Vertigo Related to Central Nervous System Disorders

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REVIEW ARTICLE

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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.**

INTRODUCTION

Vertigo can be a challenging symptom for clinicians to treat. Taking a detailed history is the first step in trying to tease out whether the vertigo may be central, meaning caused by central nervous system (CNS) pathology, rather than peripheral in origin. Following the history, neurologic examination is crucial. Having a strong understanding of the eye movements that can suggest central vertigo is extremely beneficial when trying to care for patients. Radiographic studies and vestibular testing can aid in making a diagnosis. For more information on vestibular testing, refer to the article "Vestibular Testing" by Timothy C. Hain, MD, and Marcello Cherchi, MD, PhD, FAAN,[1] in this issue of *Continuum*. Some types of central vertigo and dizziness, such as superficial siderosis and Chiari malformations, are purely radiographic diagnoses, whereas vestibular migraine is entirely a clinical diagnosis. In patients with multiple sclerosis (MS), eye movements often are the key to

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Dr Saha reports no disclosure.

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Dr Saha discusses the unlabeled/investigational use of acetazolamide and 4-aminopyridine for the treatment of episodic ataxia type 2, deferiprone as an iron chelator in the treatment of superficial siderosis, and 4-aminopyridine for the treatment of vertical nystagmus and central positional nystagmus.

determining whether the origin of the vertigo is the nervous system or the inner ear. Structural lesions, such as tumors, vascular lesions, and strokes, can be seen on imaging. Autoimmune vestibulocerebellar disorders causing vertigo are relatively rare, but because of advances in antibody testing, recognition of these disorders is increasing. This article focuses on a variety of CNS causes of vertigo important for neurologists to recognize.

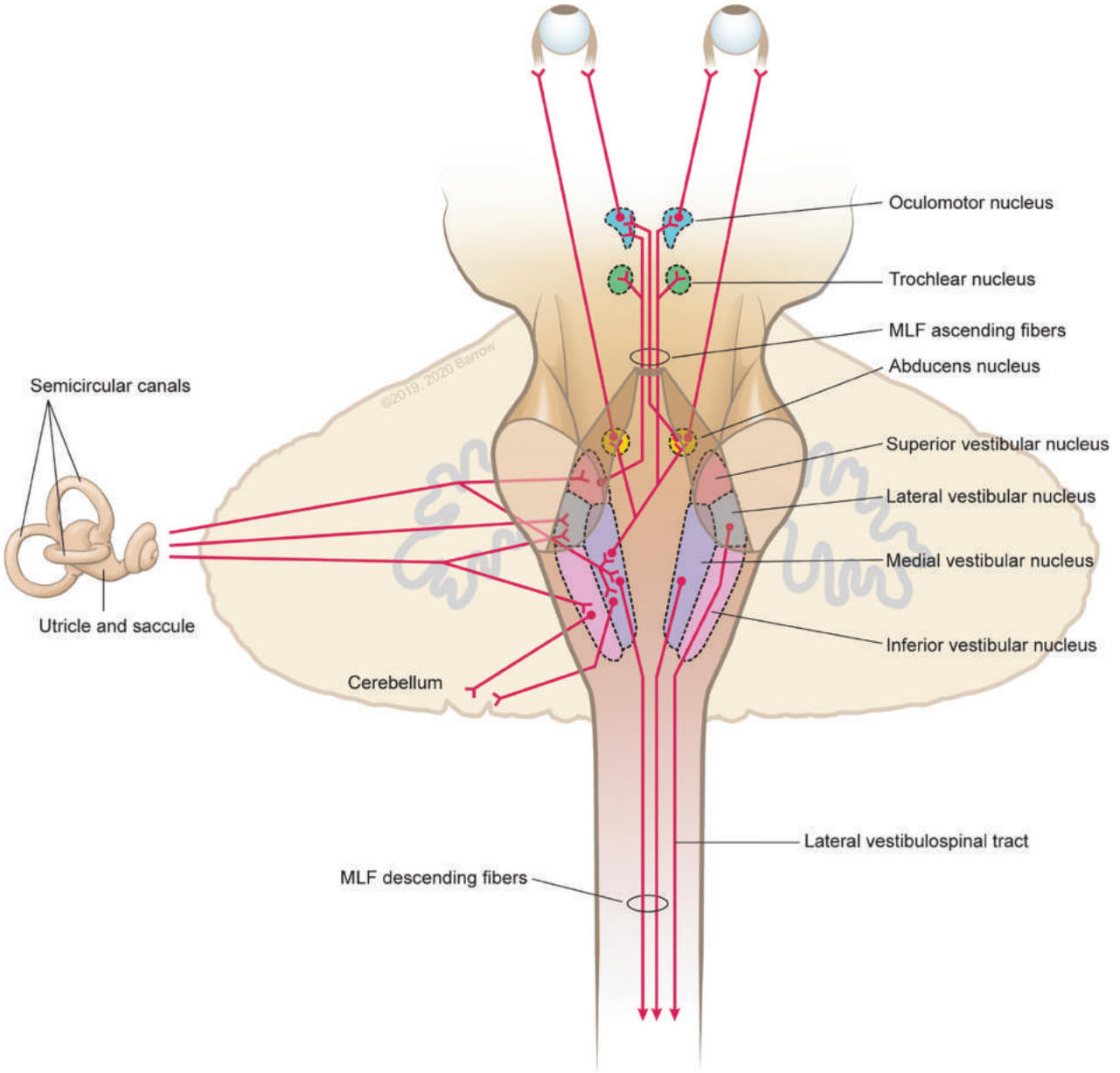

FIGURE 7-1

Structures of the central nervous system vestibular system.

MLF = medial longitudinal fasciculus.

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CENTRAL NERVOUS SYSTEM CAUSES OF VERTIGO

Central vertigo is a false sensation of motion caused by a lesion in the CNS that results in dysfunction of the vestibular nuclei or their projections to the cerebellum (FIGURE 7-1). The vestibular nuclei are located in the caudal pontine tegmentum and dorsolateral medulla and can be subdivided into four separate subnuclei: the superior, lateral (Deiters), medial, and inferior vestibular. These nuclei receive afferents from the peripheral vestibular system by way of the vestibular division of cranial nerve VIII. They also receive afferents from the cerebellum, the reticular formation in the pons, the spinal cord, and the vestibular nuclei on the opposite side. Projections from the vestibular nuclei reach the cerebellum, extraocular nuclei, and spinal cord.[2] Lesions in any of these areas can result in the symptom of vertigo. The following sections discuss the CNS disorders capable of producing lesions that result in central vertigo.

