripheral nerves.

RECENT FINDINGS:

The pattern of sensory and motor deficits may be used to distinguish lesions of the peripheral nervous system from those of the central nervous system. The spinal roots, nerve plexus, and peripheral nerves supply specific muscles and receive sensory input from distinctive cutaneous regions. Focal lesions of these structures therefore produce characteristic patterns of sensory and motor deficits. Multifocal or generalized disorders of the peripheral nervous system may be distinguished by categorizing their sensory and motor involvement, proximal and distal predominance, and degree of symmetry. Serum tests, CSF analysis, electrodiagnostic studies, MRI, ultrasound, nerve biopsy, and skin biopsy have unique roles in the diagnosis of suspected neuromuscular disorders.

SUMMARY:

A structured approach to the diagnosis of nerve and motor neuron disorders can lead to hypothesis-driven diagnostic testing. Ancillary tests should be reserved for cases in which confirming or refuting a diagnosis will change patient management.

KEY POINTS

- **The presence of neuropathic pain in an affected limb is more suggestive of a peripheral nervous system lesion than a central nervous system lesion.**

- Features that suggest a central nervous system lesion rather than a peripheral nervous system lesion include a sensory level on the trunk, hyperreflexia, hemibody symptoms, weakness of extensors in an arm, and weakness of flexors in a leg.
- Neuralgic amyotrophy may appear to localize to multiple nerves in the same limb rather than a specific part of the brachial plexus.
- Injuries to nerve roots and mixed nerves, both of which contain both sensory and motor components, may present with pain or sensory symptoms without weakness.
- Chronic inflammatory demyelinating polyradiculoneuropathy progresses for more than 8 weeks after symptom onset. Unlike acute inflammatory demyelinating polyradiculoneuropathy, it is generally not associated with dysautonomia, weakness of cranial muscles, or dyspnea.
- Mononeuritis multiplex affects named nerves but not necessarily at the common entrapment sites.
- Mononeuritis multiplex is usually an axonal process, but multifocal acquired demyelinating sensory and motor neuropathy and hereditary neuropathy with liability to pressure palsies are multifocal demyelinating neuropathies.
- Distal symmetric polyneuropathy usually begins to involve the distal upper extremities around the time that the lower extremity sensory symptoms progress to the level of the knees.
- Clinical features that should raise suspicion for a hereditary cause of neuropathy include young age of onset, family history, and high arches and hammer toes.
- Spinal bulbar muscular atrophy may cause fasciculations in the face or tongue, signs of androgen deficiency (including gynecomastia), and slowly progressive bulbar and proximal weakness.
- The pseudobulbar affect seen in patients with amyotrophic lateral sclerosis represents dysregulation of emotional output rather than a mood disorder.
- Overt dementia is not common in amyotrophic lateral sclerosis, but up to half of patients will have some impaired cognition or behavioral problems.
- Brachial amyotrophic diplegia and leg amyotrophic diplegia present with painless flaccid weakness starting in one body segment, which may or may not eventually progress to involve other body segments or cause upper motor neuron pathology.
- Systemic infections with West Nile Virus and specific enteroviruses may cause a poliolike illness characterized by flaccid paralysis with or without encephalitis.
- The extensor digitorum brevis muscle may atrophy in sensorimotor distal symmetric polyneuropathy but is often relatively spared in distal myopathies.
- The weakness in amyotrophic lateral sclerosis tends to follow a myotomal pattern, whereas the weakness in multifocal motor neuropathy may be in the distribution of specific peripheral nerves.
- Early in the course of multifocal motor neuropathy, patients may have significant weakness with little or no atrophy, suggesting that the motor axons are still intact.
- Hirayama disease (monomelic amyotrophy) presents in young men with unilateral or bilateral hand weakness that progresses for years and then plateaus.
- Proprioception is often involved early in disorders affecting the dorsal columns and late in disorders affecting the peripheral nerves.
- Patients with sensory neuronopathy may initially appear weak on confrontational testing but are able to generate full power when they look at the limb being tested.
- Sensory neuronopathy may be idiopathic or associated with Sjögren syndrome, a paraneoplastic syndrome, human immunodeficiency virus, or pyridoxine overdose.
- The most useful screening laboratory tests for the workup of distal symmetric polyneuropathy are tests for diabetes or prediabetes, serum lipids and cholesterol, a vitamin B_{12} level, and serum protein electrophoresis and immunofixation.
- Paraproteinemia may be associated with chronic inflammatory demyelinating polyradiculoneuropathy, is common in patients with distal acquired demyelinating symmetric neuropathy, and is present in most patients with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome.

- The overreliance on modest CSF protein elevations is a common reason for the overdiagnosis of chronic inflammatory demyelinating polyradiculoneuropathy.
- Electrodiagnostic testing is an important part of the workup for mononeuropathies, mononeuritis multiplex, demyelinating neuropathy, sensory neuropathy, and motor neuron disease, but it is not sensitive for small fiber polyneuropathy or pure sensory radiculopathy.
- MRI of the spine can identify common causes of radiculopathy and aid in the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy and Hirayama disease but may show degenerative changes of questionable significance in both symptomatic and asymptomatic individuals.
- Ultrasound imaging is useful in the workup of entrapment neuropathies and has emerging indications in the workup of other neuromuscular disorders.
- A nerve biopsy is the diagnostic test of choice for suspected nonsystemic vasculitic neuropathy. In the setting of known systemic vasculitis, nerve biopsy should only be performed if demonstrating peripheral nerve involvement will lead to a change in immunomodulatory treatment.

Article 2: Diabetes and Metabolic Disorders and the Peripheral Nervous System

Christopher H. Gibbons, MD, MMSc, FAAN. Continuum (Minneap Minn). October 2020; 26 (5 Peripheral Nerve and Motor Neuron Disorders):1161–1183.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an up-to-date review of the manifestations of neuropathy seen in the setting of diabetes and other metabolic disorders.

RECENT FINDINGS:

Although a number of metabolic disorders cause or are associated with peripheral neuropathy, the neuropathies associated with glucose dysregulation make up the vast majority of cases. Recent investigations have determined major differences in the neuropathies associated with type 1 and type 2 diabetes. Neuropathy in type 1 diabetes is closely linked to glycemic control, whereas neuropathy in type 2 diabetes is linked to dyslipidemia, central obesity, hypertension, insulin resistance, and glucose control. Although length-dependent axonal distal symmetric polyneuropathy is the most common clinical presentation, diabetes is also associated with acute, asymmetric, painless, and autonomic neuropathies.

SUMMARY:

The prevalence of diabetes and metabolic syndrome is increasing across the globe. The need to recognize and treat the wide array of clinical manifestations of neuropathy detected in individuals with metabolic disorders will continue to grow. As a consequence, an increasing number of well-trained physicians who can manage these patients is needed. At present, treatment is largely focused on prevention and symptomatic management. Investments into funding for both basic and clinical science are necessary to bring novel therapeutic interventions into clinical practice.

KEY POINTS

- A number of manifestations of neuropathy are seen in diabetes, including length-dependent neuropathy, acute generalized or focal neuropathies, mononeuropathies, and autonomic neuropathies.

- The risk of neuropathy in type 1 diabetes is primarily linked to glucose control, whereas the risks of neuropathy in type 2 diabetes include glucose control, hyperlipidemia, hypertension, abdominal obesity, low levels of high-density lipoproteins, and tobacco use.
- Approximately half of patients with diabetic neuropathy have neuropathic pain; however, it is important to recognize that the absence of pain does not rule out a neuropathy.
- Small unmyelinated axons are affected earlier than large fibers in most cases of axonal neuropathy in type 2 diabetes, so an examination should always include testing for signs of small fiber dysfunction (thermal or pain sensation) as well as large fiber function (reflexes, vibration detection).
- The presence of atypical features in a patient with suspected distal symmetric polyneuropathy, such as a significant asymmetry, an acute onset, or early motor involvement, suggests a different neuropathy type or diagnosis and should prompt further diagnostic evaluation, including nerve conduction studies and EMG.
- Nerve conduction studies and EMG are not required as part of the routine diagnosis of distal symmetric polyneuropathy in diabetes unless atypical features are present.
- The diagnosis of distal symmetric polyneuropathy provides a valuable opportunity to educate patients on the health benefits of addressing risk factors associated with neuropathy (glucose control, hyperlipidemia, hypertension, tobacco use), advocate for exercise, and counsel on the importance of proper foot care.
- The risks associated with neuropathy development exist in the prediabetes state. The individual components of the metabolic syndrome, including glucose dysregulation/insulin resistance, dyslipidemia (hypertriglyceridemia and low high-density lipoprotein level), central obesity, and hypertension, all contribute to the risk of developing distal symmetric polyneuropathy.
- The acute to subacute onset of pain and weakness in the hip and leg of an individual with diabetes should raise suspicion for diabetic lumbosacral radiculoplexus neuropathy. Early recognition and intervention with IV corticosteroids may improve neuropathic pain and reduce the associated morbidity.
- Treatment-induced neuropathy of diabetes should be suspected in an individual with diabetes who presents with the acute to subacute onset of neuropathic pain in a symmetric pattern that is accompanied by predominantly small fiber findings. A significant improvement in glycemic control that precedes the development of pain is the clue to the diagnosis.
- The earliest clinical manifestation of a diabetic autonomic neuropathy is a resting tachycardia.
- Cardiovascular autonomic neuropathy (particularly with orthostatic hypotension) is associated with significantly increased mortality risk in patients with diabetes, with 5- to 10-year mortality rates greater than 50%.
- Gastroparesis is a common and disabling manifestation of diabetic autonomic neuropathy, but the potential for symptomatic improvement exists with better glycemic control.
- Constipation may be a manifestation of diabetic autonomic neuropathy but is also frequently due to medication. A careful review of both prescribed and over-the-counter medications may identify potential opportunities to improve symptoms.
- Diabetic diarrhea is often profuse and watery; it frequently occurs at night with fecal incontinence. Medications should be reviewed carefully because identification and removal of offending medications may improve symptoms.
- Bladder dysfunction is common in diabetes and often related to medication side effects. As with other diabetic autonomic neuropathies, offending medications should be removed as the initial step in management.
- Sexual dysfunction is common in both men and women with diabetes and frequently is due to a combination of psychological and physical factors, both of which should be addressed.
- Neuropathy involving the sympathetic cholinergic nerves results in a length-dependent region of anhidrosis, but patients typically present with complaints of proximal hyperhidrosis.
- Recurrent hypoglycemia blunts future autonomic responses to low levels of glucose, creating a vicious cycle of recurrent hypoglycemia because of the body's inability to sense low glucose levels.
- Recurrent hypoglycemia is associated with an increase in cardiovascular mortality, although the exact mechanism for the increase in mortality is still under investigation.

- It is controversial whether chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) occurs more frequently in individuals with diabetes; however, CIDP is widely overdiagnosed. A diagnosis of CIDP in a patient with diabetes should be based on typical clinical features, not on nerve conduction study findings alone.
- Uremia is linked to an increased risk of length-dependent neuropathy but may improve with dialysis or kidney transplantation.
- An acute optic neuropathy may also be seen in uremia and should be treated with hemodialysis and corticosteroids.

Article 3: Guillain-Barré Syndrome

Kazim A. Sheikh, MBBS. Continuum (Minneap Minn). October 2020; 26 (5 Peripheral Nerve and Motor Neuron Disorders):1184–1204.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the clinical features, diagnosis and differential diagnosis, prognosis, pathogenesis, and current and upcoming treatments of Guillain-Barré syndrome (GBS).

RECENT FINDINGS:

GBS is an acute inflammatory neuropathic illness with striking clinical manifestations and significant morbidity. A substantial proportion of patients with GBS do not respond to current immunomodulatory therapies (ie, plasma exchange and IV immunoglobulin [IVIg]), highlighting the need for new therapies. Prognostic models that can accurately predict functional recovery and the need for artificial ventilation have emerged. These models are practical, and online calculators are available for clinical use, facilitating early recognition of patients with poor outcome and the opportunity to personalize management decisions. Clinical and experimental studies have identified innate immune effectors (complement, macrophage lineage cells, and activating Fcγ receptors) as important mediators of inflammatory nerve injury. Two complement inhibitors are undergoing clinical testing for efficacy in GBS.

SUMMARY:

GBS is the most common cause of acute flaccid paralysis in the United States and worldwide. New treatments for GBS have not emerged since the 1990s. Our understanding of the pathogenesis of this disorder has progressed, particularly over the past decade; as a result, new therapeutic agents targeting different components of the complement cascade are at advanced stages of clinical development.

KEY POINTS

- Guillain-Barré syndrome (GBS) encompasses a spectrum of acute neuropathic disorders, with muscle weakness being the cardinal manifestation in the majority of patients. It is the most common cause of acute flaccid paralysis in the United States and worldwide.
- The National Institute of Neurological Disorders and Stroke diagnostic criteria for paralytic GBS are simple and practical for routine clinical use; the key features of the criteria include symmetric flaccid weakness, decreased deep tendon reflexes, and exclusion of alternative causes.
- Although the first symptoms of acute inflammatory demyelinating polyradiculoneuropathy (AIDP) are often sensory, it is primarily a motor polyradiculoneuropathy causing symmetric weakness of proximal and distal muscles. The classic pattern is of ascending weakness, but symptoms may also begin proximally.

- Of patients with GBS, 25% to 30% will require intubation because of respiratory muscle weakness or pharyngeal muscle weakness (airway protection); patients should be closely monitored for the need of mechanical ventilation.
- Miller Fisher syndrome, the most common minor subtype of GBS, is characterized by a triad of ophthalmoplegia, ataxia, and areflexia.
- An altered level of consciousness or hyperreflexia with external ophthalmoplegia and ataxia reflects central nervous system involvement indicative of Bickerstaff brainstem encephalitis. Miller Fisher syndrome–related disorders are considered a clinical continuum with Bickerstaff brainstem encephalitis on one end and Miller Fisher syndrome on the other.
- Residual symptoms after GBS are common and include fatigue, pain, paresthesia, and reduced muscle strength.
- Nerve conduction studies and EMG provide confirmation of an acute neuropathic process and may differentiate between demyelinating and axonal variants of GBS. They are often relatively normal early in the course; serial studies are often necessary and may be useful for prognostication.
- Partial motor nerve conduction block without temporal dispersion may be seen in acute motor axonal neuropathy because of reversible conduction failure at the nodes of Ranvier. Other demyelinating features, such as reduced conduction velocity and prolonged minimal F-wave or distal motor latencies, are absent.
- CSF analysis typically shows albuminocytologic dissociation. A mild pleocytosis (<50 cells/mm^3) can be seen in up to 10% to 15% of patients with GBS. A pleocytosis of greater than 50 cells/mm^3 suggests an alternative diagnosis.
- Prognostic models for GBS based on clinical parameters, including Medical Research Council (MRC) sum score, which are collected as part of standard care, can reliably predict the need for mechanical ventilation in the first week and functional outcomes at 4 weeks to 6 months after admission.
- AIDP, acute motor axonal neuropathy, and acute motor-sensory axonal neuropathy share common pathologic features, including activation of components of the innate immune system such as complement activation and upregulation of Fc receptors for IgG (FcγRs). These are promising therapeutic targets.
- It is believed that GBS is triggered by environmental exposures in genetically susceptible hosts.
- *Campylobacter jejuni* is the most common trigger for GBS, particularly the axonal forms, with an estimated prevalence of 30%. However, the risk of GBS with *C. jejuni* infection is low (less than 2 in 10,000).
- Noninfectious events, including trauma, vaccinations, immunosuppression, and pregnancy, may rarely trigger GBS.
- The risk of developing GBS following influenza infection is much higher than the risk of GBS following vaccination. Patients who develop GBS following influenza or any other vaccine should not receive the same vaccine again.
- Postinfectious molecular mimicry is the predominant pathophysiologic mechanism in Miller Fisher syndrome and axonal variants and in patients who develop AIDP following *Mycoplasma pneumoniae* infection.
- Supportive and intensive care remains the cornerstone of management of patients with GBS during the acute phase of this monophasic illness, and immune therapy with plasma exchange or IV immunoglobulin (IVIg) hastens recovery.
- Randomized clinical trials indicate that IVIg and plasma exchange hasten recovery in patients with GBS, and both treatments were found to be equally efficacious.
- Of patients with GBS treated with IVIg or plasma exchange in clinical trials, 40% to 50% did not have a clinical response (ie, did not meet primary end point), emphasizing the need for new therapies.
- Randomized controlled data indicate that combination treatment with plasma exchange followed by IVIg is not superior to treatment with IVIg or plasma exchange alone, and anecdotal observations indicate that combination treatment with IVIg followed by plasma exchange is no better than IVIg alone. Combination therapy is generally discouraged.
- No evidence- or consensus-based recommendations are available for additional immunomodulatory treatments for patients with GBS for whom initial IVIg or plasma exchange treatment has failed, and further supportive medical management should be tailored according to individual needs in such cases.

- Biologics targeting the complement cascade are at various stages of clinical trials in GBS, and neonatal Fc receptor (FcRn) inhibitors (which can reduce IgG autoantibody burden) and modulators of FcγR are at advanced stages of clinical development with potential applicability to GBS.

Article 4: Chronic Inflammatory Demyelinating Polyradiculoneuropathy and Its Variants

Kelly Gwathmey, MD. Continuum (Minneap Minn). October 2020; 26 (5 Peripheral Nerve and Motor Neuron Disorders):1205–1223.

ABSTRACT

PURPOSE OF REVIEW:

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and its variants comprise a group of immune-mediated neuropathies with distinctive clinical presentations and electrodiagnostic features. Prompt recognition of these treatable disorders is mandatory as delays result in significant disability and morbidity. This article highlights the clinical presentation, pathophysiology, diagnostic evaluation, and treatment approach of these polyneuropathies.

RECENT FINDINGS:

The spectrum of CIDP is expanding with the recent characterization of neuropathies associated with nodal and paranodal antibodies. These neuropathies are distinguished by their unique presentations and are often refractory to IV immunoglobulin (IVIg) therapy. Subcutaneous immunoglobulins have recently been approved as a treatment option for CIDP and join corticosteroids, IVIg, and plasma exchange as first-line treatment.

SUMMARY:

CIDP is characterized by progressive symmetric proximal and distal weakness, large fiber sensory loss, and areflexia, with clinical nadir reached more than 8 weeks after symptom onset. Autoimmune demyelinating neuropathies fall on a continuum, with differences in the type of nerve fibers affected and pattern of deficits. Distinguishing between typical CIDP and its variants allows for selection of the most appropriate treatment.

KEY POINTS

- One-half of patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) have a typical presentation of symmetric proximal and distal weakness, length-dependent loss of large fiber sensation, and areflexia.
- Up to 18% of patients with CIDP will have an acute onset that mimics Guillain-Barré syndrome.
- CIDP is differentiated from Guillain-Barré syndrome by a protracted time course, absence of autonomic dysfunction, and absence of respiratory impairment in most patients.
- All patients with suspected CIDP should be screened for a monoclonal gammopathy.
- Albuminocytologic dissociation is expected on CSF analysis in CIDP. The presence of leukocytosis raises suspicion for other conditions, such as neurosarcoidosis, human immunodeficiency virus (HIV), or carcinomatous meningitis.
- The sural sparing pattern is an electrophysiologic hallmark of CIDP and is often found in addition to other acquired demyelinating features.

