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Acquired Ocular Motility Disorders and Nystagmus
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Key Points

- Eye movement disorders may be considered in two categories: those that cause incomplete eye movements (ophthalmoparesis) and those that cause excessive eye movements (saccadic intrusions and nystagmus).
- Central to an understanding and correct diagnosis of abnormal eye movements is the evaluation of ocular alignment, ocular motility, and each functional class of eye movements: optokinetic, vestibular, vergence, smooth pursuit, and saccades.
- Ophthalmoparesis is caused by dysfunction of extraocular muscles, the neuromuscular junction, cranial nerves, cranial nerve nuclei, and internuclear and supranuclear connections.
- The initial pathologic eye movement in nystagmus is a slow drift of the eye away from the desired position, whereas the initial pathologic eye movement in saccadic intrusions is an inappropriate saccade that intrudes on fixation.
- Identification of the characteristics of nystagmus (physiologic versus pathologic, jerk versus pendular) is necessary for diagnostic evaluation and treatment.

Introduction

The goal of all normal eye movements is to place and maintain an object of visual interest on each fovea simultaneously to allow visualization of a stable, single object. Any deviation from normal eye movements may degrade vision. The spectrum of ocular motility disorders ranges from absent or inadequate
ocular motor function (ophthalmoplegia or ophthalmoparesis) to excessive ocular motor function (spontaneous eye movements). This chapter is divided into three sections; the first details those aspects of the history and examination required for an accurate diagnosis of abnormal ocular motility, the second concerns acquired disorders of ophthalmoparesis, and the third concerns acquired abnormal spontaneous eye movements.

Clinical Approach and Diagnostic Tools

Ophthalmoparesis results in ocular misalignment; hence an object of visual interest falls on the fovea in one eye and on an extrafoveal location in the other eye, leading to the subjective appreciation of binocular diplopia (Fig. 13–1). When there are abnormal spontaneous eye movements, illusory motion of the visual world (oscillopsia) occurs if the subjective experience of retinal motion is in excess of that normally tolerated by the visual system (up to about 5 degrees per second for Snellen optotypes). An understanding of the nature and pathophysiology of these symptoms allows the correct identification and localization of an ocular motility disorder. Binocular diplopia may result from dysfunction of extraocular muscles, the neuromuscular junction, cranial nerves, cranial nerve nuclei, and internuclear and supranuclear connections. Oscillopsia may result from nystagmus and saccadic intrusions.

When diplopia is present, it is essential to determine if the diplopia resolves with covering each eye in turn (binocular diplopia). If it persists with monocular covering (monocular diplopia), it is not attributable to ocular misalignment but rather to refractive error or other ocular causes. It should be determined if binocular diplopia is horizontal, vertical, or oblique; worse in a particular direction of gaze; and worse at distance or near. Horizontal diplopia is caused by impaired abduction or adduction and vertical diplopia by impaired elevation.

Figure 13–1 Fixation with normal ocular alignment is represented by **solid black lines**. An image of the feather falls on each fovea simultaneously and a single object is seen. Binocular diplopia, which develops with an ocular misalignment (lateral deviation of the right eye as depicted by the **dashed arrow**), occurs because the image of the feather falls on an extrafoveal location in the deviated right eye (**dashed lines**). (Adapted from Leigh RJ, Zee DS: The Neurology of Eye Movements, 3rd ed. Oxford, Oxford University Press, 1999, p 337.)
or depression. Worsening diplopia in a particular gaze direction suggests that motility in that direction is impaired. The temporal course of the diplopia and any associated neurologic symptoms should be assessed; proximal muscle weakness, difficulty swallowing, and shortness of breath, for example, suggest neuromuscular dysfunction, and a deterioration of monocular vision and proptosis suggest an orbital process. These historical features are also important in the evaluation of patients with oscillopsia and spontaneous eye movements.