KEY POINT

- **Multiple sclerosis lesions causing vertigo occur most frequently in the root entry zone of cranial nerve VIII and the medial vestibular nucleus.**

Vestibular Migraine

Vestibular migraine is a common cause of vertigo seen in patients with a history of migraine. Vestibular migraine causes episodic vertigo that can appear positional, spontaneous, or visually induced. Vestibular symptoms may occur during headaches but also commonly occur without headache.[3] Between episodes, some patients may experience chronic dizziness and imbalance. Vestibular migraine remains a clinical diagnosis, and diagnostic criteria have been developed by the Bárány Society and the International Headache Society.[4] Although a clear understanding of the pathophysiology is lacking, it may be related to the presumed pathology of migraine. Pathologic nystagmus and central vestibular dysfunction have been seen in the majority of patients with vestibular migraine studied, although they are often nonspecific.[5]

Multiple Sclerosis

MS causes inflammatory demyelinating lesions throughout the CNS and is known to cause lesions specifically in areas that result in vertigo (ie, the brainstem and cerebellum). It has been estimated that 20% of patients with MS will experience true vertigo during their lifetime, and in about 5% of patients with MS, it is the presenting symptom of the disease.[6] The most common CNS sites known to cause vertigo in MS are lesions at the root entry zone of cranial nerve VIII (the lateral pontomedullary junction) and the medial vestibular nucleus.[6-8] Additionally, patients can have symptoms from lesions scattered throughout the cerebellum. In one retrospective analysis of a university-based population of patients with MS presenting with acute vertigo due to demyelinating plaques, three-fourths of the patients had a lesion in the root entry zone of cranial nerve VIII and one-fourth had a lesion in the medial vestibular nucleus.[6] It should be noted that a root entry zone lesion may cause vertigo that behaves as if caused by a peripheral vestibular lesion although the lesion may be in the CNS.

Vertigo due to MS may present acutely during an exacerbation, or it can persist in a chronic form as a result of disease burden. During an exacerbation, vertigo typically begins acutely and can be accompanied by nausea and vomiting. Patients may be ataxic and may also report diplopia. Symptoms can be explained by active (enhancing) lesions in the areas described above. The vertigo usually improves or remits as the exacerbation resolves. Treatment is usually indicated and consists of corticosteroids for most patients with MS who are able to tolerate them. Vertigo can be managed symptomatically with antiemetics or vestibular suppressants such as benzodiazepines (which are not recommended for

long-term use). Vestibular therapy is not usually of strong benefit for central vertigo in MS; however, it has been shown to improve balance and disability due to dizziness or general disequilibrium in patients with MS.[9]

Central vertigo from MS is usually seen along with various focal findings on neurologic examination. Abnormal saccades with reduced velocities, nystagmus (potentially in multiple directions), impaired suppression of the vestibulo-ocular reflex, and internuclear ophthalmoplegia (INO) are the prominent features that can be observed.[10] INO is the most common eye movement disorder seen in MS and is caused by demyelination of the medial longitudinal fasciculus in the pons or midbrain. It is a disorder of impaired conjugate lateral gaze, resulting in slowing adduction or even paralysis of the adducting eye if severe enough. The abducting eye exhibits nystagmus, and patients report diplopia. An INO can be unilateral or bilateral in patients with MS, and variants exist. It is worth noting that the presence of an INO does not necessarily mean a patient will have vertigo. Similarly, not all patients with MS with vertigo have an INO on their examination.

Patients with MS may have saccadic dysmetria from cerebellar involvement, particularly when the cerebellar peduncle is affected.[11] Cerebellar lesions can also cause impaired smooth pursuit, and gaze-evoked, downbeat, or acquired pendular nystagmus that may be associated with oculopalatal tremor and often with dizziness, imbalance, and oscillopsia (a perception of objects bouncing or oscillating). Acquired pendular nystagmus likely results from damage to the neural integrator network in the brainstem and cerebellum.[12]

Treatment of the eye movement dysfunction is both pharmacologic and nonpharmacologic. For acquired pendular nystagmus, gabapentin and memantine can be trialed. Downbeat nystagmus, typically from a lesion in the flocculus, can improve with clonazepam, baclofen, or gabapentin in some patients with MS. Recently, 4-aminopyridine (dalfampridine) has been studied and deemed effective for vertical nystagmus and central positional nystagmus.[11] Prism lenses can be helpful for some types of nystagmus and diplopia. Improvement in the nystagmus does not always result in improvement in the symptoms of dizziness or unsteadiness, but it can lessen oscillopsia for some.

Another important type of vertigo that patients with MS may experience is central positional vertigo. This can be more challenging to diagnose and may be confused with benign paroxysmal positional vertigo (BPPV). A central positional vertigo is much rarer than BPPV. BPPV is more prevalent in patients with MS than in the general population. A retrospective analysis of 1153 patients with MS with acute vertigo found that more than 50% of the patients had BPPV, and all were treated successfully with canalith repositioning maneuvers.[13] Central positional vertigo is similar to BPPV in that it is triggered by position change. However, several pearls can help differentiate it from the more common BPPV:

- **Patients with BPPV typically have a brief period of latency during a provocative maneuver such as the Dix-Hallpike test. Central positional vertigo often has no latency, so nystagmus commences immediately upon positioning.**
- **The nystagmus in BPPV fatigues after some time in the head-hanging position, whereas central positional vertigo may exhibit nystagmus that persists and is prominent even after repeat positioning.**
- **The pattern of nystagmus is perhaps the most important difference. Classic posterior canal BPPV presents with both upbeat and torsional components, whereas central positional vertigo is more likely to present without both components simultaneously.**

Therefore, since the clinical presentation of both types of vertigo can look identical, it is important that neurologists pay close attention to the directional features of nystagmus to better differentiate them and treat accordingly. Several case studies have shown the most common lesion responsible for central positional vertigo in patients with MS to be in the superior cerebellar peduncle (brachium conjunctivum)[10]; however, other lesions in the cerebellum are also known to cause central positional vertigo. Small lesions in this region may be missed if thin MRI slices are not obtained when imaging the posterior fossa (CASE 7-1).

Stroke and Transient Ischemic Attack

Strokes and transient ischemic attacks (TIAs) are known causes of central vertigo, dizziness, and imbalance when the posterior circulation is affected. A cerebellar ischemic stroke in the posterior inferior cerebellar artery (PICA) territory, the anterior inferior cerebellar artery (AICA) territory, or the superior cerebellar artery territory may be associated with vertigo or nystagmus, or both. Vertigo and nystagmus more commonly occur when the area of infarction affects the cerebellar peduncles, flocculus, nodulus, vermis, and paravermian regions and are less common with small lesions that are far lateral in the cerebellar hemisphere. Vertigo may also manifest from a brainstem infarction, which can affect the lateral medulla, medial medulla, pons, or midbrain.

Vertigo with unilateral hearing loss can be caused by a labyrinthine infarction. The labyrinth is supplied by the internal auditory artery, usually a branch of the AICA. This can be missed on brain imaging,[14,15] so clinical suspicion is imperative. In fact, AICA territory infarct can present with both peripheral and central findings. Involvement of the root entry zone of the facial nerve or the labyrinth could lead to peripheral findings such as facial paresis, hearing loss, and vertigo. At the same time, expansion of stroke can lead to involvement of the pons or cerebellum, or both, which can cause central vertigo and ataxia. Recent literature points out that audiovestibular loss in isolation can be an impending sign of AICA territory infarction, with initial symptoms of only vertigo and hearing loss occurring days or weeks before the presentation of a posterior fossa stroke.[16] Most patients with this presentation seem to have evidence of reduced basilar artery flow near the AICA origin. This type of infarct should be considered in patients with vascular risk factors who experience audiovestibular loss even if MRI is unrevealing (CASE 7-2).

Chronic vertigo due to the late effects of stroke is not an uncommon symptom; it is often a residual symptom that can persist long after the infarct occurs. It may be caused by central or peripheral damage or a combination of the two, as discussed above. Initial management usually is a short course of a vestibular suppressant followed by physical therapy. Central lesions may not respond as quickly or as successfully to therapy as peripheral insults; however, therapy can be helpful in improving balance overall after a stroke. Visually induced vertigo is common in these patients, and they report symptoms that are exacerbated or triggered by complex visual surroundings. Therapy programs with visual-vestibular stimulation during therapy can result in greater improvements in such patients.[17]

Tumors and Other Structural Lesions in the Central Nervous System

Neoplasms and vascular lesions can cause central vertigo and other neurologic symptoms based on their location in the CNS, including vestibular schwannoma, cavernous malformation, hemangioblastoma, and medulloblastoma.