- Patients with suspected CIDP do not require a nerve biopsy if the electrodiagnostic findings and clinical features are consistent with an acquired demyelinating polyradiculoneuropathy.
- More than 15 sets of diagnostic criteria for CIDP have been published; the most widely accepted is the European Federation of Neurological Sciences/Peripheral Nerve Society criteria.
- The first-line treatments for CIDP include immunoglobulins (IV and subcutaneous), corticosteroids, and plasma exchange. Given the need for long-term venous access and limited facilities capable of outpatient plasma exchange, in practice, plasma exchange is considered second- or third-line treatment by many experts.
- Clinical trials suggest IV immunoglobulin (IVIg) can be discontinued successfully without relapse in approximately 50% of patients. The treating physician should work toward reducing or discontinuing the IVIg if possible.
- Use of clinically appropriate outcome measures, such as disability scales and quality-of-life instruments, helps to inform medical decision making in CIDP.
- Multifocal motor neuropathy may mimic amyotrophic lateral sclerosis given its painless progressive weakness, but it is differentiated by its lack of upper motor neuron signs and electrophysiologic evidence of conduction block on motor nerve conduction studies.
- Distal acquired demyelinating symmetric (DADS) neuropathy is often associated with IgM monoclonal gammopathy and myelin-associated glycoprotein antibodies. Patients with DADS are often refractory to treatment.
- Autoantibodies directed toward paranodal and nodal antigens are present in approximately 10% of cases of CIDP; these cases have unique clinical presentations and are often IVIg refractory.
- Patients with nodal and paranodal autoantibodies may respond to rituximab as the autoantibodies are of the IgG4 isotype.

Article 5: Charcot-Marie-Tooth Disease and Other Hereditary Neuropathies

Christopher J. Klein, MD, FAAN. Continuum (Minneap Minn). October 2020; 26 (5 Peripheral Nerve and Motor Neuron Disorders):1224–1256.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of Charcot-Marie-Tooth disease (CMT) and other inherited neuropathies. These disorders encompass a broad spectrum with variable motor, sensory, autonomic, and other organ system involvement. Considerable overlap exists, both phenotypically and genetically, among these separate categories, all eventually exhibiting axonal injury and neurologic impairment. Depending on the specific neural and non-neural localizations, patients experience varying morbidity and mortality. Neurologic evaluations, including neurophysiologic testing, can help diagnose and predict patient disabilities. Diagnosis is often complex, especially when genetic and acquired components overlap.

RECENT FINDINGS:

Next-generation sequencing has greatly improved genetic diagnosis, with many third-party reimbursement parties now embracing phenotype-based panel evaluations. Through the advent of comprehensive gene panels, symptoms previously labeled as idiopathic or atypical now have a better chance to receive a specific diagnosis. A definitive molecular diagnosis affords patients improved care and counsel. The new classification scheme for inherited neuropathies emphasizes the causal gene names. A specific genetic diagnosis is important as considerable

advances are being made in gene-specific therapeutics. Emerging therapeutic approaches include small molecule chaperones, antisense oligonucleotides, RNA interference, and viral gene delivery therapies. New therapies for hereditary transthyretin amyloidosis and Fabry disease are discussed.

SUMMARY:

Comprehensive genetic testing through a next-generation sequencing approach is simplifying diagnostic algorithms and affords significantly improved decision-making processes in neuropathy care. Genetic diagnosis is essential for pathogenic understanding and for gene therapy development. Gene-targeted therapies have begun entering the clinic. Currently, for most inherited neuropathy categories, specific symptomatic management and family counseling remain the mainstays of therapy.

KEY POINTS

- Charcot-Marie-Tooth disease (CMT) is the most common inherited neuropathy but accounts for only a minority of the gene abnormalities among inherited neuropathies.
- Patients with inherited neuropathy often describe their symptoms as subacute in onset, but foot and ankle abnormalities (hammer toes, pes cavus, pes planus, cavovarus) and shin and hand atrophy along with needle EMG changes support the chronicity of disease course.
- The presence of ankle reflexes and normal sensation in patients with symmetric ankle weakness raises the possibility of inherited distal myopathy or inherited distal hereditary motor neuron disease mimicking CMT. The genes responsible for distal myopathy and progressive muscular atrophy should be considered in next-generation sequencing panel testing for inherited neuropathies.
- Gene names are increasingly being included in the nomenclature of inherited disorders including inherited neuropathies.
- Historical clues of inherited neuropathies should be sought, including frequent ankle sprains and foot fractures, recurrent ingrown toenails (paronychia), and painless foot ulcers.
- Prolonged blink R1 response latency greater than 13 milliseconds, regardless of severity or age, suggests primary demyelinating inherited neuropathy.
- Patients with inherited neuropathy are more susceptible to clinical declines from superimposed acquired neuropathies such as diabetes and neurotoxic chemotherapy.
- *PMP22* duplications account for approximately 70% of cases of primary demyelinating neuropathy.
- Mutations of *MFN2* are the most common known cause of primary axonal CMT.
- Not all patients with inherited demyelinating neuropathies have CMT; some may have disorders such as mitochondrial neurogastrointestinal encephalomyopathy or metachromatic leukodystrophy.
- Absence of male-to-male transmission and females being more mildly affected than males within a family suggests CMTX1-*GJB1*, the second most common form of CMT.
- Patients with hereditary sensory autonomic neuropathy commonly have pain, and some forms also have gastrointestinal dysmotility, insensate injuries with amputations, and mortality from respiratory and feeding difficulties.
- Patients with hereditary neuropathy with liability to pressure palsies need to be recognized to avoid unnecessary decompressive surgeries at points of compression.
- Family history, recurrent episodes, and, possibly, younger age of onset distinguish hereditary brachial plexus neuropathy from idiopathic neuralgic amyotrophy (Parsonage-Turner syndrome).
- Two drugs that knock down RNA expression of mutant and wild-type TTR (patisiran and inotersen) have been recently approved for hereditary transthyretin amyloidosis neuropathy.
- Standard next-generation sequencing cannot identify nucleotide repeat expansion mutations such as those occurring in Friedreich ataxia and cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS).
- Enzyme replacement therapy with recombinant α-galactosidase was the first available specific treatment for Fabry disease. Recently, migalastat, a new drug using chaperone therapy, was approved by the US Food and

Drug Administration. Migalastat is a small molecule drug that stabilizes and facilitates trafficking of rescuable mutant forms of α-galactosidase A protein, partially restoring the enzyme activity in lysosomes.

- Next-generation sequencing is simplifying the genetic diagnosis of inherited neuropathies.
- The accuracy of next-generation sequencing testing correlates to the depth of coverage of all targeted genes represented in panel testing.
- Foot and ankle surgeries should be reserved for patients for whom bracing for ankle stability has failed, with tendon transfers favored over joint fusions.

Article 6: Peripheral Neuropathies Associated With Vasculitis and Autoimmune Connective Tissue Disease

Chafic Karam, MD. Continuum (Minneap Minn). October 2020; 26 (5 Peripheral Nerve and Motor Neuron Disorders):1257–1279.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses peripheral neuropathies associated with vasculitis (isolated or in the setting of systemic vasculitis) and autoimmune connective tissue disease and provides a brief overview of their diagnostic evaluation and management.

RECENT FINDINGS:

The classification of systemic vasculitic neuropathy and nonsystemic vasculitic neuropathy continues to evolve. Classification according to the presence of antineutrophil cytoplasmic antibodies and their subtypes facilitates prognostication and management. Recent research on antineutrophil cytoplasmic antibody–associated vasculitis has added to our understanding of its neurologic complications. The treatment of vasculitis is also evolving, and new nonsystemic vasculitic neuropathy classification has impacted the treatment and management of this disorder. New classification criteria for Sjögren syndrome (which commonly causes neurologic complications) facilitate accurate and timely diagnosis.

SUMMARY:

Vasculitis and autoimmune connective tissue disease are underrecognized and treatable causes of peripheral neuropathy. Furthermore, peripheral neuropathy may reveal an underlying rheumatologic or vasculitic disorder. Rapid recognition and treatment are essential. Familiarity with the diagnosis and treatment of neuropathies in the setting of connective tissue disease and vasculitis reduces morbidity and, in some cases, mortality.

KEY POINTS

- Asymmetric signs or symptoms or stepwise progression, especially when associated with systemic symptoms, are highly suggestive of vasculitic neuropathy.
- Nerve conduction studies done on opposite limbs, even if asymptomatic, are essential to demonstrate asymmetry or multifocality, which can be missed clinically.
- Nerve biopsy is necessary for a diagnosis of definite vasculitis, but, because of the patchy nature of the disease process, a negative biopsy does not rule out vasculitis.
- Biopsy of a nearby muscle increases the diagnostic yield of biopsy for suspected vasculitic neuropathy by about 15%.

- Laboratory testing is essential to determine whether vasculitis is secondary to a systemic disorder or exposure that may require different management.
- Adult-onset asthma in a patient with a subacute asymmetric neuropathy or multifocal neuropathy strongly suggests eosinophilic granulomatosis with polyangiitis.
- Testing for antineutrophil cytoplasmic antibodies (ANCA) in the setting of vasculitis is essential to determine prognosis and appropriate treatment.
- In the rare instance in which both myeloperoxidase and proteinase 3 are positive in the same patient, drug-induced vasculitis should be suspected.
- In polyarteritis nodosa, testing for hepatitis B virus is essential. Testing for ANCA is negative, and glomerulopathy is not present.
- Appropriate blood handling, including temperature control, is essential for testing for cryoglobulinemia.
- In mild cases of cryoglobulinemic neuropathy associated with infection, immunosuppression may not be required when the infection is treated adequately.
- In nonsystemic vasculitic neuropathy, systemic symptoms and signs are usually absent and serologic markers are negative.
- Different syndromes of nonsystemic vasculitic neuropathy carry different prognoses. The diagnosis is usually made clinically, and patients should be treated if the disease is active.
- Tumor necrosis factor-α inhibitors, which are commonly used to treat rheumatoid arthritis, can cause inflammatory autoimmune neuropathies.
- Patients with Sjögren syndrome frequently present to the neurologist first because of peripheral neuropathy.
- The presence of a significant sensory neuropathy or dorsal root ganglionopathy should prompt a thorough evaluation for Sjögren syndrome.

Article 7: Peripheral Neuropathies Due to Vitamin and Mineral Deficiencies, Toxins, and Medications

Nathan P. Staff, MD, PhD, FAAN. Continuum (Minneap Minn). October 2020; 26 (5 Peripheral Nerve and Motor Neuron Disorders):1280–1298.

ABSTRACT

PURPOSE OF REVIEW:

Vitamin and mineral deficiencies, neurotoxins, and, particularly, prescription medications, are some of the most common causes of peripheral neuropathy. Recognition and prompt treatment of these neuropathies require a high index of suspicion and an accompanied detailed history. This article provides a comprehensive approach and list of items that must be considered in the setting of new-onset neuropathy.

RECENT FINDINGS:

Although many of the neuropathies described in this article have decreased in prevalence in developed countries because of public health interventions and occupational/environmental regulations, new causes for this class of neuropathy continue to be uncovered.

SUMMARY:

The peripheral nervous system is susceptible to a broad array of metabolic and toxic abnormalities, which most often lead to a length-dependent sensory-predominant axonal peripheral neuropathy. A careful history accompanied by recognition of multisystem clues can

increase recognition of these neuropathies, which is important as many have specific treatments that may either improve the neuropathy or halt its progression.

KEY POINTS

- A broad review of systems that includes skin, nails, and hematologic and gastrointestinal systems may provide clues to a neuropathy caused by vitamin deficiencies or toxins.
- Vitamin B_{12} deficiency secondary to inadequate oral intake is uncommon, except in cases of a strict vegan diet.
- Simultaneous onset of sensory symptoms in the hands and feet suggests cervical cord pathology, which may be seen in vitamin B_{12} or copper deficiencies.
- When investigating vitamin B_{12} deficiency, it is important to also consider copper deficiency because the clinical picture can be very similar.
- Vitamin B_6 supplementation is only routinely recommended in the setting of isoniazid or hydralazine treatment, in which vitamin B_6 deficiency may occur. Otherwise, vitamin B_6 supplementation itself can cause a sensory neuropathy or sensory ganglionopathy.
- Neuropathy due to thiamine deficiency has many presentations, including length-dependent sensorimotor, cranial nerve, and motor-predominant polyneuropathy, all of which may precede cognitive and systemic symptoms.
- Establishing a causal link between alcohol use and neuropathy can be difficult for a variety of reasons, but it is recommended that all patients with neuropathy ingest minimal alcohol. Early referral to a chemical dependence specialist is recommended when alcohol use disorder is suspected.
- Uremic neuropathy in the setting of chronic dialysis is typically a mild axonal sensorimotor peripheral neuropathy; other etiologies should be considered if a severe neuropathy is encountered.
- Intoxication from arsenic or thallium is preceded by severe gastrointestinal illness, and the neuropathy may mimic Guillain-Barré syndrome.
- Obtaining a detailed occupational and hobby exposure history is critical for discovering many toxic neuropathies.
- Medications may cause peripheral neuropathy in a dose-dependent fashion or may be a rare idiosyncratic reaction.
- Coasting is a phenomenon in which a neuropathy worsens for weeks to months after the discontinuation of a toxic agent. This is most often observed in chemotherapy-induced peripheral neuropathy due to platinum-based chemotherapy but can also be seen in neuropathies due to hexanes and vitamin B_6 excess.
- Oxaliplatin causes cold-induced dysesthesia.
- Paclitaxel is associated with acute toxicity causing a pain syndrome that is not clearly due to nerve damage.
- Patients with cancer are more commonly being treated with immune-checkpoint inhibitors, which result in a neurologic adverse event in 3% of patients. These neurologic adverse events include central or peripheral nervous system syndromes, which may be life-threatening.

Article 8: Management of Neuropathic Pain in Polyneuropathy

Amanda C. Peltier, MD, MS; Derek Wood, MD. Continuum (Minneap Minn). October 2020; 26 (5 Peripheral Nerve and Motor Neuron Disorders):1299–1322.

ABSTRACT

PURPOSE OF REVIEW:

Many polyneuropathies cause significant neuropathic pain, resulting in substantial morbidity and reduced quality of life. Appropriate management is crucial for maintaining quality of life for

patients with painful polyneuropathies. The US Food and Drug Administration (FDA) has only approved one new drug for painful diabetic neuropathy in the past decade, a topical capsaicin patch that was initially approved for the treatment of postherpetic neuralgia in 2009. Gabapentinoids and serotonin norepinephrine reuptake inhibitors (SNRIs) continue to have an advantage in safety profiles and efficacy. Other antiepileptic medications remain second-line agents because of fewer studies documenting efficacy.

RECENT FINDINGS:

This article reviews recent literature on complementary and pharmacologic therapies for the management of painful polyneuropathies. Exercise has emerged as an important therapeutic tool and may also improve the underlying polyneuropathy in the setting of obesity, metabolic syndrome, and diabetes.

SUMMARY:

The approach to management of painful polyneuropathies is multifactorial, using both pharmacologic and nonpharmacologic measures to improve pain severity and patient quality of life.

KEY POINTS

- Painful polyneuropathy is one of the most common causes of neuropathic pain and may affect up to 1 in 20 Americans.
- Painful polyneuropathy is associated with significantly reduced quality of life and increased health care costs, as well as costs to society in lost worker productivity.
- Neuropathic pain leads to sleep disruption and vice versa. Up to 80% of patients with neuropathic pain have sleep disturbance.
- Half of patients with painful diabetic neuropathy have depression or anxiety, and one-fourth have both.
- Although the specific role of *SCN9A* sequence variants in the pathogenesis of small fiber neuropathy is uncertain, voltage-gated sodium channels play an important role in neuropathic pain, and pharmacologic inhibition is a promising therapeutic strategy.
- No new medications for neuropathic pain have been approved in the past 10 years (although the high-dose capsaicin patch that was approved for postherpetic neuralgia in 2009 was recently approved for use in painful diabetic polyneuropathy in July 2020). The most commonly used medications are the gabapentinoids, which act on α2δ calcium channels, and medications that increase norepinephrine at the synapse.
- Each neuropathic pain medication should generally be tried at the maximal tolerated dose for 6 to 8 weeks before concluding it is ineffective.
- Differentiating painful polyneuropathy from restless legs syndrome (RLS), which may coexist with painful neuropathy, is important as most pain medications (with the exception of the gabapentinoids) are ineffective for RLS, and some agents (such as tricyclic antidepressants) may worsen RLS.
- Setting realistic treatment expectations for pain management is essential. Complete pain relief is typically not a realistic goal.
- Gabapentin is absorbed in the intestine via an active-transport mechanism and displays nonlinear pharmacokinetics with saturable absorption and decreased bioavailability at higher doses.
- Gabapentin and pregabalin have similar efficacy, although patients may respond to, or tolerate, one and not the other. Gabapentin displays nonlinear pharmacokinetics with saturable absorption and decreased bioavailability at higher doses, which may favor the use of pregabalin.
- The two most commonly used tricyclic antidepressants for painful polyneuropathy are amitriptyline and nortriptyline.
- Caution should be exercised when initiating tricyclic antidepressants in elderly individuals or those with preexisting cognitive or autonomic dysfunction as they may be more susceptible to anticholinergic side effects, and their use should be avoided in patients with severe depression or history of suicide attempt because of the risk of intentional overdose.

- Duloxetine may be a particularly good agent for patients with painful diabetic neuropathy with comorbid depression, anxiety, or fibromyalgia.
- Despite a lower efficacy compared to gabapentinoids and serotonin norepinephrine reuptake inhibitors, antiepileptic drugs and mexiletine may still be worth a trial in some patients with refractory pain.
- Topical agents (such as lidocaine patches or cream) are of modest efficacy but may add symptomatic relief in selected patients with neuropathic pain and have the advantage of minimal side effects.
- Opioid analgesics, including tramadol, should not be used as first- or second-line medications for neuropathic pain and should only be considered in severe and refractory cases when all other options have failed. In general, referral to a pain clinic is recommended if opioid therapy is being considered.
- Opioid-induced hyperalgesia causes patients to have increased pain and diffuse allodynia that is often different than their initial pain manifestation.
- High-quality clinical trial data supporting the use of cannabinoids for neuropathic pain are lacking, and side effects are common. Their use outside of clinical trials is discouraged.
- Recognition and individualized treatment of depression is important, and cognitive therapy can be a useful tool in multidisciplinary pain clinics.
- Given the multiple health benefits of exercise and improvement in other parameters of health, exercise should be highly encouraged in all patients with painful polyneuropathy.
- An algorithmic approach that integrates pharmacologic and nonpharmacologic therapy with specific attention to comorbid sleep and mood disorders is the most effective approach to neuropathic pain management.

Article 9: Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases

Colin Quinn, MD; Lauren Elman, MD. Continuum (Minneap Minn). October 2020; 26 (5 Peripheral Nerve and Motor Neuron Disorders):1323–1347.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the clinical features, diagnostic approach, and treatments available for amyotrophic lateral sclerosis (ALS) and other motor neuron diseases. The article also provides an update on the genetics and pathophysiology of ALS.

RECENT FINDINGS:

ALS remains a clinical diagnosis without a unique biomarker. The areas of greatest progress include a large expansion in the number of genes associated with familial and sporadic ALS. The discovery of these genes, along with other work, has provided a deeper understanding of the mechanisms of motor neuron failure in ALS. Areas of particular interest include the role of transactive response DNA-binding protein 43 and other RNA-processing proteins in the development of disease.