The neurologic and visual systems should be carefully examined in all patients with diplopia, ophthalmoparesis, oscillopsia, or abnormal spontaneous eye movements. The eye movement examination should include an assessment of ocular alignment and motility, as described in Chapter 1 (Fig. 13–2). In addition, stability of gaze fixation should be assessed with the eyes close to central position, viewing near and far targets, and at eccentric gaze angles. Prolonged observation for up to 2 minutes is necessary, as some types of nystagmus periodically change direction. Observation of the effect of removal of fixation on eye stability is also important, as nystagmus caused by peripheral vestibular dysfunction may only be visible under this circumstance. This can be achieved by transient coverage of the fixating eye during ophthalmoscopy in a dark room.

Each functional class of eye movements should be examined in both horizontal and vertical directions. Optokinetic nystagmus occurs reflexively during self-rotation and can be elicited at the bedside with visual tracking of an optokinetic drum or tape with alternating black-and-white vertical stripes. It consists of slow tracking, smooth pursuit movements alternating with quick resetting saccadic movements. Vestibular eye movements hold an image steady on the fovea by means of compensatory eye movements during brief, nonsustained head movements, such as during walking. These eye movements may be evaluated clinically with passive head thrusts during which the examiner applies a low-amplitude, high-acceleration head rotation while the patient fixates a target. If vestibular function is normal, the patient will maintain fixation of the target during and after the head movement. If vestibular function is impaired, the patient will not be able to maintain fixation and a corrective saccade back to the target is seen following the head rotation. Examiner-applied passive head thrusts are more sensitive than patient-initiated active head thrusts for identifying vestibular dysfunction. Vergence eye movements consist of disconjugate convergent and divergent eye movements that maintain stability of a visual image during near and far gaze shifts. Smooth pursuit is a slow eye movement

![Figure 13–2 Corneal light reflection test. A, Normal ocular alignment—a light shined in the center of one pupil falls in the center of the other pupil. B, Exotropia—a light shined in the center of one pupil falls medial to the pupil center in the other eye. C, Esotropia—a light shined in the center of one pupil falls lateral to the pupil center in the other eye. D, Right hypertropia—a light shined in the center of the pupil in the left eye falls below the pupil center in the right eye.](image-url)
(velocity 20 to 50 degrees/second), which functions to hold the image of a moving target steady on the fovea and which can be assessed by having the patient follow a slowly moving target. Saccades are fast eye movements (velocity 300 to 500 degrees/second) that rapidly shift gaze to place an object of visual interest on the fovea. Saccades present a challenging task to the brain, as their execution requires a sudden, intense neural discharge to effect a high-velocity eye movement and to overcome the elastic, damping orbital pull of extraocular muscles and suspensory ligaments. This intense neural discharge is provided by brainstem neurons called burst neurons.

### Ophthalmoparesis

**EXTRAOCULAR MUSCLES**

Thyroid ophthalmopathy is typically painless and bilateral, although it may be asymmetric. It tends to affect the inferior and medial rectus muscles first, leading to restrictions of elevation and abduction. Although it is useful to obtain thyroid function studies (thyroid-stimulating hormone, triiodothyronine, and thyroxine), it may be associated with hyperthyroid, hypothyroid, or euthyroid states. Thyroid-stimulating antibodies correlate with the presence of thyroid eye disease and can be an important disease marker in the setting of a serologic euthyroid state. Orbital computed tomography (CT) or magnetic resonance imaging (MRI) scans demonstrate enlargement of involved extraocular muscle bodies with relative sparing of muscle tendon insertions at the globe (Fig. 13–3A). Coronal images are best, because muscle enlargement may be underestimated if only axial images are acquired. Treatment options include corticosteroids, radiation, and orbital decompression surgery, as discussed in Chapter 3. Discontinuation of smoking should be strongly advised, as smoking may worsen thyroid ophthalmopathy and lessen treatment effect.