KEY POINTS

- 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.

CASE 7-1

A 36-year-old woman with multiple sclerosis presented to the emergency department with vertigo that had started that morning when she rolled over in bed to her right side to get up. She had nausea and had vomited once because of the vertigo. She denied headache, vision loss, or diplopia and had not noticed any change in hearing.

On examination, she had full extraocular movements without spontaneous or gaze-evoked nystagmus. She had a right afferent pupillary defect that had been documented on examination during a prior emergency department visit and had no skew deviation. The head impulse test was normal to the right and left sides. She had normal coordination and gait. A Dix-Hallpike test to the right was performed; she had prominent upbeating and torsional nystagmus in a counterclockwise direction after a latency of 10 seconds and felt extremely nauseated during testing. A canalith repositioning procedure was then performed, and she felt better and was discharged.

The next morning, she returned to the emergency department after experiencing vertigo with vomiting. Although her vertigo had improved after the canalith repositioning procedure was done, it had not gone away entirely and she continued to experience a spinning sensation every time she got out of bed or stood up after bending over. Neurologic examination was repeated, and her extraocular movements were intact. A Dix-Hallpike test to the right side was normal this time, and no nystagmus was observed. A Dix-Hallpike test to the left side was then performed and revealed downbeat nystagmus with immediate onset that did not fatigue. An MRI with thin slices in the posterior fossa revealed an enhancing lesion in the right middle cerebellar peduncle adjacent to the cerebellar nodulus (FIGURE 7-2) as well as scattered nonenhancing hemispheric white matter abnormalities. The patient was treated with steroids and vestibular suppressants for 3 days, and her symptoms and positional nystagmus completely resolved.

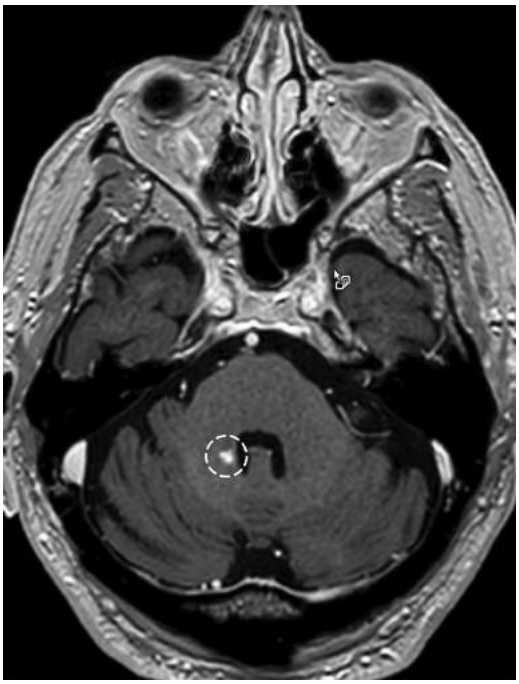

FIGURE 7-2

Axial postcontrast T1-weighted MRI shows an acute demyelinating lesion (*circle*) in the right middle cerebellar peduncle adjacent to the cerebellar nodulus.

COMMENT

This patient had multiple sclerosis, which may lead neurologists to attribute new neurologic symptoms to her known disease. However, the most common cause of positional vertigo is still benign paroxysmal positional vertigo (BPPV); therefore, the Dix-Hallpike test was an essential part of her examination. BPPV was localized to the right posterior semicircular canal based on her initial examination findings. Successful treatment of BPPV is with a canalith repositioning procedure, not medications. A canalith repositioning procedure should be performed immediately after confirming the diagnosis. Although this patient improved somewhat after the canalith repositioning procedure, her symptoms had not completely resolved; thus, another cause of her vertigo was explored. This case reminds us that even if positional vertigo is found and treated on one side, the other side must also be examined as symptoms and examination findings can sometimes be bilateral. This patient had two different types of vertigo: BPPV in the right ear and central positional vertigo as evidenced by the downbeat nystagmus during positional testing on the left. It is also imperative to remember that not all positional vertigo or positional nystagmus equates to a diagnosis of BPPV. Multiple sclerosis can cause central positional vertigo with only positional nystagmus, and the treatment is different from that of BPPV.

Vestibular schwannoma, also known as acoustic neuroma, is a tumor that arises from the Schwann cells around cranial nerve VIII. Although the tumor forms from the vestibular portion of the nerve, it most commonly presents with hearing loss as it can compress the cochlear division of the nerve. Vertigo is an infrequent presentation of vestibular schwannoma, estimated to be seen initially in less than 15% of patients. Slowly progressive unilateral hearing loss and tinnitus are more common initial symptoms, although in a small percentage of patients hearing loss may occur suddenly. When patients present with dizziness, they may describe spinning vertigo, lightheadedness, or gait imbalance. As vestibular schwannomas enlarge, they may lead to peripheral vestibular loss that contributes to the feeling of loss of balance. However, these tumors can also grow to compress the brainstem and thereby cause central vertigo.

An audiogram showing significantly asymmetric hearing loss may lead to suspicion of vestibular schwannoma. Asymmetry of 15 dB at 3 kHz on audiometry is associated with increased positive yield of finding an abnormality on MRI that explains the patient's hearing loss.[18] If a vestibular schwannoma is suspected, an MRI of the brain with and without gadolinium can be used to evaluate for an enhancing lesion in the internal auditory canal or cerebellopontine angle (FIGURE 7-3). A cerebellopontine angle meningioma can present similarly in many respects. Observation and sequential imaging, radiosurgery, and microsurgery are all management options for vestibular schwannoma. Decisions for treatment are often based on the patient's age and

CASE 7-2

A 72-year-old man with a history of hypertension and hyperlipidemia presented to his primary care physician for his annual physical examination. While there, he mentioned that just a few days earlier he had experienced sudden vertigo and hearing loss in his left ear. He was still feeling a bit dizzy, but his hearing seemed to have improved somewhat. His doctor observed some mild horizontal end-gaze nystagmus to the right. No other abnormalities were found on examination, and the patient reported that he otherwise felt well. His examination suggested a peripheral vestibulopathy, and he was counseled that his symptoms should continue to improve.

The following week, the vertigo returned and he was unsteady walking. He presented to the emergency department and was notably ataxic on examination, had left arm dysmetria, and now had bilateral end-gaze horizontal direction-changing nystagmus. Imaging revealed an anterior inferior cerebellar artery (AICA) territory infarction, and vessel studies showed a narrow basilar artery near the origin of the AICA on the left side.

COMMENT

Vertigo and fluctuating hearing loss can be a harbinger of impending AICA territory infarct. AICA territory infarcts can present with both peripheral and central findings simultaneously. In this case, the initial findings appeared peripheral in nature because of likely labyrinth involvement. However, in a patient with vascular risk factors, stroke should be suspected as an etiology early before a complete territory infarction ensues.