SUMMARY:

ALS remains a relentlessly progressive disorder with an elusive core pathophysiology. The current mainstay of treatment remains symptom management and palliation, particularly in the setting of a multidisciplinary clinic. The future holds potential for targeted therapies based on an ever-evolving understanding of the pathophysiology of both familial and sporadic ALS.

KEY POINTS

- The incidence of amyotrophic lateral sclerosis (ALS) has remained constant at around 2 per 100,000 per year to 3 per 100,000 per year and is slightly higher in men than in women.
- Of patients with ALS, 90% have sporadic disease and 10% have familial ALS, which follows an autosomal dominant pattern of inheritance.
- Patients with ALS typically have a combination of upper motor neuron and lower motor neuron signs that affect multiple segments of the body.
- Frontotemporal dementia occurs in 5% to 15% of patients with ALS, and a larger proportion of patients will have subtle findings of personality change or executive dysfunction.
- The diagnostic evaluation of ALS does not need to be extensive in the setting of the appropriate clinical history and physical examination, although it is imperative to exclude all treatable conditions.
- MRI should be performed at the lowest level of upper motor neuron findings and above in patients with suspected ALS.
- Isolated upper motor neuron examination findings should prompt careful examination of the neuraxis, with MRI performed to exclude lesional causes of upper motor neuron injury.
- Gene discovery for ALS has accelerated remarkably over the past decade, leading to improved understanding of ALS pathophysiology that will ideally result in targeted therapies in the near future.
- *SOD1* mutations were the first genetic mutations discovered in familial ALS. However, *SOD1* pathology is distinct from the pathology seen in the majority of ALS cases.
- Hexanucleotide repeat expansions in *C9orf72* are the most common cause of familial ALS.
- No single cause of ALS has been determined, although multiple critical pathways in motor neuron degeneration have been identified. Of particular current interest are abnormalities in RNA processing.
- Cytoplasmic transactive response DNA-binding protein 43 (TDP-43) inclusions are a hallmark of ALS pathology in the vast majority of patients.
- No curative therapy has been identified for ALS. The mainstay of treatment is multidisciplinary care and palliative symptom management.
- The oral drug riluzole is the most widely used disease-modifying agent in ALS and has a well-established, albeit modest, effect on survival.
- Edaravone is an IV disease-modifying agent that slowed the rate of functional decline in a small number of select ALS patients with early, diffuse, and rapidly progressing disease. However, a prior trial in a broader population was negative and questions remain regarding its long-term effectiveness in the general ALS population.
- The presence of isolated lower motor neuron or upper motor neuron abnormalities should broaden the differential diagnosis but does not preclude an ALS diagnosis.
- Monomelic amyotrophy presents in young men with atrophy of one or both arms, typically in the lower cervical myotomes. The diagnosis is typically confirmed by findings on cervical MRI, including dynamic flexion demonstrating forward displacement of the dura. Although the cause of injury is not certain, the most common theory is microvascular disturbance due to compression with resultant ischemia of the anterior horn cells at C8 and T1.
- Spinal bulbar muscular atrophy is a rare cause of motor neuropathy but should be considered in men with lower motor neuron disease, sensory neuropathy on nerve conduction studies, predominant bulbar symptoms, and facial twitching. It is caused by an X-linked trinucleotide repeat disorder in the androgen receptor gene. Neurodegeneration is due to a toxic gain of function that occurs in the setting of ligand (testosterone and dihydrotestosterone) binding to the mutant receptor.

Article 10: Spinal Muscular Atrophy

Jessica Rose Nance, MD. Continuum (Minneap Minn). October 2020; 26 (5 Peripheral Nerve and Motor Neuron Disorders):1348–1368.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of the pathophysiology and clinical presentations of spinal muscular atrophy (SMA) and reviews therapeutic developments, including US Food and Drug Administration (FDA)–approved gene-targeted therapies and mainstays of supportive SMA care.

RECENT FINDINGS:

Over the past decades, an understanding of the role of SMN protein in the development and maintenance of the motor unit and the intricate genetics underlying SMA has led to striking developments in therapeutics with three FDA-approved treatments for SMA, one targeting *SMN1* gene replacement (onasemnogene abeparvovec-xioi) and two others enhancing SMN protein production from the *SMN2* gene (nusinersen and risdiplam). These therapies are most effective in infants treated at younger ages, and improvement is most striking in babies treated as neonates. Despite improvements in motor function, patients (especially those treated at older ages) continue to experience significant weakness and require continued close monitoring of respiratory and orthopedic symptoms.

SUMMARY:

Striking therapeutic advancements have changed the clinical course of SMA dramatically, although supportive care continues to play an important role in patient care.

KEY POINTS

- Spinal muscular atrophy (SMA) is a progressive motor neuron disease caused by mutations/deletions in the survival motor neuron 1 (*SMN1*) gene. It has a broad phenotypic spectrum and is classified into categories based on age of onset, motor milestone achievement, and copy number of the paralogous *SMN2* gene.
- SMA type 1 (SMA1) is the most common form of SMA and is characterized by onset of weakness in the first few months of life. Without disease-modifying therapy, babies with SMA1 never achieve the ability to sit independently, and the average time to death or requirement for permanent ventilation for an infant with untreated SMA1 is 13.5 months.
- In SMA, both copies of the *SMN1* gene are absent. Thus, motor neuron survival is dependent on the number of *SMN2* copies. Patients with SMA with more *SMN2* copies have a milder phenotype.
- The majority of patients with SMA type 1 possess two *SMN2* gene copies. Those with SMA type 2 usually have three copies, those with SMA type 3 have three or four copies, and patients with SMA type 4 typically have more than four copies. Those with SMA type 0, which presents with arthrogryposis multiplex congenita and severe respiratory failure, typically have one copy.
- In December 2016, the US Food and Drug Administration approved nusinersen as the first therapy for SMA. An antisense oligonucleotide, nusinersen targets increased efficiency of inclusion of exon 7 during splicing of *SMN2* RNA.
- Neonates with SMA with two or three *SMN2* copies treated with nusinersen before the onset of symptoms demonstrate striking improvement in motor function, with the large majority able to walk independently.
- Onasemnogene abeparvovec-xioi is an adeno-associated virus 9–mediated *SMN1* gene replacement therapy given as a single IV dose. It is indicated for patients of all SMA types who are 2 years of age or younger at the time of dosing. Similar to nusinersen, the impact of therapy is greatest in patients treated at a younger age and greater in those with three *SMN2* copies than in those with two copies.

- Risdiplam was approved in August 2020 and is a daily oral small molecule therapy that increases production of full-length SMN protein from the *SMN2* mRNA. After 12 months, nearly half of infants with SMA type 1 treated first between 1 and 7 months of age were able to sit supported for at least 5 seconds. Older individuals with SMA type 2 or SMA type 3 treated with risdiplam also showed improvement in motor function compared to a placebo-controlled group.
- Response to nusinersen, onasemnogene abeparvovec-xioi, and risdiplam therapies is more striking when they are delivered during the first months of life. Early treatment of SMA type 1 enables patients to achieve motor milestones never before possible. Some patients with SMA type 1 treated within the first weeks of life are able to walk.
- Although striking improvement in motor milestone achievement is seen in patients with SMA after treatment with nusinersen, onasemnogene abeparvovec-xioi, or risdiplam, they still experience significant weakness.
- Clinical trials are currently evaluating agents that promote muscle growth (antimyostatin antibody) and enhance muscle function (an activator of fast skeletal muscle troponin).
- Increased need exists for early diagnosis of SMA, which drives the inclusion of SMA testing in newborn screening programs and the promotion of female carrier testing in pregnant women.
- All newborns with two, three, or four copies of *SMN2* (especially those in whom an SMA type 1 or type 2 phenotype is expected) should receive immediate therapy with either onasemnogene abeparvovec-xioi or nusinersen. In patients with five or more copies (who are expected to develop an SMA type 4 phenotype), treatment can be deferred with close monitoring for symptom development.
- The efficacy of nusinersen, onasemnogene abeparvovec-xioi, and risdiplam appears to be equivalent. Decisions between the medications should be based on the patient's age and discussion of mode of delivery and side effects with the patient or the patient's parents or guardians.
- Clinical trials evaluating the potential benefits of combination treatments with *SMN1*- and *SMN2*- enhancing therapies are anticipated or currently under way.
- The extraordinary cost of SMN-targeted therapies may complicate the process of obtaining prior insurance authorization.
- Supportive therapy, including pulmonary, nutritional, and rehabilitative management, plays a vital role in the treatment of SMA since many patients continue to experience significant weakness.
- Rehabilitative management should focus on accommodating weakness and promoting mobility to improve patients' engagement and minimize the orthopedic complications of progressive weakness. Positioning and bracing are especially important for both sitting and nonsitting patients to avoid worsening contractures and scoliosis.

Article 11: Peripheral Neuropathies Associated With Monoclonal Gammopathies

Elie Naddaf, MD; Michelle L. Mauermann, MD, FAAN. Continuum (Minneap Minn). October 2020; 26 (5 Peripheral Nerve and Motor Neuron Disorders):1369–1383.

ABSTRACT

PURPOSE OF REVIEW:

Neurologists commonly evaluate patients with a monoclonal gammopathy and peripheral neuropathy. As both monoclonal gammopathy and peripheral neuropathy are common in the general population, their coexistence may, in some instances, be purely coincidental. However, monoclonal gammopathies or underlying lymphoplasmacytic disorders can affect the peripheral

nervous system by various mechanisms. This article discusses how to approach patients with monoclonal gammopathy and peripheral neuropathy, highlighting clinical and laboratory clues that may aid in establishing a diagnosis in a timely manner.

RECENT FINDINGS:

From a hematologic standpoint, a monoclonal gammopathy may be of undetermined significance or can be associated with an underlying myeloma, lymphoplasmacytic lymphoma, or amyloidosis. Each of these conditions can cause peripheral neuropathy, with varying clinical and electrodiagnostic profiles. Treatment usually consists of treating the underlying hematologic disorder. IgM-associated peripheral neuropathy may not require treatment from a hematologic standpoint, and only anecdotal evidence exists for the use of immunotherapy in such patients. Therefore, treatment should be determined on a case-by-case basis.

SUMMARY:

Evaluating for an association between a monoclonal gammopathy and a peripheral neuropathy in a patient depends on the monoclonal gammopathy subtype and the clinical and electrodiagnostic characteristics of the peripheral neuropathy.

KEY POINTS

- The coexistence of a monoclonal gammopathy and peripheral neuropathy in an individual patient is often coincidental.
- A monoclonal gammopathy has undetermined significance from a hematologic standpoint when the patient has a low serum monoclonal protein level (<3 g/dL), less than 10% plasma cells in the bone marrow, and less than 500 mg/24 hour of M protein in the urine) and no evidence of end organ damage.
- Whereas a monoclonal gammopathy may be of undetermined significance from a hematologic standpoint, it may still be of clinical significance from a neurologic standpoint.
- IgM peripheral neuropathy usually presents with progressive sensory loss resulting in gait ataxia, with no to minimal weakness (distal acquired demyelinating symmetric [DADS] phenotype).
- IgM peripheral neuropathy, distal acquired demyelinating symmetric (DADS) phenotype, is a demyelinating neuropathy with characteristic prolongation of motor distal latencies on electrodiagnostic testing.
- Waldenström macroglobulinemia–associated peripheral neuropathy can look similar to IgM peripheral neuropathy but with more prominent systemic symptoms and cytopenias.
- Chemotherapy-induced peripheral neuropathy is the most common neuropathy type encountered in multiple myeloma.
- POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) neuropathy can mimic chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) as associated features may be easily overlooked.
- The presence of thrombocytosis in a patient with CIDP should prompt evaluation for underlying POEMS.
- Any type of monoclonal gammopathy can be associated with amyloidosis.
- Among all patients with paraproteinemic disorders, patients with immunoglobulin light chain (AL) amyloidosis appear the sickest and may display cardiorespiratory, gastrointestinal, genitourinary, and systemic symptoms at presentation.
- Most commonly, patients with AL amyloidosis with peripheral nerve involvement present with generalized autonomic failure and a painful length-dependent sensory and motor peripheral neuropathy.
- The majority of patients with AL amyloidosis are not autologous stem cell transplantation eligible at diagnosis; hence, early diagnosis is important.

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Sleep Neurology

Article 1: Neurobiology and Neuroprotective Benefits of Sleep

Logan Schneider, MD. Continuum (Minneap Minn). August 2020; 26 (4 Sleep Neurology):848–870.

ABSTRACT

PURPOSE OF REVIEW:

This article outlines the neurocircuitry underlying sleep-wake and circadian physiology with a focus on the fundamental roles that sleep and circadian health play in optimal neurologic function.

RECENT FINDINGS:

The foundation of sleep and wake promotion is laid primarily by the "fast-acting" neurotransmitters: γ-aminobutyric acid (GABA) for sleep and glutamate for wake. External to these primary systems are a host of modulatory systems that are characterized by two flip-flop switches of mutually inhibitory neurotransmitter systems that facilitate transitions between wake and sleep as well as non–rapid eye movement (non-REM) and REM sleep. Additional mechanisms are in place to help coordinate the sleep-wake states with environmental, metabolic, and behavioral demands. The complexity of the evolutionarily preserved sleep-wake and circadian systems, the proportion of the day dedicated to the natural sleeping period, as well as the neurocognitive dysfunction and neurodegeneration caused by deficient sleep highlight the importance of defining, assessing, and optimizing the sleep health of our patients and ourselves.

SUMMARY:

Exciting discoveries continue to elucidate the underlying mechanisms of sleep and wake state coordination, reinforcing fundamental healthy practices and paving the way for new interventions that preserve and promote optimal neurologic health.

KEY POINTS

- **All stages of sleep are essential, are actively promoted, and will homeostatically rebound if selectively deprived.**
- **Sleep is dynamic, cycling through stages every 90 to 120 minutes, but also changing from slow-wave predominant to REM predominant over the course of the night.**
- **Sleep health is not just defined by the duration of sleep but also by schedule regularity, alignment with circadian biorhythms, and continuity/stability.**

- Monoamines (dopamine, norepinephrine, serotonin, and histamine) are modulatory neurotransmitters that promote wakefulness.
- The "fast-acting" neurotransmitter, glutamate, is the backbone of the wake-promoting neurocircuitry. The parabrachial/precoeruleus and supramammillary nuclei are the primary wake-promoting glutamatergic centers.
- The basal forebrain (using γ-aminobutyric acid [GABA] and acetylcholine) and ventral periaqueductal gray (using dopamine) also strongly promote wake.
- A dorsal flow of acetylcholine pathways from the laterodorsal tegmental and pedunculopontine tegmental nuclei to the thalamus promotes cortical processing reflected by a desynchronized EEG.
- Orexin (hypocretin) neurons in the lateral hypothalamus are critical to stabilization of the wake state and are virtually absent in individuals with narcolepsy type 1 due to immune-mediated destruction.
- GABA is the primary neurotransmitter system involved in active sleep promotion. The main sources of GABA activity are the preoptic area and parafacial zone.
- The acetylcholine system becomes active again during REM sleep, allowing for information to transit through the thalamus for cortical processing.
- Melanin-concentrating hormone neurons in the lateral hypothalamus facilitate non-REM to REM transitions and promote REM sleep in the context of optimal environmental conditions.
- There are two flip-flop switches modulating wake-sleep and non-REM to REM transitions through balances of mutual inhibition: the former is primarily composed of the preoptic area and the monoaminergic system, and the latter is primarily composed of the ventrolateral periaqueductal gray and the sublaterodorsal nucleus.
- External to the intrinsic sleep-wake circuitry are processes—homeostatic and circadian—that adapt sleep to the needs of the organism.
- A number of state-regulating substances have been identified, the most well-known of which is the sleep-promoting molecule adenosine, which strongly correlates with sleepiness and delta power in the EEG.
- An approximately 24-hour (circadian) alerting signal promotes wakefulness during the day but dips in the latter half of the night to maintain sleep.
- Light-transducing retinohypothalamic signals are integrated with other time-giving signals in the dorsomedial hypothalamus to align central biorhythms to behavioral and environmental inputs.
- Blue light (like that from phone, computer, and television screens) suppresses the sleep-related hormone, melatonin, which begins to elevate 2 hours before habitual bedtime and peaks 2 to 3 hours before habitual wake time.
- Allowing for the recommended age-appropriate sleep opportunity every night is essential to ensure optimal daytime neurocognitive function.
- Chronic (partial) sleep deprivation of non-REM or REM sleep can result in dysfunction of multiple organ systems, ultimately resulting in death; both non-REM and REM sleep are essential.
- Increased production and decreased clearance of toxic proteins—Aβ, tau, and α-synuclein—are a fundamental dimension of the neurodegenerative consequences of sleep/circadian deficiency.
- Sufficient sleep is necessary to ensure that the brain and body properly allocate and restore energy stores.
- Central neuroinflammation and peripheral immune-compromise are consequences of insufficient sleep.
- Cytokines (eg, tumor necrosis factor α and interleukin 1β) are state-regulating substances that promote sleep in the setting of infection/inflammation.
- Vigilance and attention are neurocognitive functions most vulnerable to impairment from acute and chronic sleep deprivation, likely as a consequence of microsleeps impinging into wakefulness.
- Sleep is essential not only for reinforcing and associating important learning but also for eliminating extraneous and intrusive engrams.
- The complex problem solving and emotionally charged content of REM/dream sleep is suggested to be essential for mood regulation.

Article 2: Evaluating the Sleepy and Sleepless Patient

Raman K. Malhotra, MD, FAAN. Continuum (Minneap Minn). August 2020; 26 (4 Sleep Neurology):871–889.

ABSTRACT

PURPOSE OF REVIEW:

This article explains the clinical approach to patients presenting with sleepiness or sleeplessness in a neurologic practice setting. Addressing the patient's sleep symptoms may help improve symptoms of their other underlying primarily neurologic disorder.

RECENT FINDINGS:

New diagnostic modalities at home such as home sleep apnea testing have improved access and diagnosis of sleep apnea. Consumer health tracking devices have also helped patients focus on their sleep duration and quality, prompting them to bring their concerns to their neurologist.

SUMMARY:

Like many neurologic disorders, a detailed history and physical examination are critical in the evaluation of patients with sleepiness or sleeplessness. Patients who have neurologic disorders are more likely to have poor-quality sleep. Questions about the patient's sleep schedule or screening patients for common sleep disorders such as sleep apnea and restless legs syndrome (RLS) are useful to add to a typical neurologic evaluation to better recognize sleep disorders in this population. Polysomnography, home sleep apnea testing, multiple sleep latency tests, and actigraphy can be used with the available history and examination to determine the proper diagnosis and management plan for these patients.

KEY POINTS

- Patients with neurologic conditions frequently have poor-quality sleep and unrecognized sleep disorders.
- Excessive daytime sleepiness can lead to difficulties with school, work, and driving.
- Beyond obtaining the history from the patient, it can be equally important to ask a bed partner or other collateral source about the patient's level of alertness during the day or abnormal behaviors during sleep, as patients are not always fully appreciative of their level of sleepiness or aware of what is occurring while they sleep.
- Patients should be getting a sufficient amount of sleep, at least 7 hours for adults, as insufficient sleep is the most common cause of excessive daytime sleepiness in the United States.
- Patients reporting excessive daytime sleepiness should be asked about snoring, apneas, morning headaches, and nocturia, which are all common symptoms of obstructive sleep apnea.
- Many medications used to treat neurologic conditions and other medical disorders can cause excessive daytime sleepiness.
- Obesity, enlarged neck circumference, and high blood pressure are more commonly seen in patients with obstructive sleep apnea.
- Abnormal findings on the cardiac, pulmonary, or neurologic examination place a patient at higher risk of sleep disorders such as sleep-disordered breathing (obstructive or central sleep apnea), sleep-related movement disorders, and parasomnias.
- Sleep diaries in conjunction with actigraphy are helpful in evaluating duration and timing of sleep and critical for diagnosing circadian rhythm disorders and insufficient sleep syndrome.

- Polysomnography can be helpful when evaluating patients for sleep-disordered breathing, hypersomnia, or abnormal movements during sleep. Polysomnography measures sleep time and the apnea-hypopnea index, which is used to make a diagnosis of sleep apnea.
- Home sleep apnea tests can be useful in the evaluation of obstructive sleep apnea in adult patients who are considered at risk of moderate or severe obstructive sleep apnea based on history and examination and in those who do not have other neurologic or cardiopulmonary disorders that put them at risk of other sleep-disordered breathing.
- The multiple sleep latency test (MSLT) is used to objectively measure hypersomnia and help make a diagnosis of narcolepsy. MSLTs demonstrating a mean sleep latency of 8 minutes or less and at least two sleep-onset rapid eye movement (REM) periods are found in patients with narcolepsy.
- Gathering information about a patient's bedtime, wake time, and sleep routine is critical in determining the cause of a patient's insomnia or sleeplessness. This information can be obtained during the clinic visit but sometimes requires sleep logs or diaries collected over several days or weeks.
- Neurologic and psychiatric disorders commonly cause insomnia. In addition, insomnia can be a side effect of many medications used to treat these disorders, and use and withdrawal of recreational drugs can also cause sleeplessness.
- Polysomnography and home sleep apnea testing are not routinely used for the evaluation of insomnia unless the clinician is concerned about another sleep disorder such as obstructive sleep apnea or periodic limb movement disorder contributing to sleep complaints.
- Consumer sleep trackers are not currently used in the routine evaluation of patients with sleep problems such as insomnia, although they may help increase awareness of the importance of sleep and may help patients start a conversation with their clinician.

Article 3: Central Disorders of Hypersomnolence

Lynn Marie Trotti, MD, MSc. Continuum (Minneap Minn). August 2020; 26 (4 Sleep Neurology):890–907.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses the central disorders of hypersomnolence, a group of disorders resulting in pathologic daytime sleepiness, particularly narcolepsy type 1 and narcolepsy type 2, idiopathic hypersomnia, and Kleine-Levin syndrome. Disease features, diagnostic testing, epidemiology, pathophysiology, and treatment are reviewed.

RECENT FINDINGS:

Increasing evidence implicates autoimmunity in narcolepsy type 1, including a strong association with human leukocyte antigen–DQB1*06:02, association with a polymorphism in the T-cell receptor alpha locus in genome-wide association, and the identification of autoreactive T cells in patients with this type of narcolepsy. In contrast, the cause or causes of narcolepsy type 2 and idiopathic hypersomnia are unknown. Multiple treatment options exist, including two medications approved for the treatment of narcolepsy by the US Food and Drug Administration (FDA) in 2019. These include solriamfetol, a dopamine- and norepinephrine-reuptake inhibitor, and pitolisant, an H_3-inverse agonist/antagonist that increases histaminergic neurotransmission.

SUMMARY:

The central disorders of hypersomnolence all cause severe sleepiness but can be differentiated based on ancillary symptoms, diagnostic testing, and pathophysiology. It is important that these disorders are identified because multiple treatments are available to improve functioning and quality of life.

KEY POINTS

- Diagnosis of hypersomnia due to a medical disorder, hypersomnia due to a medication or substance, or insufficient sleep syndrome requires that the excessive daytime sleepiness is believed to be caused by a diagnosed medical or neurologic disorder, a medication or substance, or short sleep durations.
- The diagnosis of hypersomnia associated with a psychiatric disease does not imply that the psychiatric disease is necessarily caused by sleepiness or vice versa, just that the two conditions coexist.
- The five core clinical features of narcolepsy type 1 are excessive daytime sleepiness, cataplexy, sleep paralysis, sleep-related hallucinations, and disrupted nocturnal sleep. Many patients will not have all five symptoms.
- Cataplexy is very specific to narcolepsy type 1 and is not seen in the other hypersomnia disorders. Clinically, the presence or absence of cataplexy differentiates narcolepsy type 1 and narcolepsy type 2.
- The core clinical features of idiopathic hypersomnia are excessive daytime sleepiness, long sleep durations, and prominent sleep inertia, although not all symptoms are present in all patients.
- The phenotype of narcolepsy type 2 is intermediate between narcolepsy type 1 and idiopathic hypersomnia and has features of each.
- Kleine-Levin syndrome manifests as recurrent, severe hypersomnolence that is associated with cognitive dysfunction, altered perception, altered eating, or disinhibition.
- The two main diagnostic outputs of the multiple sleep latency test (MSLT) are the mean sleep latency and the number of sleep-onset rapid eye movement (REM) periods. The REM latency from the preceding night study should be counted toward the total sleep-onset REM period count.
- Sleep-onset REM periods can be suppressed by medications, most notably serotonergic antidepressants. Ideally, REM-suppressant medications would be withdrawn prior to testing. A 2-week medication-free period is recommended, although this may be too short for medications with very long half-lives (eg, fluoxetine).
- Short habitual sleep times, medications, and illicit drugs may all affect MSLT results and must be considered prior to ordering and interpreting the MSLT.
- Excessive daytime sleepiness and CSF orexin (hypocretin) deficiency are sufficient to diagnose narcolepsy type 1, even in the absence of cataplexy.
- Patients with hypersomnia who test negative for human leukocyte antigen–DQB1*06:02 are very unlikely to be orexin (hypocretin) deficient, such that the usefulness of lumbar puncture for orexin (hypocretin) is very low in this group.
- The MSLT may be normal in a substantial number of patients suspected of having idiopathic hypersomnia. In these patients, idiopathic hypersomnia may alternatively be diagnosed by recording at least 11 hours of sleep per 24 hours, either by polysomnography or estimated by wrist actigraphy over at least 7 days.
- The population prevalence of narcolepsy type 1 is approximately 1 per 2000. Narcolepsy type 2 may be 3 to 4 times more common than narcolepsy type 1, based on a large population-based MSLT study and insurance database claims.
- Kleine-Levin syndrome is rare, with a prevalence estimated at 1 to 5 cases per 1 million.
- Narcolepsy type 1 is strongly suspected to be autoimmune, with multiple alterations within T-cell pathways implicated.
- Scheduled naps are likely to be more useful for people with narcolepsy type 1 than with idiopathic hypersomnia.
- Modafinil has been shown in randomized controlled trials to improve sleepiness in people with narcolepsy type 1, narcolepsy type 2, and idiopathic hypersomnia.

- Modafinil, armodafinil, and pitolisant may all decrease the efficacy of hormonal birth control pills. Additional or alternative birth control methods should be used while taking these medications and for 21 days after their discontinuation.
- Sodium oxybate is dosed at bedtime and in the middle of the night and improves sleep consolidation and deep sleep.
- A sodium oxybate prescription requires enrollment in a US Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategy program because of the potential for serious risks.
- Solriamfetol is a dopamine- and norepinephrine-reuptake inhibitor approved by the FDA for narcolepsy treatment in 2019. It reduces sleepiness in patients with narcolepsy.
- Pitolisant increases histaminergic neurotransmission and was approved by the FDA for narcolepsy treatment in 2019. It reduces sleepiness and cataplexy in people with narcolepsy and may reduce sleepiness in people with idiopathic hypersomnia.
- Cataplexy can be treated with sodium oxybate, antidepressants, and pitolisant.
- Lithium may aid in the prevention of symptomatic episodes and reduce the severity of episodes in people with Kleine-Levin syndrome.

Article 4: Obstructive Sleep Apnea

Douglas B. Kirsch, MD, FAAN. Continuum (Minneap Minn). August 2020; 26 (4 Sleep Neurology):908–928.

ABSTRACT

PURPOSE OF REVIEW:

Obstructive sleep apnea (OSA) is often overlooked by clinicians; however, undiagnosed OSA can lead to negative outcomes for patients, including patients with underlying neurologic conditions. Clinicians should be aware of what questions to ask, what diagnostic tests to use, and what treatments to consider in patients with OSA.

RECENT FINDINGS:

OSA influences many neurologic conditions, including stroke, epilepsy, headache, and neuromuscular conditions. Treatment of OSA is effective, especially with patient-tailored options, the correct education, and support.

SUMMARY:

OSA is a serious medical condition with impacts on patients' health, safety, and quality of life. Clinicians should identify patients at high risk for OSA and arrange for appropriate diagnosis and treatment, which, in turn, may lead to the improvement of or reduction in risk for neurologic and other health conditions.

KEY POINTS

- Obstructive sleep apnea (OSA) is a common disorder, with nearly 1 billion people worldwide with the condition.
- OSA can impact a patient's quality of life and safety and can complicate comorbid medical conditions, including cardiovascular, psychiatric, and neurologic disorders.
- Daytime sleepiness in patients with OSA is one of the most dangerous effects, particularly in patients who are sleepy behind the wheel or who work in jobs requiring alertness for safety.
- While weight and neck size are primary physical factors in predicting risk for obstructive sleep apnea, retrognathia is a common finding in patients who have OSA but are of normal weight.
- Patients who are at risk for OSA should have a standardized evaluation of their breathing during sleep; two primary methods, which include in-laboratory polysomnography and home sleep apnea testing, define the severity of the sleep-related breathing disorder.

- OSA is a treatable condition with a variety of options to improve the patient's breathing during sleep, which should be applied based on knowledge of the disorder and the patient's wishes and preferences.
- Positive airway pressure therapy is an effective treatment for OSA and, contrary to some opinions, mostly tolerated well by patients when they are well prepared and educated and get appropriate follow-up.
- While men have a higher incidence of OSA, women may also have the disease, particularly those in higher-risk groups (eg, postmenopausal, obese, and retrognathic).
- OSA is associated with an increased risk for many medical conditions, including hypertension and arrhythmias.
- Many screening tools exist to screen for obstructive sleep apnea in different populations, including the STOP-BANG Questionnaire; the American Academy of Neurology also has tools that may be useful in clinical practice.

Article 5: Rapid Eye Movement Sleep Behavior Disorder and Other Rapid Eye Movement Parasomnias

Michael J. Howell, MD, FAAN. Continuum (Minneap Minn). August 2020; 26 (4 Sleep Neurology):929–945.

ABSTRACT

PURPOSE OF REVIEW:

The discovery of rapid eye movement (REM) sleep and, in particular, REM sleep behavior disorder (RBD) have brought elusive nightmarish experiences to scientific scrutiny. This article summarizes a century of sleep research to examine the maladies of dreaming, their pathophysiologic significance, and management.

RECENT FINDINGS:

Under healthy physiologic conditions, REM sleep is characterized by vivid mentation combined with skeletal muscle paralysis. The loss of REM sleep atonia in RBD results in vivid, potentially injurious dream enactment to patients and bed partners. RBD is common, affecting at least 1% of the population and is primarily caused by α-synuclein pathology of REM sleep–related brainstem neurons. The majority of patients with RBD ultimately develop a neurodegenerative syndrome such as Parkinson disease, dementia with Lewy bodies, or multiple system atrophy. Among patients with Parkinson disease, RBD predicts an aggressive disease course with rapid cognitive, motor, and autonomic decline. RBD is diagnosed by the presence of dream enactment episodes (either recorded or clinically recalled) and physiologic evidence of REM sleep without atonia demonstrated on polysomnography. Bedroom safety is of paramount importance in the management of RBD while pharmacokinetic options include melatonin or clonazepam.

SUMMARY:

The injurious dream enactment of RBD is common and treatable. It is a syndrome of α-synuclein pathology with most patients ultimately developing Parkinson disease, dementia with Lewy bodies, or a related disorder.

KEY POINTS

- Approximately 75 million people worldwide have rapid eye movement (REM) sleep behavior disorder (RBD), 1% of the population and 5% of older adults.

- Emotionally salient memories are consolidated during REM sleep.
- Nightmares and sleep paralysis peak in incidence prior to adolescence.
- In addition to quantifying REM motor activity and characterizing nocturnal behaviors, polysomnography helps rule out mimicking conditions such as obstructive sleep apnea and periodic limb movements, the disorders that primarily compose the differential diagnosis for RBD.
- Patients with RBD associated with narcolepsy are more often female, younger, and do not appear to be at higher risk of neurodegeneration.
- The most commonly prescribed therapies for RBD are melatonin and clonazepam.
- Melatonin treats RBD by normalizing circadian features of REM sleep.
- RBD is a prodromal syndrome of α-synuclein neuropathology with the majority of patients converting to a neurodegenerative disorder.
- RBD predicts the non–tremor-predominant subtype of Parkinson disease with freezing of gait and a more aggressive clinical course.
- Patients who have RBD with comorbid hyposmia and constipation but who are not taking an antidepressant are at high risk of phenoconversion to a neurodegenerative disorder in less than 5 years.
- Recent insights suggest that antidepressants do not induce RBD but instead appear to unmask dream enactment in an individual who is already burdened by early α-synuclein pathology.
- The North American Prodromal Synucleinopathy Consortium is an important resource for patients with RBD who are interested in enrolling in neuroprotective clinical trials.

Article 6: Parasomnias Occurring in Non–Rapid Eye Movement Sleep

Michael H. Silber, MBChB, FAAN. Continuum (Minneap Minn). August 2020; 26 (4 Sleep Neurology):946–962.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses the clinical manifestations, diagnosis and differential diagnosis, pathophysiology, and management of parasomnias occurring in non–rapid eye movement (REM) sleep.

RECENT FINDINGS:

Disorders of arousal are characterized by dissociated sleep, with wake and sleep phenomena intermingling, and local sleep, in which different areas of the brain exist simultaneously in different states of wakefulness or sleep. The frequency of arousals from slow-wave sleep with delta or mixed-frequency activity has a high sensitivity but relatively low specificity for the diagnosis of arousal parasomnias.

SUMMARY:

Disorders of arousal (sleepwalking, sleep terrors, and confusional arousals) are characterized by incomplete awakenings from slow-wave sleep, limited recall of imagery, and partial or complete amnesia. They occur most frequently in childhood. Management includes correction of precipitating factors, attention to safety, behavioral techniques, and medications. Sleep-related eating disorder is a variant of arousal disorders and may be associated with the use of short-acting hypnotics and restless legs syndrome. Complex nocturnal visual hallucinations can occur with visual loss, dementia with Lewy bodies, use of β-adrenergic receptor antagonists, and anxiety. Exploding head syndrome occurs at wake-sleep transition or on waking

during the night, is usually benign, and requires treatment only if significant sleep disruption occurs.

KEY POINTS

- Disorders of arousal (sleepwalking, sleep terrors, and confusional arousals) share fundamental characteristics: incomplete awakening from slow-wave sleep usually in the first half of the night, limited recall of imagery, unresponsiveness to attempts to intervene, and partial or complete amnesia for events.
- Violent behavior during arousal parasomnias is rare, but occasionally patients may injure themselves or others, usually if the victim attempts to restrain the patient.
- Sexsomnias (sexual behaviors during sleep) are a variant of sleepwalking; they are more common in men and potentially associated with medicolegal consequences.
- The lifetime prevalence of sleepwalking is about 7%. Approximately 20% of childhood sleepwalkers sleepwalk as adults, whereas the prevalence of de novo sleepwalking in adults is probably less than 1%.
- The pathophysiology of disorders of arousal involves dissociated sleep, in which behaviors occur during abnormal states overlapping between wakefulness and slow-wave sleep. During episodes, certain areas of the brain show sleep phenomena (local sleep), whereas other regions appear awake.
- Precipitating factors for disorders of arousal include those that deepen slow-wave sleep (eg, sleep deprivation, shift work) and those that fragment sleep (eg, noise, stress, and medical disorders such as sleep apnea).
- Sodium oxybate and benzodiazepine receptor agonists such as zolpidem can precipitate disorders of arousal, but evidence for other medications is weak.
- Disorders of arousal are usually diagnosed clinically, but video-EEG polysomnography may be needed if uncertainty exists about the diagnosis, an additional sleep disorder such as sleep apnea is suspected, or behaviors are associated with violence.
- It is essential to review the video on a polysomnogram whenever an arousal from non–rapid eye movement (REM) sleep occurs, as the EEG findings in disorders of arousal are nonspecific and confusional arousals may be subtle and missed by the recording technologist.
- The differential diagnosis of disorders of arousal includes nocturnal seizures, REM sleep behavior disorder, nightmares, and nocturnal panic attacks.
- Management of disorders of arousal includes reassurance, correction of precipitating factors, addressing safety, behavioral therapies, and medications such as clonazepam.
- Sleep-related eating disorder is a variant of arousal parasomnias in which patients eat often unusual combinations of high-caloric food with complete or partial loss of awareness.
- Sleep-related eating disorder is associated with sleepwalking, restless legs syndrome, and the use of zolpidem and similar hypnotics.
- Management of sleep-related eating disorder includes controlling restless legs syndrome; discontinuation of short-acting hypnotics; and the use of medications such as clonazepam, selective serotonin reuptake inhibitors, or topiramate.
- Complex nocturnal visual hallucinations are vivid images on waking during the night, usually involving immobile people or animals with distorted appearances that vanish if the lights are switched on.
- Etiologies of complex nocturnal visual hallucinations include diminished visual acuity (Charles Bonnet syndrome), dementia with Lewy bodies, midbrain or thalamic infarcts (peduncular hallucinations), narcolepsy, the use of β-adrenergic receptor antagonists, and anxiety disorders.
- The differential diagnosis of complex nocturnal visual hallucinations includes hypnagogic or hypnopompic hallucinations, nightmares, REM sleep behavior disorder, epileptic seizures, and visual migraine auras.
- Exploding head syndrome is characterized by a sudden loud noise or painless explosion in the head occurring at either wake-sleep transition or on waking during sleep.
- Exploding head syndrome is a benign parasomnia that should be differentiated from nocturnal headaches by the absence of pain; it generally requires no treatment unless sleep onset or continuity is markedly impacted.

Article 7: Restless Legs Syndrome and Other Common Sleep-Related Movement Disorders

Celia Garcia-Malo, MD; Sofia Romero Peralta, MD; Diego Garcia-Borreguero, MD, PhD.
Continuum (Minneap Minn). August 2020; 26 (4 Sleep Neurology):963–987.

ABSTRACT

PURPOSE OF REVIEW:

In this article, the different sleep-related movement disorders are discussed with special attention given to restless legs syndrome (RLS).

RECENT FINDINGS:

The differential diagnosis of sleep-related movement disorders can often be challenging; therefore, it is essential to have accurate information to make a correct diagnosis. This article focuses on RLS, highlighting the change in the paradigm of initial treatment, the role played by iron (pathophysiologic and therapeutic), and how to approach possible complications occurring with long-term treatment.

SUMMARY:

RLS is one of the most common neurologic conditions, and it is common in clinical practice to find patients experiencing symptoms suggestive of RLS. Neurologists must be careful and thorough in the diagnosis, excluding RLS mimics. The decisions regarding which specific sleep-related movement disorder is present and how it should be treated are important because in certain cases, especially in RLS, adverse effects and long-term complications are frequently reported with the use of certain drugs.