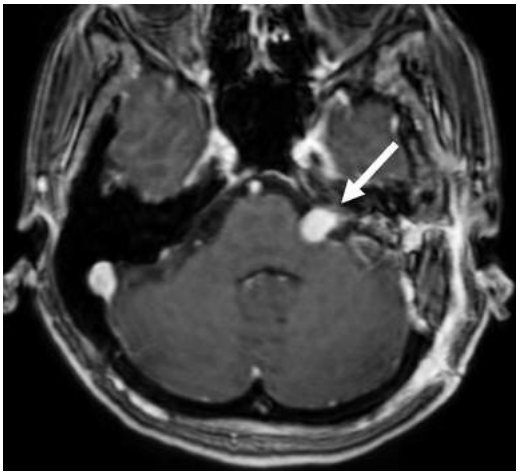

FIGURE 7-3
Vestibular schwannoma. Axial postcontrast T1-weighted MRI shows an enhancing left cerebellopontine angle extraaxial mass (*arrow*), consistent with vestibular schwannoma.

surgical risk factors, quality-of-life considerations, the size of the tumor and its rate of growth, the status of vestibular and hearing function, and the desire or need to preserve hearing function.

Cavernous malformations are either sporadic or inherited vascular malformations. When sporadic, they are usually single lesions that may be associated with a developmental venous anomaly. Cavernous malformations are made up of dilated capillaries with thin walls and are often surrounded by hemosiderin from recurrent hemorrhage. They are described on MRI as having a popcorn ball appearance (FIGURE 7-4). About one-fourth of cavernous malformations are found in the posterior fossa, usually in the pons or the cerebellum; these tend to have higher annual bleeding rates than supratentorial cavernous malformations. Vertigo can be a presenting symptom of a cavernous malformation, especially if active hemorrhage is present. Nausea, vomiting, and diplopia can also accompany the acute vertigo in these cases. Cavernous malformations may be managed with observation if lesions are asymptomatic. Brainstem lesions are often initially managed

KEY POINTS

- 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.

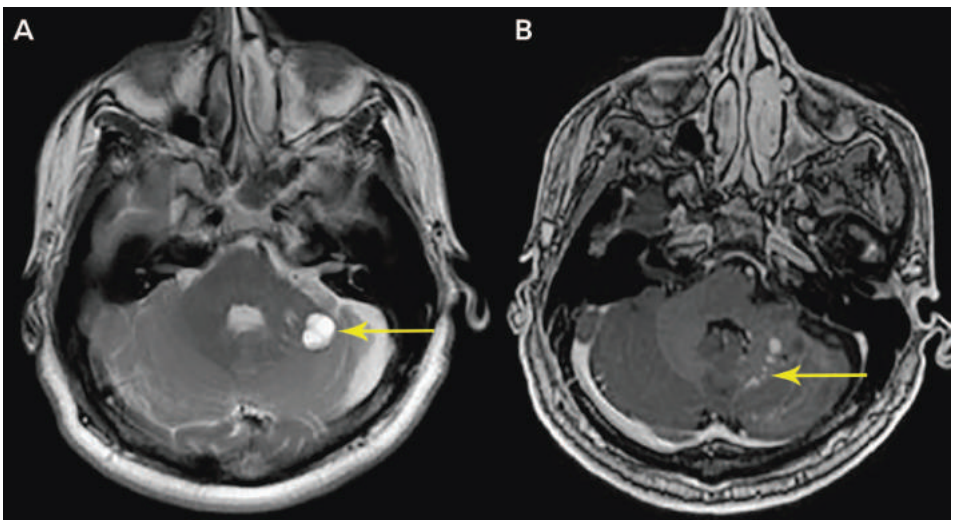

FIGURE 7-4
Cavernous malformation. Axial T2-weighted (*A*) and postcontrast T1-weighted (*B*) images of a left cerebellar cavernous malformation. A T2-hyperintense cystic component and T2-hypointense rim of hemosiderin surround the lesion (*A*, *arrow*). An adjacent developmental venous anomaly, a common association, is seen on the postcontrast image (*B*, *arrow*).

conservatively, but repeat hemorrhage may prompt surgical resection. A systematic review of patients with brainstem cavernous malformations who underwent surgical resection showed that 58% of patients had eventual neurologic improvement, 26% remained stable, and 12% worsened. Mortality was 2%.[19]

Hemangioblastomas are tumors that grow slowly in the spinal cord, cerebellum, or brainstem. They can be sporadic but are often seen in patients with von Hippel-Lindau disease, along with various other tumors. Because of the strong association with von Hippel-Lindau disease, finding a CNS hemangioblastoma often prompts genetic evaluation for the disease in patients who have not yet been diagnosed.[20] Hemangioblastoma can cause vertigo and ataxia because of compression of structures in the brainstem or cerebellum or because of hemorrhage in those areas. In the cerebellum, where they usually present, hemangioblastomas often appear as enhancing nodules within a cyst. Rarely, hemangioblastomas can occur in the cerebellopontine angle and may be misdiagnosed as vestibular schwannoma since the symptoms and MRI findings can be similar.[20] Hemangioblastomas are very vascular and may require embolization of feeding arteries before surgical resection.

Medulloblastoma is the most common malignant brain tumor diagnosed in children. It presents with headache, nausea, and vomiting, often because of fourth ventricle involvement causing increased intracranial pressure. In addition, patients may have dizziness or vertigo due to brainstem compression and cerebellar involvement. Midline cerebellar lesions may cause more gait or truncal ataxia than lateral cerebellar tumors, which can cause more limb dysmetria. Medulloblastoma is usually seen on MRI in the cerebellum, with some areas of enhancement and possible obstruction of the fourth ventricle. Central patterns of nystagmus can be seen in primary gaze or with end gaze on examination; however, medulloblastoma is also known to cause central positional vertigo only. Therefore, BPPV is sometimes suspected but should be considered unlikely when patients are young and the symptoms do not improve with repositioning maneuvers or when the nystagmus is sustained.[21]

Meningitis and Encephalitis

Acute bacterial meningitis may cause bilateral hearing and vestibular loss, especially in children. The most common organisms known to cause this include *Streptococcus pneumoniae*, *Neisseria meningitidis,* and *Haemophilus influenzae* type b. Cases attributed to *H. influenzae* type b have decreased since a vaccine was introduced. The causative lesion may be in the inner ear end organs, the vestibulocochlear nerve, brainstem, or auditory and vestibular pathways. Infection may spread to the inner ear from the subarachnoid space via the cochlear aqueduct or the cochlear modiolus.[22]

Dizziness and bilateral vestibulopathy may sometimes occur with chronic meningitis. Inflammation within the central audiovestibular pathways and cranial nerve nuclei may be responsible for these symptoms. The list of specific causes of chronic infectious meningitis is long and includes tuberculosis, fungal infections such as coccidioidomycosis and cryptococcosis, and Lyme disease.

Occasionally, certain types of localized brainstem encephalitis may cause dizziness. The term *rhombencephalitis* refers to inflammation affecting the brainstem or cerebellum, or both; it may be associated with dizziness,

unsteadiness, nausea, diplopia, headache, and altered awareness. *Listeria monocytogenes* is the most common infectious cause of rhombencephalitis.[23]

Sarcoidosis, a noninfectious disorder of unknown etiology, is a granulomatous process that can affect multiple body systems. Less commonly, it can affect the nervous system exclusively, presenting as neurosarcoidosis. Sarcoidosis has a predilection for the basal meninges and can affect the vestibulocochlear nerve exit or, rarely, can manifest with granulomas in the cerebellopontine angle. Combined evidence from retrospective review has shown that audiovestibular manifestations of sarcoidosis are primarily caused by cranial nerve VIII neuropathy.[24]

Carcinomatous or lymphomatous meningitis may also cause multiple evolving cranial neuropathies and brainstem symptoms. This involves seeding of malignant cells to the leptomeninges. It can be seen in solid cancers, such as breast or lung, and with hematologic malignancies. Primary brain tumors can also spread to the meninges. Headache, cranial neuropathies, nausea, and dizziness are common at presentation. Imaging reveals diffuse leptomeningeal enhancement, often in the cerebellar folia and ventral surface of the brainstem, when patients have dizziness or unsteadiness.