KEY POINTS

- Restless legs syndrome (RLS) is mainly characterized by an uncomfortable urge to move the lower limbs, frequently accompanied by abnormal sensations, and is more common during the evening or night, particularly when the patient is at rest. Most patients with RLS have difficulties initiating or maintaining sleep.
- Medical conditions most consistently associated with RLS are iron deficiency, pregnancy, chronic kidney failure, multiple sclerosis, polyneuropathy, Parkinson disease, major depressive disorder, generalized anxiety disorder, and attention deficit hyperactivity disorder.
- Periodic limb movements (PLMs) constitute the main motor sign of RLS.
- Some studies have found that RLS might be a risk factor for developing cardiovascular disease, including coronary heart disease and stroke.
- RLS is a strongly hereditable condition, as suggested by the fact that more than 50% of patients have one first-degree relative who is affected.
- Several risk polymorphisms for RLS have been identified.
- Because patients with RLS require higher peripheral ferritin levels than controls do to obtain equivalent CSF ferritin levels, it is suggested that impaired transport across the blood-brain barrier constitutes part of the pathophysiology.
- Central iron deficiency constitutes the best-documented biological abnormality for RLS.
- RLS regional central iron deficiency also involves a failure to provide adequate iron transport across the blood-brain barrier, associated with a regional failure to import adequate iron into critical neuronal cells (eg, neuromelanin cells of the substantia nigra).

- Two abnormalities in different neurotransmitter systems are present in RLS, which have, until now, been the main targets of therapeutic action: on the one hand, increased dopaminergic function, leading to sensory symptoms and PLMs, and on the other hand, hyperarousal and sleep loss, and probably PLMs, which are caused by increased glutamatergic function.
- Five clinical criteria must be met to establish the diagnosis of RLS.
- Laboratory parameters to assess in RLS include a complete blood cell count and systemic iron parameters.
- The decision of whether to initiate RLS treatment should strongly depend on a risk-benefit assessment that includes the impact that RLS symptoms have on overall function and quality of life (including sleep disturbance).
- Choosing a first-line treatment will depend on iron status. Systemic iron parameters should be assessed with a blood test.
- Because of long-term complications, the therapeutic role of dopamine agonists as the first-line treatment of RLS is undergoing reconsideration.
- Classic features of initial augmentation are breakthrough episodes during the daytime, an increase in symptom frequency or symptom intensity, shorter duration of treatment effect, symptoms in previously unaffected body parts, worsening of sleep efficacy or sleep quality, increased PLMs during sleep or wakefulness, the need for additional medication, or overall decrease in therapeutic efficacy.
- The most effective strategy to prevent augmentation would be to not use dopaminergic treatment at all or to at least keep the dopaminergic load as low as possible by using the minimum effective dose for the shortest required period of time.
- Gabapentin, pregabalin, and gabapentin enacarbil have proven various degrees of efficacy for RLS.
- Opioids are considered a second-line treatment for RLS when symptoms are refractory to other treatments or when complications derived from them occur.
- To define the presence of PLMs as a disorder, polysomnography must show the occurrence of PLMs in a considerable number (≥5 PLMs per hour in children and ≥15 PLMs per hour in adults) in patients who have insomnia or excessive daytime sleepiness.
- Painful legs and moving toes is a rare syndrome, characterized by leg pain and repetitive stereotyped toe movements.
- Painful legs and moving toes has been associated with alterations in the dopaminergic system.
- Sleep-related leg cramps is a frequent disorder. It is considered a disorder when the frequency or intensity of cramps impacts sleep quality.
- Sleep-related bruxism is related to the presence of snoring, obstructive sleep apnea, and other sleep disorders. Dental problems, jaw muscle pain, and tension headaches can occur as a consequence.
- Sleep-related rhythmic movement disorder is a sleep-related movement disorder, occurring typically in children.
- The most common forms of sleep-related rhythmic movement disorder are body rocking, head rolling, or body rolling.
- Physiologic hypnic fragmentary myoclonus is commonly a physiologic condition but sometimes can be intense or frequent enough to lead to arousals and, hence, disturbing sleep quality.
- Propriospinal myoclonus is an abnormal involuntary movement, occurring in the sleep-wake transition period, consisting of flexion-extension rhythmic-arrhythmic jerks arising in axial muscles and spreading to other body parts.

Article 8: Circadian Rhythm Sleep-Wake Disorders

Phyllis C. Zee, MD, PhD; Sabra M. Abbott, MD, PhD. Continuum (Minneap Minn). August 2020; 26 (4 Sleep Neurology):988–1002.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of circadian physiology and discusses common presentations and treatment strategies for the circadian rhythm sleep-wake disorders.

RECENT FINDINGS:

Circadian rhythms are present throughout the body, and appreciation for the role that circadian dysregulation plays in overall health is increasing, with mounting associations between circadian disruption and cardiometabolic disease risk.

SUMMARY:

It is important to recognize the ubiquitous role that circadian rhythms play throughout the brain and body. An understanding of circadian neurophysiology will provide insight into the means by which patients with a variety of neuropathologies at the level of the retina, optic nerve, or hypothalamus may also be at risk for circadian dysfunction.

KEY POINTS

- In mammals, circadian rhythms are coordinated by the suprachiasmatic nucleus located in the anterior hypothalamus, directly above the optic chiasm.
- The daily rhythmic activity within the suprachiasmatic nucleus is regulated by a complex transcription-translation feedback loop containing positive and negative elements.
- Light exposure in the early biological evening causes delays of circadian timing, whereas light exposure during the late biological evening advances circadian timing.
- Melatonin administration in the early evening results in advances in circadian timing, whereas morning melatonin administration delays the circadian clock.
- Delayed sleep-wake phase disorder is characterized by a delay in sleep-wake timing with respect to the time that the individual desires or is required to be awake and asleep, resulting in a combination of difficulty awakening, daytime sleepiness, and difficulty falling asleep.
- There appear to be at least two forms of delayed sleep-wake phase disorder. The first type includes those who experience a delay in both sleep-wake behaviors and circadian biomarkers such as melatonin, often referred to as *circadian delayed sleep-wake phase disorder*. Patients with the second type experience a delay in their sleep-wake behaviors, but melatonin timing is not delayed, referred to as *noncircadian* or *motivated delayed sleep-wake phase disorder*.
- The first genetic mutation associated with familial delayed sleep-wake phase disorder was recently identified: a mutation in the *CRY1* gene is associated with a lengthening of the circadian period.
- Overall, greater sensitivity to evening delaying signals, decreased exposure to morning advancing signals, and a longer intrinsic period all likely contribute in varying degrees to the development of delayed sleep-wake phase disorder.
- Treatment of circadian delayed sleep-wake phase disorder primarily focuses on the use of timed exposure to light and melatonin, with a goal of advancing sleep-wake timing.
- Advanced sleep-wake phase disorder is characterized by a significant advance in sleep-wake timing, often presenting with reports of either early morning awakenings or early evening sleepiness.

- The primary recommendation for the treatment of advanced sleep-wake phase disorder is the use of evening bright light to delay circadian rhythms.
- Irregular sleep-wake rhythm disorder is characterized by multiple irregular bouts of sleep and wake, without a clear circadian rhythm.
- Non–24-hour sleep-wake rhythm disorder is characterized by a sleep-wake schedule that is typically slightly longer than 24 hours and can be seen in blind individuals who lack light perception, as well as in some sighted individuals.
- Shift work disorder results when individuals develop sleep-wake symptoms that are specifically related to being required to work during times that they would normally be sleeping.
- The health consequences of shift work disorder can be quite significant and extend beyond just the sleep symptoms. The overall risk appears to increase with greater duration of exposure (>5 years) and exposure to rotating shift work at a younger age.
- The wake-promoting agents modafinil and armodafinil have been approved by the US Food and Drug Administration for the treatment of sleepiness associated with shift work disorder.
- Jet lag disorder occurs as a result of rapidly crossing multiple time zones, resulting in a temporary mismatch between an individual's biological time and the environmental light-dark cycle.
- It is important to keep circadian rhythm sleep-wake disorders in mind, particularly in neurologic patients who may have impaired light input through the retina and optic nerves, neurodegeneration at the level of the suprachiasmatic nucleus, or pathology of the melatonin-producing pineal gland.

Article 9: Insomnia

Maria Nichole Perez, MD; Rachel Marie E. Salas, MD, MEd, FAAN. Continuum (Minneap Minn). August 2020; 26 (4 Sleep Neurology):1003–1015.

ABSTRACT

PURPOSE OF REVIEW:

This article provides updated information regarding the diagnosis and treatment of chronic insomnia disorder. In addition to discussing the latest recommendations regarding pharmacotherapeutic options for insomnia, this article also discusses the increased use of nonpharmacologic treatment approaches, including cognitive-behavioral therapy intervention, integrative medicine, mindfulness and meditation, and other therapeutic options in clinical practice.

RECENT FINDINGS:

Insomnia is one of the most common sleep disorders in patients with other neurologic disorders. The definition and criteria for insomnia were updated with the release of the *International Classification of Sleep Disorders, Third Edition*. The American Academy of Sleep Medicine has updated clinical practice guidelines for the pharmacologic treatment of chronic insomnia in adults. New diagnostic and therapeutic options (eg, pharmacologic and behavioral therapies, at-home devices) have emerged to optimize and personalize the evaluation and management of sleep disorders such as insomnia. Although some of these devices and treatment options are still in the early stages of development, several are currently in clinical trials or will soon be available.

SUMMARY:

This article emphasizes complexities related to the evaluation and management of patients with chronic insomnia disorder and describes alternative therapeutic options for patients with this common sleep disorder.

KEY POINTS

- Insomnia can be a symptom of another medical disorder (eg, chronic pain, sleep apnea, anxiety, and depression) or its own disorder (ie, chronic insomnia disorder).
- Many individuals may have chronic insufficient sleep but do not report any daytime consequences and, therefore, do not qualify for an insomnia diagnosis due to the absence of a related functional impairment.
- The typical person has a circadian rhythm set to go to bed at 11:00 PM and awaken at 7:00 AM.
- While it remains important for individuals to get enough sleep (ie, 7 to 9 hours each night), it is just as important, and for some individuals even more important, that the timing of their sleep-wake schedule is consistent.
- Patients with circadian rhythm sleep-wake disorders experience insomnia or excessive sleepiness, but they can experience both depending on the nature of their circadian rhythm misalignment.
- Chronic insomnia disorder remains a clinical diagnosis based on meeting the diagnostic criteria and does not require polysomnography.
- Cognitive-behavioral therapy for insomnia, a structured and personalized nonpharmacologic program, generally conducted by a sleep behavioral psychologist who guides individuals to modify their cognitive processes and sleep behaviors in an effort to improve their sleep, remains the gold standard therapy for insomnia.
- The American Academy of Sleep Medicine and the American College of Physicians both recommend cognitive-behavioral therapy for insomnia as the first-line treatment for chronic insomnia disorder.
- Online cognitive-behavioral therapy for insomnia has been shown to improve insomnia severity, sleep efficiency, subjective sleep quality, wake after sleep onset, sleep-onset latency, total sleep time, and the number of awakenings from sleep.
- Medications to treat chronic insomnia may sometimes be used, ideally in a short-term manner.
- Mindfulness meditation alone has shown significant improvement in sleep efficacy.
- Pranic healing is a type of biofield therapy modality that uses a standardized process; it is intended to complement allopathic medicine and not replace it.
- Autonomous sensory meridian response is a sensory-type strategy in which individuals experience a tinglinglike sensation typically across the scalp and back of the neck in response to specific triggering of audio and visual stimuli to induce states of relaxation.
- While more research is needed to assess its clinical benefits, cranial electrical stimulation is one example of a clinical tool that is increasingly being considered as a potential treatment option for insomnia.

Article 10: Sleep in Patients With Neurologic Disease

Sara E. Benjamin, MD. Continuum (Minneap Minn). August 2020; 26 (4 Sleep Neurology):1016–1033.

ABSTRACT

PURPOSE OF REVIEW:

This article provides a discussion of the current evidence and contemporary views on the relationship between sleep disorders and neurologic disease.

RECENT FINDINGS:

Disrupted or disordered sleep can be associated with increased morbidity and mortality, the risk of cardiovascular events, increased seizure frequency, and altered immune responses. Studies have implicated disrupted sleep and circadian rhythm dysfunction with both amyloid-β (Aβ) deposition and tau deposition. A bidirectional relationship exists between disrupted sleep and the progression of Alzheimer disease pathology. Insomnia has been reported as a prodromal

symptom in autoimmune encephalitis. Primary sleep disorders have now been increasingly recognized as a common comorbid condition in multiple sclerosis, making it imperative that neurologists feel comfortable differentiating multiple sclerosis fatigue from excessive daytime sleepiness caused by primary sleep disorders to optimally treat their patients.

SUMMARY:

Sleep disorders are common across the population. By recognizing sleep disorders in patients with neurologic conditions, neurologists can provide comprehensive care and, in some cases, reduce neurologic disease burden.

KEY POINTS

- Obstructive sleep apnea may lead to inflammation, increasing the risk of stroke.
- Atrial fibrillation prevalence is four times higher in patients with sleep apnea, serving as a significant risk factor for cardioembolic stroke.
- Sleep period length and circadian rhythm differences can be linked to ischemic stroke risk.
- Sleep apnea can be both screened for and diagnosed with various valid tools that include questionnaires that can be completed by the patient or care provider and with in-center or ambulatory sleep diagnostic services.
- When deep sleep is attenuated, amyloid-β (Aβ) and tau protein, which are hallmarks for Alzheimer disease, can accumulate.
- Patients with Alzheimer disease often have an irregular sleep-wake rhythm. Behavioral interventions, including appropriate timing of natural-light exposure and physical activity, may be helpful in reinforcing an appropriate circadian rhythm.
- Rapid eye movement (REM) sleep behavior disorder is commonly a precursor to α-synucleinopathies with reported presentation as much as 10 to 15 years prior to Parkinson disease motor manifestations.
- Sleep disruption is common in Parkinson disease, and this often leads to excessive daytime sleepiness in this patient population.
- Huntington disease and palatal myoclonus represent the two movement disorders for which movements have been commonly recognized to persist while sleeping, unlike other movement disorders such as Parkinson disease, where sleep allows for a quiescent phase in the stereotyped movements.
- Insomnia and other sleep disturbances are often prodromal symptoms in autoimmune encephalitis.
- Anti-IgLON5 disease is an autoimmune encephalopathy with sleep disruptions as a prominent part of the presentation. Other common features are bulbar symptoms and gait disturbance.
- Fatigue and excessive daytime sleepiness are common symptoms experienced by patients with multiple sclerosis. Optimizing approaches to help distinguish symptoms of fatigue from sleepiness can improve early identification of underlying sleep disorders and, therefore, overall management of these two common and debilitating functional symptoms.
- If a patient with multiple sclerosis reports severe daytime sleepiness that does not correlate with the onset of other multiple sclerosis symptoms, an evaluation for a coexisting sleep disorder, such as obstructive sleep apnea (using polysomnography) and particularly narcolepsy (using polysomnography and multiple sleep latency testing), should be considered.
- Risk factors for sleep apnea in patients with epilepsy include seizure medications that cause weight gain, benzodiazepine medication use, and obstructive and central sleep apnea events associated with a vagal nerve stimulator.
- Further studies are needed to better classify the impact on seizure control incurred by treating sleep apnea.
- Central sleep apnea and sudden unexpected death in epilepsy (SUDEP) may be related.
- Both migraine headaches and tension headaches are exacerbated by poor sleep.
- Patients who concurrently have migraine/tension headaches along with insomnia have reported dual symptom benefit after undergoing cognitive-behavioral therapy for insomnia.
- Hypnic headaches are a rare headache type with frequent awakenings due to a dull headache pain. Treatment options include lithium, caffeine, indomethacin, and melatonin.

Article 11: Sleep-Wake Disorders in Childhood

Amy Licis, MD, MSCI. Continuum (Minneap Minn). August 2020; 26 (4 Sleep Neurology):1034–1069.

ABSTRACT

PURPOSE OF REVIEW:

The presentation of sleep issues in childhood differs from the presentation in adulthood and may be more subtle. Sleep issues may affect children differently than adults, and distinct treatment approaches are often used in children.

RECENT FINDINGS:

Sodium oxybate was approved by the US Food and Drug Administration (FDA) in October 2018 for an expanded indication of treatment of sleepiness or cataplexy in patients with narcolepsy type 1 or narcolepsy type 2 aged 7 years or older, with side effect and safety profiles similar to those seen in adults. Restless sleep disorder is a recently proposed entity in which restless sleep, daytime sleepiness, and often iron deficiency are observed, but children do not meet the criteria for restless legs syndrome or periodic limb movement disorder.

SUMMARY:

Children's sleep is discussed in this article, including normal sleep patterns and effects of insufficient sleep. Sleep disorders of childhood are reviewed, including insomnia, obstructive sleep apnea, restless legs syndrome, parasomnias, narcolepsy, and Kleine-Levin syndrome. Children with neurologic issues or neurodevelopmental disorders frequently have sleep disorders arising from an interaction of heterogeneous factors. Further attention to sleep may often be warranted through a polysomnogram or referral to a pediatric sleep specialist. Sleep disorders may cause indelible effects on children's cognitive functioning, general health, and well-being, and awareness of sleep disorders is imperative for neurologists who treat children.

KEY POINTS

- Environmental cues, homeostatic sleep pressure, and individual differences in circadian rhythms help determine sleep timing.
- The evolution in sleep schedules may follow brain maturation, with the sleep schedules of younger children providing more frequent opportunities for sleep-related memory consolidation.
- The mechanisms by which sleep disorders or sleep restriction may impair development remain unclear.
- Sleep disorders such as circadian rhythm disorder (delayed-phase type), restless legs syndrome, or obstructive sleep apnea can exacerbate insomnia, as can medical conditions such as asthma, psychiatric conditions such as depression or anxiety, or medication side effects.
- No medications for the treatment of insomnia in children are approved by the US Food and Drug Administration, and the literature on their efficacy is limited.
- The threshold for obtaining a polysomnogram should be low because symptoms may be subtle in children.
- The American Academy of Sleep Medicine advises against the use of ambulatory sleep studies in children because further research is required to assess whether factors likely to be present in children, such as restless sleep, monitoring intolerance, frequency of arousal-based respiratory events requiring EEG electrodes for detection, and sleep fragmentation, may or may not reduce the validity of ambulatory sleep studies for the pediatric population.

- A postoperative polysomnogram is advisable after adenotonsillectomy, especially if presurgical obstructive sleep apnea (OSA) was moderate to severe.
- Restless sleep disorder is a newly proposed entity, in which restless sleep and daytime sleepiness are noted but children do not meet the criteria for restless legs syndrome (RLS) or periodic limb movement disorder. Restless sleep disorder is associated with iron deficiency.
- Putative mechanisms for RLS include dopaminergic dysfunction and iron deficiency.
- Specific populations of children may have a high rate of RLS or increased periodic limb movements, including children taking antidepressants, antipsychotics, or antiepileptic medications or children predisposed to anemia or uremia through chronic kidney disease, former preterm status, or autism.
- Vitamin D deficiency may be a particularly important etiologic factor for RLS in children with skin tones with relatively higher concentrations of melanin.
- Dopamine agonists should be used sparingly in children, because children appear to be even more likely to experience augmentation than adults.
- Parasomnias seem to be relatively common in children with autism.
- Conditions that promote arousal or sleep drive can increase the likelihood of parasomnias, such as OSA, periodic limb movement disorder, sleep deprivation, or sedating medications.
- The frequency of parasomnias can be lessened by reducing sleep fragmentation, such as by treating OSA or periodic limb movement disorder, and by obtaining adequate sleep.
- Safety measures should be discussed for patients with parasomnias, such as locking doors and windows, restricting access to weapons or sharp objects, placing gates on stairs, and possibly installing door alarms to alert others in the household.
- In children, it is unclear to what degree narcolepsy type 1, narcolepsy type 2, and idiopathic hypersomnia are distinct entities.
- An autoimmune-induced loss of orexin (hypocretin) neurons in the lateral hypothalamus is thought to be the primary cause of narcolepsy, with resulting instability of sleep-wake states.
- The fundamental complaint of patients with narcolepsy is sleepiness that exceeds expectations for a given sleep duration.
- Particularly in children, cataplexy can be atypical, with mouth opening, tongue protrusion, and stuttering speech, sometimes with such frequent clustering that episodes present as apparent facial weakness, and sometimes lacking a clear emotional trigger.
- Active motor phenomena with a degree of emotional triggering have been described soon after narcolepsy onset in children, including eyebrow-raising, perioral and tongue movements, facial grimacing, body swaying, and stereotyped motor behavior.
- Multiple comorbidities have been associated with narcolepsy, including anxiety, depression, thyroid disorders, hypertension, OSA, peripheral neuropathy, headaches, and glucose intolerance.
- The first step in establishing a diagnosis of narcolepsy is recognizing a concerning level of hypersomnia and referring patients to a pediatric sleep specialist experienced in treating patients with narcolepsy.
- Historical details that identify concerning hypersomnia in children include falling asleep unintentionally, resuming napping, taking multiple daily naps, or struggling to complete homework despite adequate sleep duration.
- Diagnosing narcolepsy in children can sometimes be challenging and confounded by testing limitations.
- The most common symptomatology of Kleine-Levin syndrome encompasses the tetrad of hypersomnia, confusion, apathy, and derealization.
- Menstrual-associated hypersomnia is considered a variant of Kleine-Levin syndrome.
- Medical or behavioral issues intrinsic to autism can compound sleep issues, such as epilepsy or gastrointestinal issues, medication side effects, bedtime resistance, or difficulty with self-soothing.
- An intrinsic complexity underlies the sleep issues observed in children with neurodevelopmental issues, and multiple molecular mechanisms and sequelae may act in synchrony to affect sleep.

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SPINAL CORD DISORDERS

ARTICLE 1: SPINAL CORD ANATOMY AND LOCALIZATION

Todd A. Hardy, PhD, MBBS, FRACP. Continuum (Minneap Minn). February 2021; 27 (1 Spinal Cord Disorders):12–29.

ABSTRACT

PURPOSE OF REVIEW:

This article focuses on clinically relevant teaching points in spinal anatomy and localizing the lesion in myelopathy.

RECENT FINDINGS:

The principles underlying spinal cord lesion localization are well established, but improvements in MRI and the discovery of pathologic antibodies associated with causes of transverse myelitis distinct from multiple sclerosis, such as aquaporin-4 IgG and myelin oligodendrocyte glycoprotein IgG, have assisted in diagnosis.

SUMMARY:

The spinal cord has a highly organized neuroanatomy of ascending and descending tracts that convey sensory, motor, and autonomic information. Using integration of clues from the patient's history and neurologic examination, the effective clinician can distinguish spinal cord from peripheral nerve or brain pathology, often determine the level and parts of the spinal cord affected by a lesion, and focus on a likely diagnosis. The advent of MRI of the spine has revolutionized investigation of spinal cord disorders, but an important place for strong clinical acumen still exists in assessing the patient with a myelopathy.

KEY POINTS

- Lumbar puncture is typically performed at the L3-L4 or L4-L5 level.
- The butterfly-shaped area of the spinal cord in cross section is known as the central gray matter.
- The descending motor pathways in the cord before the anterior horns are called upper motor neurons, and those of the anterior horns and somatic motor nerves are called lower motor neurons.
- The monosynaptic spinal reflex is caused by activation of peripheral stretch receptors transmitting an impulse along primary sensory afferents that synapse directly on alpha motor neurons, causing a final efferent motor response.
- The artery of Adamkiewicz is the large radiculomedullary artery that supplies the anterior spinal artery between T9 and T12 in most individuals.

- The somatotopic organization of the spinal cord allows determination of the approximate or, in some cases, precise level of a spinal cord lesion.
- The Uhthoff phenomenon commonly occurs when patients with multiple sclerosis experience an exacerbation of symptoms with an increase in body temperature.
- Spinal injury can lead to either a flaccid or spastic bladder, with a range of symptoms, including urinary frequency, urgency, incontinence, and urinary retention due to a lack of coordination between the detrusor muscle of the bladder and the urinary sphincter.
- The patient's previous medical history and the temporal onset of neurologic symptoms can be used to narrow the differential diagnosis of a spinal cord lesion.
- The likelihood of upper motor neuron pathology is increased if hyperreflexia occurs accompanied by other upper motor neuron signs, such as an extensor plantar response or pyramidal weakness, or both.
- The C4 dermatome abuts the T2 dermatome on the chest.
- A truncal sensory level is defined as the highest dermatomal area of normal sensation to pinprick and temperature on the trunk.
- A lesion affecting the spinothalamic tract of the right hemicord only will cause impaired temperature and pinprick sensation on the left trunk and lower limb two to three vertebral levels below the level of the cord lesion because the spinothalamic tracts ascend as they decussate.
- The term *paresis* is used to denote weakness, whereas *plegia* is used to denote absence of any voluntary movement.
- Spinal shock occurs when hyperacute or acute injury (particularly trauma) to the spinal cord results in flaccid areflexia below the level of the lesion.
- Neurogenic shock occurs due to acute pathology above the level of T6, which leads to loss of sympathetic tone below the lesion causing hypotension and unopposed vagal activity leading to bradycardia.
- Autonomic dysreflexia occurs when patients have injury above the T6 level, leading to an exaggerated sympathetic nervous system response to sensory stimuli below the level of the lesion (eg, bladder filling).
- A central intraaxial spinal cord lesion often causes sensory symptoms and signs in the upper limbs and trunk before the lower limbs and sacral regions (called a suspended sensory level). This is because the lower extremity spinothalamic tracts run more laterally than those of the upper extremities and so take longer to be affected by an expanding central cord lesion.
- A partial transverse myelitis refers to spinal cord inflammation in which symptoms and signs occur that are attributable to only a portion of the spinal cord in cross section rather than involving the entire transverse diameter. A complete transverse myelitis is attributable to spinal cord inflammation involving its entire cross section.
- Patients with a longitudinally extensive transverse myelitis should be tested for aquaporin-4 IgG and myelin oligodendrocyte glycoprotein IgG.

ARTICLE 2: VASCULAR MYELOPATHIES

Nicholas L. Zalewski, MD. Continuum (Minneap Minn). February 2021;
27 (1 Spinal Cord Disorders):30–61.

ABSTRACT

PURPOSE OF REVIEW:

Neurologists should be able to identify clinical and neuroimaging features that distinguish vascular disorders from other causes of myelopathy.

RECENT FINDINGS:

Although certain clinical features suggest a vascular etiology in acute and chronic myelopathy settings, accurate MRI interpretation within the clinical context is key. Recent studies have

shown vascular myelopathies are frequently misdiagnosed as transverse myelitis, and recognition of this diagnostic pitfall is important. Many different vascular mechanisms can cause myelopathy; this article provides a comprehensive review that simplifies disease categories into arterial ischemia, venous congestion/ischemia, hematomyelia, and extraparenchymal hemorrhage.

SUMMARY:

It is important to recognize and manage vascular disorders of the spinal cord as significant causes of acute, subacute, and progressive myelopathy.

KEY POINTS

- Two large retrospective studies recently showed that patients initially diagnosed with idiopathic transverse myelitis frequently had alternative myelopathy diagnoses, with vascular etiologies among the most common.
- Vascular disorders of the spinal cord have important time-to-treatment considerations as delays in diagnosis can be associated with worse outcomes, highlighting the importance of considering vascular causes early.
- The vascular anatomy of the spinal cord consists of a single anterior spinal artery and paired posterior spinal arteries that run along the length of the spinal cord.
- Open or endovascular thoracic aortic aneurysm repair is the most common procedure associated with spinal cord infarction, representing approximately 50% of periprocedural spinal cord infarction cases. Spinal cord infarction has also been associated with other aortic surgeries and an array of other procedures (eg, cardiac surgery, spinal decompression, epidural injection, angiography, nerve block, embolization, other vascular surgery, and thoracic surgery).
- During spinal cord ischemia, the goal of treatment is to increase spinal cord perfusion pressure through collaterals by lowering pressure within the spinal canal via CSF drainage or mean arterial blood pressure augmentation.
- Two large studies highlighted the frequent misdiagnosis of spinal cord infarction as "transverse myelitis" in approximately 15% of referred cases.
- Although an older patient population with vascular risk factors is common in spinal cord infarction, mechanisms affecting younger patients also occur (eg, fibrocartilaginous embolism, vertebral dissection), highlighting that spinal cord infarction can occur at any age.
- From the earliest days, it has been recognized that spinal cord infarction frequently results in acute deficits localized to an anterior spinal artery territory (bilateral corticospinal tract, lower motor neuron at lesion level, and pain/temperature loss) or, less frequently, a posterior spinal artery territory (dorsal column dysfunction); these deficits may distinguish spinal cord infarction from other myelopathies.
- Severe acute pain (back, chest, neck, limb) at or before onset is another helpful feature that is reported in approximately 70% of patients with spinal cord infarction but is atypical acutely in myelitis.
- Once spontaneous spinal cord infarction is suspected, it is important to understand the typical MRI appearance in acute, subacute, and chronic settings.
- A low threshold for MRI of the entire spine should exist, unless the localization is clear (eg, cervical spinal cord in quadriplegia). Diffusion-weighted imaging/apparent diffusion coefficient should be performed, but the sensitivity is incomplete and sometimes takes days to evolve. In the initial hours of symptoms, imaging is likely normal or equivocal.
- It is reasonable to discuss risks and benefits of IV recombinant tissue plasminogen activator within the first 4.5 hours after onset if suspicion of spinal cord infarction is high and the patient understands the limited evidence.
- Atherosclerosis, arterial dissection, and fibrocartilaginous embolism are the most common presumed mechanisms of spontaneous spinal cord infarction.
- Outcomes after spontaneous spinal cord infarction are variable. Despite severe deficits, approximately 50% of patients ultimately ambulate without a gait aid.

- The incidence of spinal dural arteriovenous fistula is 5 to 10 cases per million per year. An older population is typical (40 to 80 years), with male predominance (80%), and patients frequently report previous back surgeries or trauma that may contribute to the development of a fistula.
- The clinical presentation of spinal dural arteriovenous fistula typically includes a gradually progressive thoracic myelopathy with leg weakness/numbness, bowel/bladder dysfunction, symptoms frequently referable to the conus/roots, and episodic worsening with exertion/Valsalva. The strongest clinical clue is dramatic worsening of deficits with activities elevating venous pressure, such as exertion, Valsalva, or lumbar puncture.
- Inappropriate corticosteroid use for suspected alternative diagnoses can lead to clinical worsening in spinal dural arteriovenous fistulas from exacerbation of venous hypertension and thus should be avoided.
- Spinal cord T2-hyperintense signal is present in approximately 95% of cases of spinal dural arteriovenous fistula, is often longitudinally extensive (three or more vertebral body segments), and frequently extends to the conus (90% of cases).
- Flow voids (engorged perimedullary veins) are seen on the dorsal more than the ventral surface of the cord in approximately 80% of cases of spinal dural arteriovenous fistula.
- Gadolinium enhancement of the spinal cord is common in spinal dural arteriovenous fistula, and clinicians should not be misled to suspect an inflammatory or neoplastic etiology when features are suspicious for spinal dural arteriovenous fistula.
- Although digital subtraction angiography is the gold standard to identify a fistula, a noninvasive spinal magnetic resonance angiogram can initially be considered to potentially help localize the fistula before the formal angiography.
- Treatment options for spinal dural arteriovenous fistula include embolization of the fistula via digital subtraction angiography or surgical disconnection of the draining vein. Improvement or stabilization is expected after treatment.
- Intraparenchymal spinal cord hemorrhage (hematomyelia) is very rare. Trauma is the most common cause, followed by intramedullary spinal cord cavernous malformations and arteriovenous malformations; many additional causes have also been reported.
- A well-defined lobulated masslike lesion within the parenchyma of the spinal cord with heterogeneous T1- and T2-weighted signal intensity surrounded by a well-defined dark T2-hypointense rim (hemosiderin deposition) with classic popcorn appearance is typical of an intramedullary spinal cord cavernous malformation, which can be best appreciated with gradient recalled echo and susceptibility-weighted imaging.
- Management of intramedullary spinal cord cavernous malformation is focused on avoiding further deterioration with recurrent hemorrhage; observation is typically recommended for asymptomatic cavernous malformations or those with minimal symptoms.
- Although spinal dural arteriovenous fistula (type I) comprises 70% of spinal arteriovenous shunts, 30% of cases are secondary to types II through V: intramedullary glomus arteriovenous malformation (type II), intramedullary juvenile arteriovenous malformation (type III), perimedullary arteriovenous fistula (type IV), and extradural arteriovenous fistula (type V).
- The predominant clinical presentation of spinal arteriovenous malformation is acute myelopathy secondary to hematomyelia.
- Spinal epidural hematoma is most commonly encountered in trauma or after surgery, epidural catheterization, or lumbar puncture.
- Treatment of symptomatic spinal epidural hematoma is emergent surgery, with improved outcomes when performed within 12 hours of symptom onset.

ARTICLE 3: MYELITIS AND OTHER AUTOIMMUNE MYELOPATHIES

Sebastian Lopez Chiriboga, MD; Eoin P. Flanagan, MBBCh. Continuum (Minneap Minn). February 2021; 27 (1 Spinal Cord Disorders):62–92.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an update on the clinical diagnosis and management of immune-mediated myelopathies, including the relevance of imaging, ancillary testing with an emphasis on autoantibody biomarkers, recognition of myelitis mimics, and therapeutic approach.

RECENT FINDINGS:

The imaging characterization of immune-mediated myelopathies and the discovery of neural autoantibodies have been crucial in improving our ability to accurately diagnose myelitis. The identification of autoantibodies directed against specific central nervous system targets has led to major improvements in our understanding of the mechanisms underlying inflammation in myelitis. It has also allowed distinction of these myelopathy etiologies from noninflammatory etiologies of myelopathy and from multiple sclerosis and provided insight into their risk of recurrence, treatment response, and long-term clinical outcomes. Prompt recognition and appropriate testing in the setting of acute and subacute myelopathies is critical as timely administration of immunotherapy can help improve symptoms and prevent permanent neurologic disability. A patient should not be classified as having "idiopathic transverse myelitis" without a comprehensive evaluation for a more specific etiology. Achieving the correct diagnosis and learning to recognize noninflammatory myelitis mimics is crucial as they have therapeutic and prognostic implications.

SUMMARY:

Identifying the clinical and radiographic features of immune-mediated myelitis and recognizing mimics and pitfalls will help clinicians treat confirmed autoimmune myelitis appropriately.

KEY POINTS

- The differential diagnosis of immune-mediated myelopathies is broad and includes noninflammatory myelopathies from compressive, vascular, neoplastic, metabolic, nutritional, infectious, toxic, and inherited causes.
- The length of the T2-hyperintense lesion seen on sagittal spinal cord imaging is a very useful discriminator between multiple sclerosis (less than three vertebral segments) and aquaporin-4 (AQP4) IgG–seropositive neuromyelitis optica spectrum disorder (NMOSD) (three or more vertebral segments).
- Idiopathic transverse myelitis should be considered a diagnosis of exclusion, with a comprehensive evaluation for both inflammatory and noninflammatory etiologies before assigning that diagnosis.
- Significant advances in the field of autoimmune neurology, including the discovery of neural autoantibodies, have assisted in identifying a specific cause for patients previously classified as having idiopathic transverse myelitis.
- Better radiographic characterization of immune-mediated myelopathies and their mimics has improved our ability to diagnose patients with myelopathies of uncertain etiology.
- The time from onset to maximal neurologic deficit is the most important feature to determine when evaluating a myelopathy as it helps narrow the differential diagnosis.

- The time to nadir in myelopathy can be classified as hyperacute (<12 hours), acute/subacute (1 to 21 days), or chronic progressive (progression beyond 21 days).
- In spinal cord infarction, the rapid onset of severe deficits reaching nadir within a few hours (up to 12 hours) is typical and occurs in approximately 80% of patients.
- Most patients with idiopathic or disease-associated transverse myelitis reach nadir in 1 to 21 days.
- The natural evolution of attacks of myelitis associated with central nervous system inflammatory demyelinating diseases is subacute development reaching nadir within 21 days with potential plateau, followed by subsequent improvement that may be sped up by intervening with treatment.
- AQP4-IgG–seropositive NMOSD can coexist with systemic autoimmune disorders, including systemic lupus erythematosus, Sjögren syndrome, and antiphospholipid syndrome. Testing for AQP4-IgG in such cases is prudent as a seropositive result confirms a coexisting autoimmune neurologic disorder rather than a neurologic manifestation of a systemic connective tissue disease.
- Typical findings of myelitis on neurologic examination include a sensory level across the trunk and an upper motor neuron pattern of weakness, hyperreflexia, spasticity, and extensor plantar responses, but these may take time to develop.
- Detailed evaluation of the gadolinium enhancement pattern on MRI is critical in the evaluation of myelopathies as it can provide clues to determine specific etiologies.
- A lesion extending less than three vertebral segments (a short lesion) is most suggestive of multiple sclerosis, and multiple peripheral short T2 hyperintensities within the spinal cord with or without typical brain lesions is strongly suggestive of multiple sclerosis.
- Multiple sclerosis lesions are usually wedge-shaped on axial images and involve the periphery of the cord in either the lateral or dorsal columns.
- Short lesions are less common with AQP4-IgG–seropositive NMOSD, occurring in about 15% of patients.
- An isolated longitudinally extensive T2-hyperintense lesion that extends over three or more vertebral segments is typical of AQP4-IgG–seropositive NMOSD and supports this diagnosis over MS.
- Similar to AQP4-IgG–seropositive NMOSD, MOG-IgG–associated disorder myelitis is frequently associated with longitudinally extensive transverse myelitis, although often multifocal cord lesions are seen rather than the solitary lesion typical of AQP4-IgG–seropositive NMOSD.
- Patients with MOG-IgG–associated disorder often have conus involvement.
- Linear dorsal subpial enhancement extending inward from the posterior aspect of the cord and spanning over multiple vertebral segments is seen in approximately 60% of cases of spinal cord sarcoidosis. When this dorsal subpial enhancement is accompanied by central canal enhancement, an axial trident sign can be seen, which is very suggestive of spinal cord sarcoidosis.
- Obtaining an MRI of the brain is standard in the evaluation of autoimmune myelopathy, and the features of the lesions detected can help suggest the underlying diagnosis.
- AQP4-IgG and MOG-IgG are two important antibody biomarkers of transverse myelitis that should be tested in patients with transverse myelitis in whom the clinical and paraclinical findings are not suggestive of MS.
- For AQP4-IgG and MOG-IgG, serum yields the optimal sensitivity (more so than CSF) and cell-based assays are the most reliable.
- Care is needed with low-positive MOG-IgG results as false positives can occur, particularly when ordered in low-probability situations, and the positive MOG-IgG test result should not replace clinical judgment.
- With AQP4-IgG cell-based assays, false positives are extremely rare, although with older-generation techniques, false positives at low titer can be found.
- Several neural autoantibodies are associated with paraneoplastic myelopathies, and the most commonly encountered are amphiphysin and collapsin response mediator protein-5 (CRMP-5)/anti-CV2.
- The majority of autoimmune/inflammatory myelitis episodes will be accompanied by an elevated CSF white blood cell count, and its absence should at least raise consideration of alternative etiologies (eg, vascular myelopathies).
- Understanding the differential diagnosis of autoimmune/inflammatory myelopathy is crucial as many diagnostic pitfalls can lead the clinician to the wrong diagnosis.