Chiari Malformation

Chiari malformations can be classified as types I through IV based on the anatomic structures involved in the malformation. Chiari malformation type I, the most common type, is a congenital lesion that may not manifest with symptoms until adulthood. In Chiari malformation type I, the cerebellar tonsils extend below the foramen magnum. Diagnosis is radiographic, and most sources agree that it is defined as tonsillar herniation of greater than or equal to 5 mm below the foramen magnum (FIGURE 7-5). Of note, the degree of herniation does not necessarily correlate with the extent of symptoms experienced by patients. Chiari malformation type I can be asymptomatic but when symptomatic often presents with some combination of posterior headache, neck pain, weakness, dysphagia, or vertigo and gait imbalance.

The vertigo in patients with Chiari malformations is usually induced by position change such as neck extension. This may be caused by pressure being applied to the brainstem or cerebellum or their blood supply.[25] Vertigo is usually episodic and brief, often relieved by changing position. Nausea and vomiting may also accompany the vertigo.

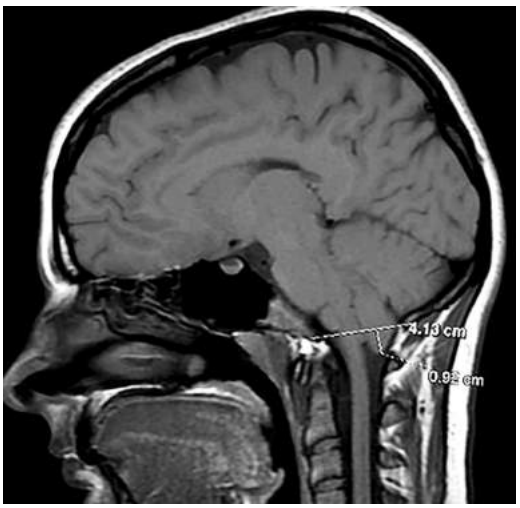

FIGURE 7-5
Sagittal T1-weighted MRI of a patient with Chiari malformation type I. Cerebellar tonsillar herniation of 9 mm through the foramen magnum is noted. This is measured by first drawing a line from the opisthion to the basion (which forms a line across the foramen magnum) and then measuring the distance from that line to the most inferior margin of the cerebellar tonsils.

KEY POINTS

- 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.

Although several patterns of nystagmus have been reported, most commonly a downbeat nystagmus is observed when examining a patient in primary gaze, especially when the patient is supine with the head slightly tilted back. Downbeat nystagmus localizes to the cervicomedullary junction. Vertigo can improve in some patients who are candidates for surgical decompression to treat Chiari malformation type I; however, if nystagmus was present before surgery, it may not entirely resolve following decompression surgery. Since surgical decompression is a major surgery, attempts to exclude significant contributing migraine or greater occipital neuralgia alone or in combination should be made before surgical decompression.

Superficial Siderosis

Superficial siderosis is an uncommon disorder that can affect various areas in the CNS, including the brainstem, spinal cord, cerebellum, supratentorial brain, nerve roots, and cranial nerves. It frequently leads to progressive symptoms of vertigo, ataxia, and hearing loss. The two types of superficial siderosis are cortical superficial siderosis and infratentorial superficial siderosis. Cortical superficial siderosis affects the supratentorial brain and can be seen in cerebral amyloid angiopathy.[26] Infratentorial superficial siderosis more commonly affects the vestibular end organs, cranial nerve VIII, the brainstem, the cerebellum, and the spinal cord.

Patients with superficial siderosis develop neuronal damage over time from hemosiderin deposition on the leptomeningeal surfaces of the nervous system. The hemosiderin is a product of blood breakdown and deposits in areas adjacent to the CSF.[27] Superficial siderosis develops from small amounts of bleeding in the brain or spinal cord and may be caused by repeat episodes of bleeding or a onetime event of bleeding, such as a traumatic or aneurysmal subarachnoid hemorrhage. If the bleeds are chronic and recurrent, the source is usually from disruption of dural integrity caused by various etiologies, such as a

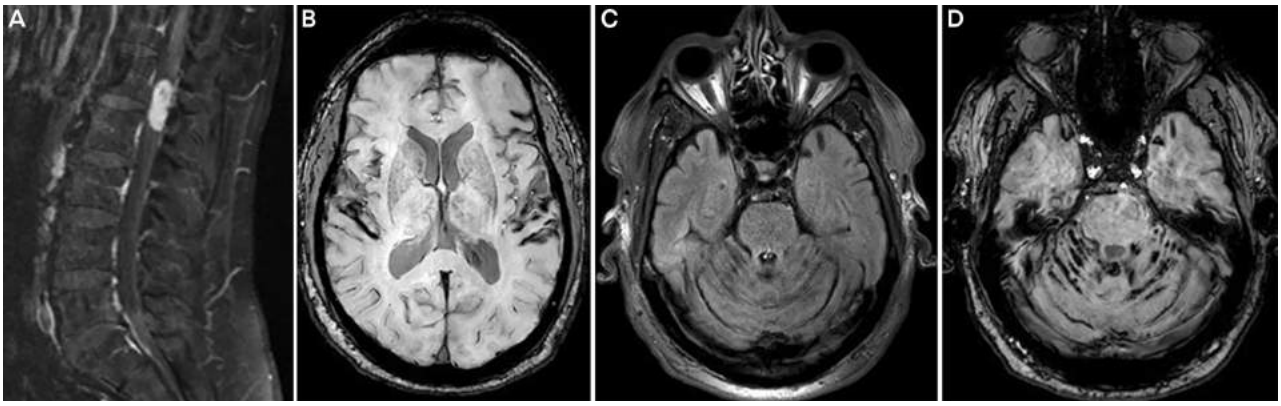

FIGURE 7-6

Myxopapillary ependymoma causing superficial siderosis. *A*, Sagittal postcontrast T1-weighted MRI shows an intradural mass at L1-L2 that was confirmed to be a myxopapillary ependymoma. This is a well-defined intradural tumor that enhances homogenously. *B*, Axial susceptibility-weighted imaging (SWI) shows superficial siderosis supratentorially, with pial surfaces coated with low signal hemosiderin. *C*, Axial fluid-attenuated inversion recovery (FLAIR) MRI shows some mild cerebellar atrophy. *D*, Axial SWI shows a significant degree of superficial siderosis infratentorially from prior hemorrhage related to the myxopapillary ependymoma.

meningocele, pseudomeningocele, nerve root avulsion, or tumor.[28] Myxopapillary ependymoma is the most common tumor seen to cause infratentorial superficial siderosis.