- For most autoimmune/inflammatory myelopathies, after reasonable exclusion of alternative etiologies such as extrinsic compression, spinal cord infarction, and infections, expert consensus recommends prompt administration of high-dose IV corticosteroids with 1 g IV methylprednisolone once daily for 5 days.
- In patients with myelitis as a manifestation of central nervous system inflammatory demyelinating disease with severe neurologic deficits despite steroids, plasma exchange should be considered.

ARTICLE 4: INFECTIOUS MYELOPATHIES

Michel Toledano, MD. Continuum (Minneap Minn). February 2021;
27 (1 Spinal Cord Disorders):93–120.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews infectious etiologies of spinal cord dysfunction, emphasizing the importance of recognizing common clinicoradiographic syndromes and interpreting them in the context of exposure risk and individual host susceptibilities.

RECENT FINDINGS:

This article discusses the shifting spectrum of neurologic infectious diseases, the growing population of patients who are immunocompromised, and the emergence of effective antiretroviral therapies. In addition, it discusses new molecular and serologic tests that have the potential to enhance our ability to rapidly and accurately diagnose infectious diseases of the spine.

SUMMARY:

When evaluating patients with suspected infectious myelopathies, it is imperative to narrow the range of pathogens under consideration. The geography, seasonality, and clinicoradiographic presentation and immunocompetence status of the patient define the range of potential pathogens and should guide testing and initial management.

KEY POINTS

- Infections can result in spine pathology through direct invasion of neural structures or by immune-mediated mechanisms triggered by systemic infection in the absence of neuroinvasion.
- Although considerable overlap exists, recognizing common clinicoradiographic syndromes is critical when generating a differential diagnosis for infectious myelopathies.
- The sensitivity of CSF varicella-zoster virus polymerase chain reaction starts decreasing steadily the further away from symptom onset. A low serum to CSF IgG ratio demonstrating intrathecal production of antibodies is more sensitive.
- Varicella-zoster virus myelitis can occur in the absence of a characteristic herpes zoster rash.
- The myelitis associated with *Mycoplasma pneumoniae* is likely caused by parainfectious or postinfectious immune-mediated mechanisms.
- Meningomyelitis is the most common spinal cord manifestation of syphilis.
- Treponemal tests remain positive for life following infection. Negative treponemal tests essentially rule out a diagnosis of syphilis.
- Elsberg syndrome is characterized by subacute onset of sacral myeloradiculitis and is commonly associated with herpes simplex virus type 2.
- Meningoradiculitis is the most common spinal manifestation of *Borrelia burgdorferi*.
- Neuroschistosomiasis can present as an insidious lumbosacral myeloradiculitis.

- Human T-cell lymphotropic virus type 1–associated myelopathy presents with slowly progressive proximal greater than distal spastic paraparesis and early urinary retention.
- Human immunodeficiency virus–associated vacuolar myelopathy occurs most commonly in advanced infection, but the pathophysiology does not seem to be caused by viral cord infection or inflammation.
- Although tabes dorsalis was common in the preantibiotic era, it is only rarely seen in contemporary practice.
- The clinical presentation of poliomyelitis is usually monoparesis with reflex loss.
- Despite the strong epidemiologic link with enterovirus D68, the etiology of epidemic acute flaccid myelitis remains elusive.
- Viremia is short-lived with most flaviviruses, and polymerase chain reaction is insensitive. Blood or CSF IgM in the acute setting establishes the diagnosis.
- *Aspergillus* can present with spinal cord ischemia and hemorrhage.
- Ampicillin should be initiated empirically in cryptogenic spinal cord abscess for *Listeria* coverage.
- Tuberculous spondylitis (Pott disease) is the most common spinal manifestation of tuberculosis.
- Fever is present in less than 50% of patients with pyogenic spondylodiskitis or epidural abscess.
- Fungal and mycobacterial infection can cause adhesive arachnoiditis, resulting in spinal block and myelopathy with or without syringomyelia.
- Unlike intracerebral disease, which predominantly involves the brain parenchyma, most spinal neurocysticercosis occurs in the subarachnoid space, resulting in compressive myelopathy.

ARTICLE 5: NEOPLASTIC MYELOPATHIES

Amy A. Pruitt, MD, FAAN. Continuum (Minneap Minn). February 2021;
27 (1 Spinal Cord Disorders):121–142.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the current classification system of primary spinal cord tumors and explores evolving diagnostic and therapeutic strategies for both primary tumors and metastatic tumors to various compartments of the spinal cord.

RECENT FINDINGS:

The 2016 World Health Organization classification system allows for more precise prognostication of and therapy for spinal cord tumors and has identified new entities, such as the diffuse midline glioma, H3 K27M mutant. Whole-exome sequencing reveals that the genetic background of primary glial spinal cord neoplasms differs from that of their intracranial histologic counterparts in ways that can potentially influence therapy. Targeted and immune checkpoint therapies have improved survival for patients with melanoma and lung cancer and have simultaneously produced novel complications by enhancing radiation toxicity in some cases and by facilitating the emergence of novel autoimmune and paraneoplastic syndromes involving the spinal cord, such as neuromyelitis optica spectrum disorder and syndromes associated with anti-Hu and collapsin response mediator protein-5 (CRMP-5) antibodies. These conditions must be distinguished from tumor or infection. Epidural spinal cord compression treatment paradigms have changed with the advent of robotic surgery and advances in radiation therapy.

SUMMARY:

Neoplastic myelopathies subsume a wide spectrum of pathologies. Neoplastic cord involvement may be primary or secondary and may be approached diagnostically by the particular spinal cord compartment localization. Primary spinal cord tumors account for only 2% to 4% of primary

central nervous system tumors, ranging from low-grade glial neoplasms to malignant tumors. Metastatic malignancy to the epidural or leptomeningeal spaces is more common than primary cord tumors. Differential diagnoses arising in the course of evaluation for cord tumors include myelopathies related to radiation or chemotherapy and paraneoplastic syndromes, all of which are sources of significant morbidity. Knowledge of genetic syndromes and the biologic behavior of diverse histologies together with selective application of surgery, radiation, and targeted therapies can facilitate diagnosis, minimize surgical morbidity, and prolong quality of life.

KEY POINTS

- Although spinal cord tumors represent only 2% to 4% of all primary central nervous system tumors, they cause significant morbidity and are often confused clinically and radiographically with non-neoplastic processes.
- Neoplastic myelopathies are classified by the compartment affected as intramedullary, intradural-extramedullary, and extradural tumors. Differential diagnostic considerations and workup are dictated by the particular neuroanatomic compartment involved.
- Overall, metastatic tumors, which are usually in the epidural space, account for many more cases of adult spinal cord tumors than do primary spinal tumors, whereas in children (in whom primary tumors are more common), the intramedullary compartment is the most common tumor site.
- Ependymomas are the most common primary intramedullary spinal tumors in adults, but the most common primary spinal tumors overall in adults are meningiomas.
- Lung, breast, prostate, thyroid, and renal cell cancers represent the majority of spinal metastatic tumors, the vast majority of which are extradural. Leptomeningeal dissemination is seen most frequently with adenocarcinoma of the breast and lung, non-Hodgkin lymphoma, melanoma, and gastrointestinal tumors.
- Ependymomas are the most common intramedullary primary spinal cord tumor in all age groups.
- Back, radicular, or central pain, often asymmetric and without motor involvement, is the most common symptom preceding the diagnosis of intramedullary neoplasm.
- Spinal glial tumors show no association between increasing grade of malignancy and patient age at diagnosis.
- Cellular ependymomas may be World Health Organization (WHO) grade II or grade III and arise from the intraspinal canal, usually in the cervical and thoracic regions; myxopapillary ependymoma, a WHO grade I tumor, is most frequently seen in the conus medullaris arising from the filum terminale, where they comprise 90% of tumors.
- Ependymomas are often well-demarcated isointense lesions that enhance with gadolinium.
- Gross total resection of astrocytomas is unlikely, but ependymomas, which are often encapsulated, are more amenable to total resection.
- Recognized for the first time in the 2016 WHO classification of tumors is the WHO grade IV diffuse midline glioma, H3 K27M mutant, previously called diffuse intrinsic pontine glioma.
- Most H3 K27M-mutant diffuse midline gliomas occur in the thalamus and brainstem, but brainstem cases can extend to the spinal cord and show a propensity for intramedullary drop metastases and leptomeningeal dissemination.
- Pilocytic astrocytomas of the spinal cord account for about 11% of pediatric spinal cord tumors. These often are associated with neurofibromatosis type 1. Most are well circumscribed and WHO grade I.
- Hemangioblastoma, a WHO grade I tumor, is rare except in von Hippel-Lindau syndrome, an autosomal dominant disorder characterized by chromosome 3p deletion; von Hippel-Lindau syndrome accounts for up to 30% of cases of hemangioblastoma.
- Meningiomas are the most common primary spinal cord neoplasm in adults, accounting for one-fourth of all primary spinal cord tumors. The majority of meningiomas are WHO grade I slow-growing tumors. Genetic predisposition (neurofibromatosis type 2) and prior radiation are risk factors.
- Radiosurgery is used for incomplete resection or recurrence of spinal meningioma, and protons are gaining a larger role in the treatment of spinal meningioma. No role for chemotherapy has been established, but intracranial meningiomas have been reported to respond to everolimus, sunitinib, and bevacizumab.

- Schwannomas are benign nerve sheath tumors, the majority of which are WHO grade I. They represent nearly 30% of spinal root tumors, and multiple schwannomas can be found in patients with neurofibromatosis type 2 or schwannomatosis.
- Extradural metastases are most likely to occur from lung, breast, prostate, thyroid, and renal cancers, whereas leptomeningeal dissemination of solid tumors is most commonly seen from breast and lung cancers, melanoma, non–Hodgkin lymphoma, and gastrointestinal tumors.
- Treatment of epidural cord compression is palliative, with the principle goals of pain relief, preservation of neurologic function, maintenance of spinal stability, and improvement in quality of life while avoiding the toxic consequences of radiation and chemotherapy.
- A thin rim of peripheral enhancement and a flame-shaped appearance in the region of enhancement at the superior and inferior margins should suggest a non–central nervous system metastatic intramedullary tumor rather than one of primary spinal cord origin.
- Compared with patients with nonparaneoplastic neuromyelitis optica spectrum disorder (NMOSD), patients with paraneoplastic NMOSD are older at symptom onset and more frequently male. Thus, older patients presenting with NMOSD, particularly if male, should be investigated for neoplasia.
- In the context of immune checkpoint inhibitor treatment, paraneoplastic antibody–associated spinal cord syndromes have emerged. Reported antibodies include anti-Hu/ANNA-1, CRMP-5/anti-CV2, and aquaporin-4 IgG.

ARTICLE 6: METABOLIC AND TOXIC MYELOPATHIES

Natalie Elizabeth Parks, MD. Continuum (Minneap Minn). February 2021;
27 (1 Spinal Cord Disorders):143–162.

ABSTRACT

PURPOSE OF REVIEW:

This article describes the clinical presentation, relevant diagnostic investigations, and treatment of metabolic and toxic myelopathies.

RECENT FINDINGS:

Metabolic myelopathies, including those due to deficiency of vitamin B_{12}, folate, copper, or vitamin E, are preventable and typically respond to supplementation. In metabolic myelopathy, early recognition and treatment are important to reduce morbidity, particularly due to subacute combined degeneration of the spinal cord. Toxic myelopathies, including those due to medical interventions (eg, methotrexate, radiation), dietary toxins (eg, lathyrism, konzo), and drugs of abuse (eg, heroin), typically result in permanent neurologic deficits. Toxic myelopathy due to hepatic dysfunction may be reversible if patients receive early intervention, whereas nitrous oxide myelopathy responds to vitamin B_{12} replacement and cessation of exposure. In toxic myelopathy, it is best to avoid the provoking factor when possible or attempt to mitigate risk by identifying risk factors for developing myelopathy.

SUMMARY:

Metabolic and toxic myelopathies are important causes of morbidity that require a high index of suspicion for diagnosis.

KEY POINTS

- Vitamin B_{12} deficiency is common among older adults.

- Subacute combined degeneration of the spinal cord presents with posterior column dysfunction (reduced vibration/proprioception) along with variable severity of lateral column dysfunction (upper motor neuron signs).
- Vitamin B_{12} deficiency may be present despite serum cobalamin within the normal range, although plasma methylmalonic acid or plasma homocysteine, or both, may be elevated.
- The treatment for subacute combined degeneration of the spinal cord due to vitamin B_{12} deficiency is IM or subcutaneous cyanocobalamin 1000 mcg/d for 5 days followed by 1000 mcg once per month.
- Vitamin B_{12} replacement should be given indefinitely following subacute combined degeneration of the spinal cord due to vitamin B_{12} deficiency.
- Nitrous oxide causes inactivation of vitamin B_{12}, which may result in subacute combined degeneration of the spinal cord.
- Folate deficiency is uncommon since the introduction of national fortification programs aimed at improving folate levels among reproductive-age women to reduce neural tube defects in their offspring.
- Serum folate level reflects recent folate intake, whereas red blood cell folate level reflects intake over approximately the past 3 months.
- Copper deficiency is an underrecognized cause of subacute combined degeneration of the spinal cord.
- Copper deficiency may be caused by bariatric surgery, celiac disease, or excessive zinc intake as a supplement or in denture cream.
- Serum copper and serum ceruloplasmin levels are typically low in copper deficiency.
- Vitamin E deficiency that results in spinocerebellar ataxia is an increased risk among those with impaired fat absorption from disorders such as cystic fibrosis and rare genetic conditions, including ataxia with vitamin E deficiency and abetalipoproteinemia.
- Grass peas (*Lathyrus sativus*) contain a neurotoxin that may result in neurolathyrism manifesting with acute-onset spastic paraparesis.
- Bitter cassava contains cyanogens that may cause konzo, manifesting with spastic paraparesis, due to cyanide toxicity.
- Subacute combined degeneration of the spinal cord may occur with intrathecal methotrexate, which is a folate antagonist.
- Tumor necrosis factor-α inhibitors and immune checkpoint inhibitors are associated with transverse myelitis.
- Subacute myelo-optico-neuropathy was caused by clioquinol, a metal chelator that may cause copper deficiency.
- Reintroduction of heroin following a period of abstinence may cause acute-onset complete myelopathy.
- Radiation myelopathy is a delayed effect of radiation occurring 6 to 24 months after radiation exposure.
- Hepatic myelopathy occurs in chronic liver disease with portosystemic shunting.
- Decompression myelopathy occurs within 1 hour of diving and is treated with hyperbaric oxygen therapy, typically with good recovery.

ARTICLE 7: SPONDYLOTIC AND OTHER STRUCTURAL MYELOPATHIES

Shamik Bhattacharyya, MD, MS. Continuum (Minneap Minn). February 2021; 27 (1 Spinal Cord Disorders):163–184.

ABSTRACT

PURPOSE OF REVIEW:

This article highlights both common structural causes of myelopathy, such as spondylotic disease, and infrequent but treatable causes, such as syringomyelia, spinal cord herniation, arachnoid cyst, arachnoid band and web, epidural lipomatosis, Hirayama disease, and arachnoiditis.

RECENT FINDINGS:

Neuroimaging improvements and availability have uncovered many structural abnormalities in the spines and spinal cords of patients who were asymptomatic or minimally symptomatic. Recent published clinical series have improved our knowledge of the natural history of structural abnormalities and the risks of intervention versus conservative management.

SUMMARY:

Myelopathy from a suspected structural cause is a common reason for neurologic consultation. Correlation between the history, examination, and imaging are especially important to determine whether intervention is necessary or conservative management is the best option.

KEY POINTS

- Cervical spondylotic myelopathy is caused by degenerative disease of the cervical spine resulting in narrowing of the spinal canal.
- Cervical spondylotic myelopathy is overdiagnosed in some patients (symptoms misattributed to imaging findings) and missed in others (mild symptoms that are not investigated).
- Congenital narrowing of the spinal canal is a frequent risk factor for the development of cervical spondylotic myelopathy.
- Patients with Klippel-Feil syndrome clinically have decreased neck mobility, a low posterior hairline, and a short neck; imaging shows fusion of multiple cervical vertebral bodies.
- Cervical spondylotic myelopathy is likely caused by a combination of canal narrowing, stretch of the spinal cord over the stenotic region, and microvascular ischemia.
- Cervical spondylotic myelopathy can have acute, subacute, and chronic presentations.
- Acute cord injury from extension in patients with cervical spondylotic myelopathy causes central cord syndrome in which patients have urinary retention and greater weakness in their arms than in their legs.
- Chronic cervical spondylotic myelopathy causes initial symptoms of progressive gait disorder.
- Lack of neck pain does not exclude cervical spondylotic myelopathy.
- Bladder and bowel sphincter dysfunction are atypical in chronic progressive cervical spondylotic myelopathy.
- The Babinski sign is not very sensitive for cervical spondylotic myelopathy and may be absent in early disease. The Hoffman sign may be positive more often.
- MRI of the cervical spine without contrast is the preferred study to evaluate for cervical degenerative disease.
- X-ray of the cervical spine is useful to evaluate instrumentation and for dynamic instability of bony structures with flexion and extension of the neck.
- The majority of older adults will have degenerative changes of the cervical spine on MRI.
- Categorization as moderate or severe stenosis of the cervical spine based on the degree of CSF obliteration has modest correlation with clinical symptoms.
- Clinical myelopathy from cervical spinal stenosis can occur without any T2 cord signal changes.
- The presence or absence of cord signal hyperintensity does not correlate with outcome after surgery.
- T2 hyperintensity in the spinal cord from cervical spondylotic myelopathy may have a snake-eye appearance, with areas of hyperintensity in the anterior horns bilaterally.
- The natural history of untreated cervical spondylotic myelopathy is unclear and has considerable variability.
- Minor trauma is an unusual precipitant of acute myelopathy in patients with asymptomatic severe cervical spine stenosis.
- Patients with untreated cervical spondylotic myelopathy often have a stepwise course, with periods of stability and then episodes of acute deterioration. Some patients relentlessly progress, whereas others can remain stable for years.
- Conservative therapy for cervical spondylotic myelopathy generally involves physical therapy and gentle cervical spine range-of-motion exercises.
- Cervical spinal stenosis can be decompressed via either an anterior or a posterior approach. No clear consensus exists on which approach is superior.