Symptoms of superficial siderosis can vary, but the most commonly seen is hearing loss that is progressive and leads to deafness. Cerebellar ataxia is also common and progressive, often with associated gaze-evoked nystagmus and saccadic dysmetria. Gait imbalance can result from a combination of cerebellar damage and vestibulopathy since damage to the vestibular end organs and nerve is possible. Less common symptoms and signs of superficial siderosis include myelopathy, cognitive deficits, and seizures. Rarely, patients may report anosmia, which is caused by damage to cranial nerve I,[27] the second most frequently affected cranial nerve in superficial siderosis.

The hearing loss seen in superficial siderosis usually affects high frequencies early on. It can be asymmetric at first but will progress and cause profound damage bilaterally with time. It is typically more severe than what would be expected for hearing loss due to presbycusis (hearing loss associated with aging).[29] Hearing aids can be used in earlier stages, and cochlear implantation has been shown to have some benefit based on systematic review of available studies.[30]

When vestibular damage is present, patients may report dizziness or vertigo and exhibit gait instability. Since some gait instability in superficial siderosis is usually because of cerebellar damage, the vestibular system is often forgotten as a potential site of damage. However, cranial nerve VIII has a long course from the end organs through the internal auditory canal, making it vulnerable to damage.[28] Damage to cranial nerve VIII can be assessed using various vestibular tests, such as videonystagmography, rotary chair testing, vestibular evoked myogenic potentials, and video head impulse testing. Overall, most patients with superficial siderosis appear to have both peripheral and central vestibulopathy.[31]

Before imaging was available, the diagnosis of superficial siderosis was made postmortem. Today, however, the diagnosis is made by MRI. Hemosiderin is seen easily on MRI sequences, including gradient recalled echo (GRE), T2-weighted, and susceptibility-weighted imaging (SWI). Superficial siderosis appears as rims of hypointensity (FIGURE 7-6). Although imaging remains the gold standard for diagnosis of superficial siderosis, it does not help in determining whether a patient is symptomatic from the superficial siderosis seen on the scans. A study of patients with superficial siderosis confirmed with MRI showed that only 15% of them actually exhibited symptoms of superficial siderosis.[32]

Treatment of superficial siderosis can be symptomatic depending on the particular symptoms of the individual patient. However, it also must focus on identifying any underlying structural lesion that may be the etiology of the patient's superficial siderosis. Imaging of various types can be used. The entire neuraxis should be evaluated,[33] as spinal lesions can be the culprit when no obvious source is seen in the brain. The highest rate of success in finding an underlying etiology of superficial siderosis has been when either spinal MRI or CT myelography was used.[28] Surgical treatment may commence when a source of chronic persistent CSF leakage of blood is identified, if amenable to intervention. This may or may not result in improvement of patient symptoms; however, it can halt progression of symptoms for some. Iron chelators have been studied as potential treatments in superficial siderosis. A long-term open-label observational study suggested that the iron chelator deferiprone can be used safely in patients with superficial siderosis and is well tolerated. All patients had a

KEY POINTS

- **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.**

reduction in iron seen in the brain on MRI after treatment with deferiprone, and half the patients had clinical improvement in symptoms in a study of four patients without controls.[34] It should also be noted that deferiprone has a US Food and Drug Administration (FDA) boxed warning for the possibility of agranulocytosis/neutropenia, thus patients must be monitored while taking it. Larger randomized trials are needed to determine whether iron chelators are an effective treatment for superficial siderosis.

Neurodegenerative Disease

Vertigo and dizziness are commonly seen in patients with Parkinson disease, multiple system atrophy, progressive supranuclear palsy, and cerebellar ataxia.[35]

Cerebellar ataxia has numerous potential etiologies, such as genetic disease, vitamin deficiencies, paraneoplastic disease, environmental/toxin exposures, and as a result of adverse effects of medications. Although the possible causes are myriad, the manifestations can be similar. Vertigo is often paroxysmal, and bedside examination usually reveals central nystagmus. Typical patterns include spontaneous downbeat nystagmus and direction-changing horizontal end-gaze nystagmus. Downbeat nystagmus results from degeneration of the cerebellum, leading to floccular hypofunction.[36] Prism glasses and medications can be trialed to help alleviate symptoms. Some evidence supports the use of aminopyridines for downbeat nystagmus and gait ataxia in these patients.[37] Currently, no medications are approved by the FDA for the treatment of cerebellar ataxia.

In Parkinson disease and the atypical conditions that cause parkinsonism, such as multiple system atrophy, central orthostatic hypotension may be a cause of presyncopal dizziness. This is because of involvement of the central autonomic network that helps to regulate visceromotor, neuroendocrine, and pain responses (**FIGURE 7-7**). The central autonomic network is made up of multiple brain regions, including the amygdala, hypothalamus, nucleus of the tractus solitarius, and ventrolateral medulla.[38] Specific groups of neurons in the medulla have been found to be affected in patients with Parkinson disease and, to a greater extent, patients with multiple system atrophy, leading to impaired sympathetic vasomotor outflow and impaired release of vasopressin.[39] The damage to these neurons is proposed to explain the orthostatic hypotension and autonomic reflex impairment that affect patients. Beyond nonpharmacologic treatments, medications such as the α-adrenergic agonist midodrine and droxidopa, a norepinephrine precursor, are FDA approved for the treatment of symptomatic neurogenic orthostatic hypotension.

Episodic Ataxias

Seven autosomal dominant episodic ataxias have been identified, aptly named episodic ataxia type 1 through episodic ataxia type 7. Of these types, most cases encountered are usually episodic ataxia type 1 or episodic ataxia type 2. In patients with episodic ataxia type 2, vertigo is severe and episodic, often accompanied by nausea and vomiting as well as unsteadiness. Patients with episodic ataxia type 2 usually start having episodes during adolescence, and each episode can last hours. Stress is a common trigger, as are heat, exertion, alcohol, and caffeine.[40] Genetic testing usually reveals mutations in the *CACNA1A* gene, specifically in the P/Q-type calcium channel α1A subunit. Episodic ataxia type 2 is felt to be caused by a loss of P/Q-type calcium channel function in the