- C5 radiculopathy can be a postoperative complication of cervical spine surgery.
- Upper extremity strength recovers best following surgery for cervical spondylotic myelopathy, whereas recovery of leg strength and sensory dysfunction are less complete.
- An enlarged central canal is often incidentally found on imaging and is generally not pathogenic.
- Chiari type I malformation can be clinically silent and associated with syringomyelia.
- Syrinx formation from spinal cord injury can be delayed by many years.
- Free CSF flow impairment in the spinal subarachnoid space is a common theme among the different predisposing causes of syringomyelia.
- A small midline syrinx causes interruption of crossing spinothalamic tracts and a capelike distribution of numbness to pain and temperature.
- The natural history of syringomyelia is unpredictable. Many patients remain asymptomatic, whereas others can progress with time.
- Idiopathic spinal cord herniation is characterized by a defect through which the spinal cord is displaced, typically in the ventral dura and generally presenting with progressive myelopathy.
- Spinal arachnoid cysts are intradural-extramedullary cysts in the subarachnoid space that can cause myelopathy by compression of the spinal cord.
- Spinal arachnoid webs are intradural bands of arachnoid tissue that usually attach to the dorsal surface of the spinal cord.
- Spinal arachnoid webs may not be seen directly on MRI but rather inferred from change in caliber of the spinal cord with dorsal cord indentation.
- Spinal epidural lipomatosis refers to accumulation of fat in the epidural space that can be asymptomatic or cause symptoms from compression of nerve roots or the spinal cord.
- Hirayama disease is characterized by the insidious onset of weakness and atrophy of the hand and forearm, predominantly in young males in their teens or twenties without other cranial or pyramidal signs.
- In Hirayama disease, when imaged with the neck extended and flexed, the diameter of the dural sac decreases during flexion with corresponding stenosis and pressure on the spinal cord without movement in the bony elements.
- Spinal adhesive arachnoiditis refers to progressive fibrosis of the arachnoid membrane with injury to the nerve roots, tethering of the spinal cord, and disruption of free flow of CSF.
- Arachnoiditis often presents after a time delay from the initial spinal injury ranging from weeks to years.

ARTICLE 8: HEREDITARY MYELOPATHIES

John K. Fink, MD. Continuum (Minneap Minn). February 2021; 27 (1 Spinal Cord Disorders):185–204.

ABSTRACT

PURPOSE OF REVIEW:

This article guides clinicians in the clinical recognition and differential diagnosis of hereditary myelopathies.

RECENT FINDINGS:

Rather than a disease, a disease process, or relating to specific cellular vulnerability, the term *hereditary myelopathy* refers to diverse inherited disorders in which major aspects of the clinical syndrome reflect disturbance of elements within the spinal cord (specifically, the dorsal columns and dorsal root ganglia, corticospinal tracts, and anterior horn cells). It is important to note that the clinical features of almost all hereditary myelopathies reflect not only disturbance of elements within the spinal cord but also disturbance of extraspinal structures (particularly,

but not limited to, peripheral nerves and the cerebellum) and that these extraspinal clinical features can be very helpful in recognizing specific myelopathy syndromes. The value of classifying disorders as inherited myelopathies lies primarily in facilitating their clinical recognition and differential diagnosis. It is useful to recognize that many hereditary myelopathies conform to one of four clinical paradigms: (1) spinocerebellar ataxia, (2) motor neuron disorder, (3) leukodystrophy, or (4) distal motor-sensory axonopathy predominantly affecting the central nervous system. Although they are myelopathies, spinal dysraphisms such as spina bifida and myelomeningocele are not included in this context because they are not usually due to single-gene mutation and have low hereditability.

SUMMARY:

This article illustrates clinical paradigms of hereditary myelopathy with clinical examples emphasizing the spectrum, clinical recognition, and differential diagnosis of hereditary myelopathies.

KEY POINTS

- In addition to symptoms arising from disturbance within the spinal cord, neurologic involvement in nearly all hereditary myelopathies includes structures outside the spinal cord.
- Many hereditary myelopathic syndromes can be recognized as one of four clinical paradigms: (1) spinocerebellar ataxia, (2) motor neuron disorder, (3) leukodystrophy, or (4) central nervous system–predominant distal motor-sensory axonopathy.
- Spinocerebellar degenerations (eg, Friedreich ataxia, spinocerebellar ataxia type 3, Bassen-Kornzweig syndrome, and vitamin E deficiency) are recognized by a combination of progressive cerebellar ataxia, often accompanied by peripheral neuropathy; dorsal column (or dorsal root ganglia) impairment (which may cause sensory ataxia); and variable corticospinal tract involvement.
- Spinocerebellar ataxia type 3 is caused by a trinucleotide repeat (CAG) expansion that, like other polyglutamine expansions, is thought to be pathogenic through protein misfolding.
- The vast majority of patients with Friedreich ataxia are homozygous for expanded trinucleotide repeat in the *FXN* gene, which encodes a mitochondrial protein. Rarely, individuals will have an expanded trinucleotide repeat in one *FXN* allele and a point mutation in the other *FXN* allele.
- In primary lateral sclerosis, there is either no evidence of lower motor neuron involvement, or, at most, minimal evidence of chronic denervation is seen on EMG late in the disease. At the other extreme, spinal muscular atrophy is characterized by muscular weakness and atrophy due to anterior horn cell degeneration with preservation of corticospinal tracts.
- Demyelinating peripheral neuropathy, which may accompany childhood-onset leukodystrophies (eg, Krabbe disease and metachromatic leukodystrophy), may be absent in the rare adolescent- and adult-onset forms of these disorders.
- Childhood-onset adrenoleukodystrophy and adolescent- and adult-onset adrenomyeloneuropathy are X-linked disorders in which *ABCD1* gene mutation leads to impaired peroxisomal beta-oxidation and accumulation of very long chain fatty acids systemically.
- Adrenoleukodystrophy/adrenomyeloneuropathy phenotypes include rapidly progressive childhood, adolescent, and adult cerebral forms; slowly progressive myelopathic forms (characterized by slowly progressive spastic paraparesis and peripheral neuropathy, often with complete sparing of the brain); and isolated adrenal insufficiency.
- Clinical distinction of leukodystrophies from axonopathies is based on the presence of additional neurologic findings, particularly cognitive impairment, optic neuropathy, deafness, and sensory disturbance.
- Sensory impairment in uncomplicated motor-sensory axonopathies (eg, uncomplicated hereditary spastic paraplegia) typically results in mild dorsal column impairment affecting longer fibers and manifests as impaired vibration perception in the toes with preservation of other sensory modalities.

- *ATL1*/atlastin gene mutation is the most common cause of childhood-onset autosomal dominant hereditary spastic paraplegia. *ATL1* hereditary spastic paraplegia usually causes nonprogressive infantile-onset spastic gait and resembles spastic diplegic cerebral palsy.
- Central nervous system–predominant distal motor-sensory axonopathy (eg, uncomplicated hereditary spastic paraplegia) can be considered analogous to Charcot-Marie-Tooth disease type 2, in which axonopathy affects predominantly the distal ends of long motor and sensory fibers in the peripheral nervous system.
- *SPAST* mutations are the most common cause of autosomal dominant hereditary spastic paraplegia.

ARTICLE 9: DISORDERS OF THE CAUDA EQUINA

Samantha LoRusso, MD. Continuum (Minneap Minn). February 2021; 27 (1 Spinal Cord Disorders):205–224.

ABSTRACT

PURPOSE OF REVIEW:

Cauda equina dysfunction (often referred to as *cauda equina syndrome*) is caused by a diverse group of disorders that affect the lumbosacral nerve roots. It is important to recognize dysfunction of the cauda equina quickly to minimize diagnostic delay and lasting neurologic symptoms. This article describes cauda equina anatomy and the clinical features, differential diagnosis, and management of cauda equina disorders.

RECENT FINDINGS:

The diagnosis of disorders of the cauda equina continues to be a challenge. If a compressive etiology is seen, urgent neurosurgical intervention is recommended. However, many people with clinical features of cauda equina dysfunction will have negative diagnostic studies. If the MRI is negative, it is important to understand the diagnostic evaluation and differential diagnosis so that less common etiologies are not missed.

SUMMARY:

Cauda equina dysfunction most often occurs due to lumbosacral disk herniation. Nondiskogenic causes include vascular, infectious, inflammatory, traumatic, and neoplastic etiologies. Urgent evaluation and surgical intervention are recommended in most cases of compressive cauda equina syndrome. Other types of treatment may also be indicated depending on the etiology.

KEY POINTS

- Cauda equina syndrome results from dysfunction of lumbosacral nerve roots leading to symptoms of urinary retention and incontinence, constipation, bowel incontinence, sexual dysfunction, sensory changes (particularly saddle anesthesia), back pain, and lower extremity weakness.
- Examination findings that suggest cauda equina dysfunction include reduced or absent reflexes in the lower extremities, loss of perineal or lower extremity sensation, reduced rectal tone, and lower extremity flaccid weakness.
- The sensory changes in cauda equina syndrome can be unilateral or bilateral, with the most common areas of involvement being the posterior thighs, buttocks, and perineum.
- No single symptom or sign has been found to have consistently high sensitivity and specificity in diagnosing MRI-positive cauda equina syndrome.
- If any question exists regarding the localization to the cauda equina based on history and examination, then imaging of the entire neuraxis (brain and spinal cord) should be considered.

- Neurosurgery should be consulted immediately in a case of suspected cauda equina dysfunction due to a compressive lesion.
- The degree of neurologic dysfunction before surgery is the most consistent prognostic factor in cauda equina syndrome.
- Disk herniations are the most common cause of cauda equina dysfunction, occurring the majority of the time at the L4-L5 or L5-S1 levels.
- Constitutional symptoms, such as fevers, night sweats, and weight loss, should lead to consideration of an infectious etiology of cauda equina dysfunction in the appropriate clinical setting.
- Elsberg syndrome likely accounts for about 10% of patients with a clinical presentation of cauda equina syndrome and myelitis.
- Myxopapillary ependymomas are the most common primary tumor to affect the cauda equina.
- Sarcoidosis is likely the most common inflammatory disorder that can present with cauda equina dysfunction.
- Trauma, especially from motor vehicle accidents, falls, and gunshot wounds, is a potential cause of cauda equina syndrome, often because of a low lumbar or transverse sacral fracture.
- Although not technically a disorder of the cauda equina, pudendal neuropathy can closely mimic cauda equina syndrome since it originates from the S2 through S4 nerve roots and innervates the perineum.

ARTICLE 10: NEUROIMAGING OF SPINAL CORD AND CAUDA EQUINA DISORDERS

Felix E. Diehn, MD; Karl N. Krecke, MD, FACR. Continuum (Minneap Minn). February 2021; 27 (1 Spinal Cord Disorders):225–263.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the neuroimaging of disorders of the spinal cord and cauda equina, with a focus on MRI. An anatomic approach is used; diseases of the extradural, intradural-extramedullary, and intramedullary (parenchymal) compartments are considered, and both neoplastic and non-neoplastic conditions are covered. Differentiating imaging features are highlighted.

RECENT FINDINGS:

Although T2-hyperintense signal abnormality of the spinal cord can have myriad etiologies, neuroimaging can provide specific diagnoses or considerably narrow the differential diagnosis in many cases. Intradural-extramedullary lesions compressing the spinal cord have a limited differential diagnosis and are usually benign; meningiomas and schwannomas are most common. Extradural lesions can often be specifically diagnosed. Disk herniations are the most commonly encountered mass of the epidural space. Cervical spondylotic myelopathy can cause a characteristic pattern of enhancement, which may be mistaken for an intrinsic myelopathy. A do-not-miss diagnosis of the extradural compartment is idiopathic spinal cord herniation, the appearance of which can overlap with arachnoid cysts and webs. Regarding intrinsic causes of myelopathy, the lesions of multiple sclerosis are characteristically short segment but can be confluent when multiple. Postcontrast MRI can be particularly helpful, including when attempting to differentiate the long-segment myelopathy of neurosarcoidosis and aquaporin-4 (AQP4)-IgG–seropositive neuromyelitis optica spectrum disorder (NMOSD) and when characterizing spinal cord tumors such as primary neoplasms and metastases. Spinal dural arteriovenous fistula is another do-not-miss diagnosis, with characteristic MRI features both precontrast and postcontrast. Tract-specific white matter involvement can be a clue for

diseases such as subacute combined degeneration, paraneoplastic myelopathy, and radiation myelitis, whereas gray matter–specific involvement can suggest conditions such as cord infarct, viral myelitis, or myelin oligodendrocyte glycoprotein (MOG)-IgG associated disorder.

SUMMARY:

Knowledge of the neuroimaging findings of the many causes of spinal cord and cauda equina dysfunction is critical for both neurologists and neuroradiologists. A structured approach to lesion compartmental location and imaging feature characterization is recommended.

KEY POINTS

- IV administration of gadolinium with postcontrast T1-weighted imaging performed in at least the sagittal plane, if not also the axial plane, is recommended for complete evaluation of suspected intrinsic myelopathy with blood–spinal cord barrier breakdown.
- Inclusion of diffusion-weighted imaging in the MRI protocol is suggested for any hyperacute or acute myelopathy, particularly to help assess for infarct.
- The central canal can be physiologically prominent and thereby evident as a normal variant on MRI; this is thin, usually only a few millimeters in diameter, and should not be confused with a syrinx.
- The normal gray matter is slightly more hyperintense than the white matter, which may simulate abnormal T2 hyperintensity anteriorly and centrally on sagittal T2-weighted images.
- The most common mass in the epidural space is a disk herniation. Most disk herniations are located in the ventral/ventrolateral epidural space and remain in anatomic continuity with their parent disk, a key clue to the diagnosis.
- A highly prevalent finding for dorsal disk herniations is that the abnormal epidural soft tissue still typically maintains continuity with the parent disk in the ventrolateral epidural space, wrapping around the thecal sac dorsally.
- The heterogeneous internal signal characteristics of synovial cysts are wide-ranging and include T1 and T2 hypointensity or hyperintensity or a combination.
- MRI of extradural abscesses may show associated adjacent inflammatory changes, including in the paraspinal soft tissues and bones, or frank findings of spondylodiskitis.
- On CT, ossification of the posterior longitudinal ligament is readily identifiable as flowing ossification along the expected course of the posterior longitudinal ligament in and along the midline at the ventral aspect of the spinal canal.
- After gadolinium administration, T1-weighted images in cervical spondylotic myelopathy often demonstrate a characteristic narrow transverse (pancakelike) band of cord enhancement at or slightly caudal to the focus of spinal stenosis.
- Findings that suggest a relatively high grade and symptomatic lumbar stenosis include redundancy/tortuosity of the cauda equina nerve roots and the sedimentation sign.
- If Hirayama disease is suspected clinically or based on neutral position MRI, flexion MRI should be performed as it can demonstrate findings to better advantage and increase diagnostic confidence.
- For enhancing intradural-extramedullary masses, the two most likely possibilities are meningiomas and nerve root sheath tumors (schwannomas and neurofibromas).
- Characteristic, although not entirely specific, imaging findings suggestive of spinal meningioma include dural tail(s) of contrast enhancement and avid and homogeneous enhancement of the lesion, which may be relatively T2 hypointense because of cellularity or calcification.
- When an isolated, incidental, small enhancing nodule of the cauda equina nerve roots is encountered, the most likely consideration is a nerve sheath tumor.
- Myxopapillary ependymomas are usually relatively large, oval or sausage shaped, well circumscribed, T2 hyperintense, and avidly enhancing.
- Varied appearances of arachnoiditis include nerve roots that are irregularly clumped, clumped into a mass of neural tissue centrally, or dispersed to the margins of the dura (the empty thecal sac sign).

- The most common location for an arachnoid cyst is dorsal to the thoracic cord; although these lesions tend to be well circumscribed, their wall is often imperceptible, especially on MRI.
- Typically, arachnoid webs cause mass effect on and flattening of the dorsal cord, with a characteristic but not pathognomonic morphology termed the scalpel sign that is best seen sagittally on either T2-weighted images or CT myelography.
- On MRI or CT myelography, the characteristic findings of idiopathic spinal cord herniation include ventral displacement of a short segment of cord that is focally distorted/kinked, with the subarachnoid space being lost ventrally and expanded dorsally.
- Neoplasms tend to expand the spinal cord, to have a mass or masslike appearance, and to enhance. The presence of associated adjacent cord cysts or hemorrhage typically suggests a neoplastic process.
- Internal or adjacent heterogeneity, including related to the presence of cystic change (polar cyst) or hemorrhage (T2-hypointense hemosiderin cap sign) at the margins of the lesion, is more commonly encountered with ependymoma than with astrocytoma.
- Although astrocytomas usually enhance, they may not; when they do enhance, it may be fairly mild in amount/intensity or ill-defined.
- Hemangioblastomas have a propensity to be eccentrically located and abut the surface of the spinal cord, with an enhancing pial/subpial nodule especially dorsally. The neoplasms may present as cystic or partially cystic lesions with nodular enhancement.
- Two highly specific enhancement characteristics of intramedullary spinal cord metastases are reasonably prevalent in these lesions and not commonly seen in primary cord tumors: the rim and flame signs.
- Characteristically, multiple sclerosis lesions are short segment (fewer than two segments craniocaudally), asymmetrically and eccentrically located (not involving the entire cross-sectional area), and affect white or white plus gray matter. Common cross-sectional locations include the lateral and dorsal aspects of the cord.
- Three characteristic features of aquaporin-4-IgG–seropositive neuromyelitis optica spectrum disorder that may be present are involvement of the cervicomedullary junction, T1-hypointense components of the lesion, and foci on axial images that are at least as T2 hyperintense as CSF (bright spotty lesions).
- The enhancement pattern in aquaporin-4-IgG–seropositive neuromyelitis optica spectrum disorder is often patchy and heterogeneous, and ring or partial ring enhancement can strongly suggest the diagnosis over neurosarcoidosis.
- The classic finding of neurosarcoidosis of the cord is a long-segment myelopathy, with characteristic enhancement at the dorsal subpial/pial aspect of the cord.
- Selective viral involvement of the anterior horn cells can result in acute flaccid paralysis. An example is the 2014 outbreak related to enterovirus D68, which typically resulted in long-segment T2 hyperintensity of the central gray matter, particularly in the cervical cord.
- When present, the spinal cord T2 hyperintensity of paraneoplastic myelopathy is often long segment, symmetric, and tract specific, such as confined to the lateral or dorsal columns.
- MRI is relatively insensitive for subacute combined degeneration but, when positive, demonstrates T2 hyperintensity of the dorsal columns with an inverted V or inverted rabbit ears morphology on axial images, especially in the cervical and upper thoracic cord.
- A key ancillary imaging clue for radiation-induced myelopathy is associated vertebral body marrow T1 hyperintensity (fatty marrow replacement) encompassing the radiation port.
- Similar to arterial infarcts in the brain, restricted diffusion (with high signal on diffusion-weighted imaging and low signal on apparent diffusion coefficient images) can be seen in acute spinal cord infarcts.
- On T2-weighted images of an anterior spinal artery infarct, preferential involvement of the gray matter manifests as an H-shaped or butterfly-shaped appearance, or as an owl-eyes or snake-eyes sign.
- Because of the shared blood supply of the spinal cord and vertebral bodies, vertebral body infarcts may be observed, usually 1 to 2 weeks after the initial presentation of spinal cord infarct.
- Enhancement of the ventral cauda equina roots may be evident in the subacute phase of spinal cord infarct.

- **The classic finding of a spinal dural arteriovenous fistula is increased posterior pial serpentine vascularity, typically best seen on T2-weighted sagittal images as prominent flow voids within the dilated veins along the dorsal cord surface.**
- **Adjacent hemorrhage in the spinal cord extending craniocaudally away from a cavernous malformation is relatively prevalent; a 2020 retrospective series demonstrated that this finding is more common than some classic features of these lesions, such as popcorn morphology and T2-hypointense rim.**