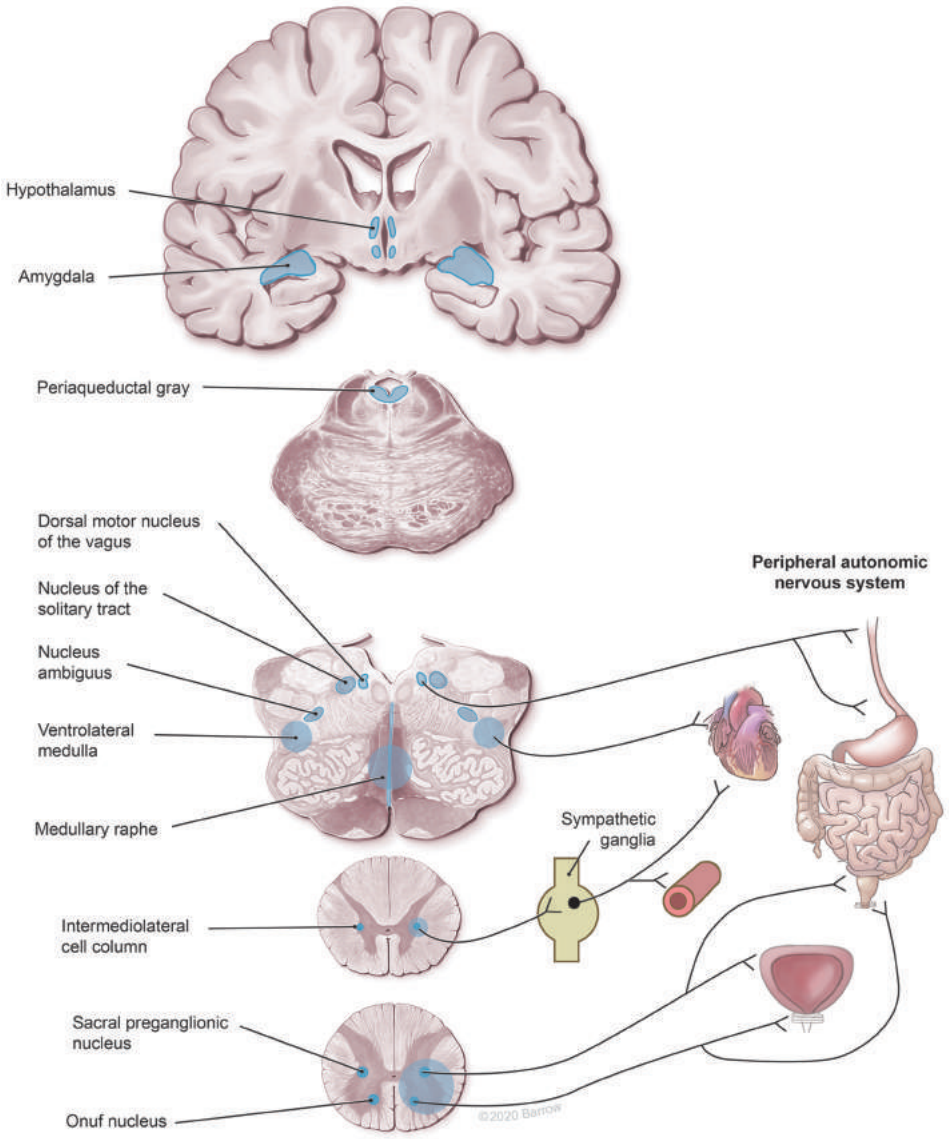

FIGURE 7-7

The central autonomic network with its multiple involved brain regions and connection to the peripheral autonomic nervous system.

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cerebellum, in both Purkinje cells and granule layer neurons.[41] Neurologic examination can be helpful, as these patients often have central pattern nystagmus not only during their episodes but even between episodes (CASE 7-3). Cerebellar damage accrues over time.

Several medications may be used to treat episodes of vertigo in patients with episodic ataxia type 2. Both acetazolamide and 4-aminopyridine have demonstrated efficacy. A randomized controlled trial in patients with episodic ataxia showed 4-aminopyridine 5 mg 3 times a day to be effective in reducing episodes, possibly by increasing excitability of Purkinje cells and increasing levels of γ-aminobutyric acid (GABA).[42,43] One recently published trial, the

KEY POINTS

- **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.**

CASE 7-3

A 23-year-old man presented for neurologic consultation because of episodic vertigo. He had started having the episodes of vertigo around age 18. Episodes were monthly on average, lasting 3 to 4 hours each time. He was a college athlete and noticed that episodes often occurred after tough workouts with his team. He always had nausea with episodes and sometimes vomited; his vision would blur, and he would have to sit down because he was so unsteady. No one else in his family experienced similar episodes. Neurologic examination showed normal coordination and gait; however, he was noted to have downbeat nystagmus in primary gaze.

MRI of his brain was normal. Videonystagmography was ordered, and the tracing confirmed downbeat nystagmus in primary gaze (FIGURE 7-8). Genetic testing using sequence analysis was ordered and revealed a heterozygous pathogenic variant in *CACNA1A*. He was started on acetazolamide 250 mg once daily and titrated to 250 mg 2 times a day, which resulted in complete cessation of his episodic vertigo.

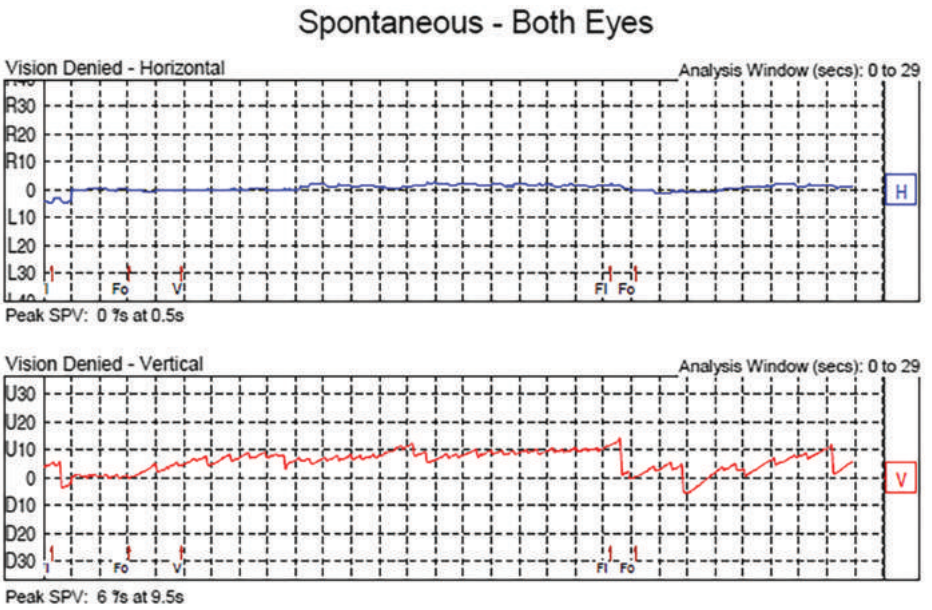

FIGURE 7-8
Videonystagmography of the patient in CASE 7-3 showing downbeat nystagmus in primary gaze. This was also present in supine, head-hanging right, and head-hanging left positions.

COMMENT

Episodic ataxia type 2 is confirmed with genetic testing. In this patient without a family history, the disease may have been caused by a de novo pathogenic variant. Whereas downbeat nystagmus is common during episodes, it is often observed in patients even between episodes. Most patients find benefit with relatively low doses of acetazolamide, as did this patient.

EAT2TREAT (Fampridine and Acetazolamide for the Treatment of Episodic Ataxia Type 2) study, found that both acetazolamide as well as 4-aminopyridine significantly reduced the number of attacks in patients with episodic ataxia type 2 compared to placebo.[44]

It is worth noting that overlap exists between other neurologic disorders and episodic ataxia type 2. For example, other *CACNA1A* gene mutations in the same subunit are seen in patients with spinocerebellar ataxia type 6 and in patients with familial hemiplegic migraine type 1. Cerebellar atrophy can be seen in all of these conditions. Some patients with spinocerebellar ataxia (particularly spinocerebellar ataxia type 6) may experience episodic vertigo similar to patients with episodic ataxia type 2; however, they do not find benefit with the medications discussed above.

Autoimmune Vestibulocerebellar Disorders

The literature on autoimmune vestibulocerebellar disorders is actively expanding as more is learned about the autoantibodies that are biomarkers for these disorders. Typically, the antibodies target antigens in the vestibulocerebellar pathways, vestibular nuclei, or vestibular end organs. This results in autoimmune syndromes characterized by symptoms such as dizziness and ataxia that can progress rather quickly. Clinicians must be proficient not only in diagnosis but also in initiating treatment in hopes of halting this progression.

The presentation of patients with these disorders is subacute, meaning that patients usually have an onset of cerebellar symptoms over weeks to months. Symptoms may begin first with a prodrome of nausea and vomiting.[45] Truncal and appendicular ataxia begin after this, along with vertigo, dysarthria, diplopia, and dysphagia.[46] Extraocular movements are abnormal and may include any the following: positional vertical nystagmus (upbeat or downbeat), spontaneous downbeat nystagmus, spontaneous or gaze-evoked horizontal nystagmus, opsoclonus, periodic alternating nystagmus, or internuclear ophthalmoplegia.[47]

The diagnostic workup centers on testing for specific autoantibodies after a clinical syndrome is suspected. In general, antibody testing should be done on both serum and CSF samples. Diagnostic certainty results from the combination of a characteristic clinical syndrome and positive result of the accompanying antibody in either serum or CSF, or both. CSF is often abnormal and a mild pleocytosis may be seen.[46] Mildly elevated protein and IgG index are also sometimes seen. In some instances, antibody testing may be negative and repeat testing may be considered. Diagnosis is still sometimes made despite negative antibody testing if the clinical syndrome is characteristic and patients have supportive findings from CSF studies and a positive response to immunotherapy. It is possible that numerous additional autoantibodies remain to be discovered, and not all known antibodies are included in every commercial panel. Neurologists should carefully ensure that the panel they order includes the antibody or antibodies they suspect in a particular syndrome. Brain imaging, such as MRI, is often normal but can show cerebellar atrophy in some patients. It is still usually a part of the workup, especially to exclude other potential causes.

These antibodies are often classified as either intraneuronal/cytoplasmic or cell surface antibodies. Intraneuronal/cytoplasmic antibodies are usually seen in paraneoplastic syndromes, and the underlying process is thought to be cytotoxic T-cell–mediated neuronal disruption.[48] The antibodies seen include anti-Yo

KEY POINTS

- **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.**

CASE 7-4

A 62-year-old woman initially presented to the emergency department with a flulike illness, with nausea and vomiting for several days. She was afebrile, and basic laboratory tests suggested dehydration. She was given IV fluids and discharged in stable condition.

She continued to feel unwell over the next 3 months. She reported being unsteady on her feet and was seeing double, so her family brought her back to the emergency department. She denied a history of alcohol overuse. The emergency department physician consulted neurology, and the neurologist examining her saw that she had horizontal gaze-evoked nystagmus. She was noted to be ataxic when walking. Her brain MRI showed mild and diffuse cerebellar atrophy (FIGURE 7-9). Laboratory studies, including thyroid-stimulating hormone (TSH); vitamins B_1, B_{12}, and E; and a celiac panel, were normal. CSF studies were similarly benign, with normal cell count, protein, and glucose and negative Gram stain and culture. Serum and CSF paraneoplastic and autoimmune antibodies were ordered.

She was admitted to the hospital, where CT of the chest/abdomen/pelvis was obtained and revealed an ovarian mass that was confirmed with follow-up MRI. She underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy and was then given an empiric trial of IV immunoglobulin (IVIg) over 5 days. Her gait improved modestly, but the nystagmus, although less prominent, still persisted at the time of discharge to rehabilitation. Follow-up on antibody panels after discharge showed a positive anti-Yo titer in CSF, but it was negative in serum.

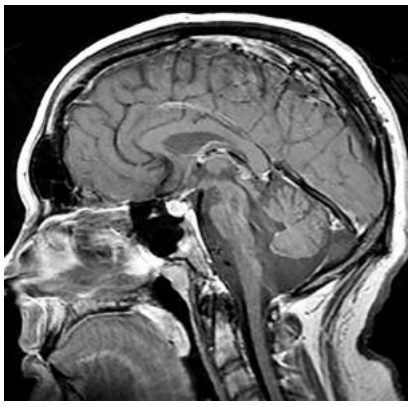

FIGURE 7-9
Imaging of the patient in CASE 7-4. Sagittal postcontrast T1-weighted MRI shows mild and diffuse cerebellar atrophy.

COMMENT

This case illustrates a typical time course for an autoimmune vestibulocerebellar disorder, as it began with a prodrome and was followed by a subacute worsening of symptoms before diagnosis. This case highlights the necessity to sometimes begin treatment before obtaining all test results, as it can take time before antibody panel test results are available.

(Purkinje cell cytoplasmic antibody 1 [PCA-1]), anti-Hu antibody (antineuronal nuclear antibody type 1 [ANNA-1]), anti-Ri antibody (antineuronal nuclear antibody type 2 [ANNA-2]), Ma1 and Ma2 antibodies, amphiphysin antibody, CV2 antibody (collapsin response mediator protein-5 [CRMP5]), and glutamic acid decarboxylase 65 (GAD65) antibody. Several additional antibodies have been described in smaller numbers of patients thus far.[47] In general, these antibodies are part of paraneoplastic syndromes, and thus a search for an underlying malignancy followed by any treatment indicated is imperative. The most common antibody causing paraneoplastic cerebellar degeneration is the anti-Yo antibody, usually associated with gynecologic and breast malignancies in women older than age 60.[49] Overall prognosis has generally been poor for paraneoplastic syndromes, but a trial of immunotherapy is still usually warranted (CASE 7-4).

The antibodies against extracellular cell surface/synaptic antigens are often nonparaneoplastic and may cause autoimmune vestibulocerebellar syndromes. Antibodies include contactin-associated proteinlike 2 (CASPR2) antibody, voltage-gated calcium channel antibodies (both P/Q type and N type), anti-Tr (delta/notchlike epidermal growth factor-related [DNER]) antibody, and metabotropic glutamate receptor 1 (mGLuR1) antibody. These antibodies exert direct effects after binding, and functional modifications of ion channels and neurotransmitter receptors lead to impairments in vestibulocerebellar pathways.[47] They are overall less likely to be associated with malignancies and generally respond more positively to immunotherapy, leading to better long-term prognoses.

Immunotherapy is the first treatment for an autoimmune vestibulocerebellar syndrome, either at the time of diagnosis or when the diagnosis is strongly suspected based on clinical observations and data. Corticosteroids, plasma exchange, and IV immunoglobulin (IVIg) are all potential treatment options. If these treatments fail, the second line of treatment usually consists of either rituximab or cyclophosphamide.[47] A maintenance form of immunotherapy is chosen depending on factors such as how the patients respond to initial treatment, how their disease progresses, and their antibody type. A variety of options for maintenance treatment exist, including rituximab, cyclophosphamide, azathioprine, methotrexate, and IVIg. The specific course of treatment, including dosing and duration of treatment, must be tailored to the individual patient. Additionally, if an underlying tumor is found, tumor therapy must commence as quickly as possible and can often be done in parallel to immunotherapy. A team of specialists that includes an oncologist is usually necessary.

KEY POINT

- **Identifying the specific antibody causing an autoimmune vestibulocerebellar disorder can help prognosticate and determine the likelihood of a malignancy eventually being found.**

CONCLUSION

Vertigo and dizziness can be challenging symptoms to address, in part because a description of these symptoms is often difficult for patients to formulate. Whereas some etiologies are peripheral, others localize to the CNS. The process of determining whether vertigo has a central etiology begins with meticulous history taking followed by a detailed examination with particular attention to eye movements, coordination, gait, and speech. Careful examination skills are paramount in diagnosing central vertigo, as brain imaging has limitations in certain etiologies. A variety of treatments ranging from medications and therapies to even surgical interventions may be employed to treat central vertigo.

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