Orbital pseudotumor is typically painful and unilateral. Any extraocular muscle may be involved; orbital CT or MRI scans demonstrate enlargement of

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**Figure 13–3**  
A, Axial T1-weighted magnetic resonance imaging scan with gadolinium showing enlargement of the extraocular muscles from thyroid eye disease. Involvement is asymmetric, with greater muscle enlargement in the left orbit than in the right. Muscle tendon insertions at the globe are relatively spared. B, Contrast-enhanced computed tomography scan showing enlargement of the left medial rectus muscle body and muscle tendon insertion from orbital pseudotumor.
involved extraocular muscle bodies and muscle tendon insertions at the globe (Fig. 13–3B), in contrast to that seen in thyroid ophthalmopathy, in which there is sparing of the tendon insertions (Fig. 13–3A). The posterior sclera and orbital fat may also be radiographically abnormal. Spontaneous resolution is common. Nonsteroidal anti-inflammatory medications and steroids relieve pain, hasten recovery, and decrease the risk of recurrence.16

Infiltration by amyloid or infections and inflammation in sarcoidosis and Wegener’s granulomatosis may also cause this phenotype. Lymphoid malignancies are the most common orbital neoplasms.17 Metastasis of other neoplasms to extraocular muscles is rare. Orbital disease is covered in detail in Chapter 3.

Chronic progressive external ophthalmoplegia (CPEO) causes a slowly progressive, bilateral, symmetric ocular immobility and bilateral ptosis. The pupils are not affected, but the orbicularis oculi typically is. Characteristically the saccadic velocities are reduced throughout the movement, making it more easily differentiated from neuromuscular junction disorders. The extraocular muscles are sometimes seen to be atrophic on orbital imaging. Patients are often asymptomatic because of the slowly progressive, bilateral nature of the disease. Mitochondrial genetic defects are the most common etiology, in which deletions or duplications arise. The phenotype may occur on its own or with cardiac problems and retinitis pigmentosa and other disorders such as Kearns-Sayre syndrome. It may also arise within a myodonic epilepsy with ragged red fibers (MERFF) and a mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS) disorder. A CPEO phenotype may also be seen in oculopharyngeal dystrophy, myotonic dystrophy, congenital myopathies such as myotubular myopathy, and in association with neuropathies such as Refsum’s and Stephen’s syndromes and abetalipoproteinemia.

THE NEUROMUSCULAR JUNCTION

Myasthenia gravis (MG) is the most common disease of the neuromuscular junction. Ocular motility dysfunction in MG can mimic nearly any abnormal eye movement; it may resemble internuclear ophthalmoplegia, cranial nerve or nuclear palsies, but the pupil is only very rarely involved. Features strongly suggestive of neuromuscular junction impairment include moment to moment or visit to visit variability in ocular motility, eyelid or extraocular muscle fatigue with prolonged upgaze, Cogan’s lid twitch, the peek sign, orbicularis oculi weakness, ptosis, and enhanced ptosis.18–20 Upgaze should be maintained for at least 2 minutes to assess adequately the appearance or worsening of ptosis or impaired ability to maintain eye elevation. Cogan’s lid twitch may be seen with saccadic return of the eyes to the central position following a few seconds of sustained downgaze.18 The upper eyelid may elevate excessively, twitch, and become ptotic again. The peek sign is positive when prolonged eye closure allows orbicularis oculi weakness to cause lid separation and globe exposure, despite initial complete eye closure.19 Enhanced ptosis is seen when ptosis in a less or nonptotic eyelid increases on manual elevation of the more ptotic lid.20 This phenomenon is based on Hering’s law of equal neural innervation to both eyelids; when maximal innervation is applied to a severely ptotic lid in an attempt to hold it open, the same maximal innervation may minimize the appearance of ptosis in a contralateral less or nonptotic lid. Manual elevation of the more
ptotic lid decreases the innervation of both lids, allowing the contralateral lid to become more ptotic (Fig. 13–4). Another phenomenon attributable to Hering’s law is that of lid retraction in the eye contralateral to a ptotic lid. Frontalis overactivity resulting from the attempt to hold ptotic lids open is often seen.

A positive edrophonium chloride test (Fig. 13–5) provides diagnostic support for MG. It is most useful when there is a defined deficit such as significant ptosis or a fixed ocular motility defect that may be monitored for improvement. Edrophonium chloride is a reversible acetylcholinesterase inhibitor that decreases breakdown of acetylcholine in the synaptic cleft, thereby improving neuromuscular transmission. Sensitivity and specificity of the edrophonium test in the setting of ocular MG are 60% to 80% and 86%, respectively. Rare potential test risks include cardiac arrhythmias, syncope, respiratory failure, and seizures; however, this risk is approximately 0.16%. In one series a mean dose of only 3.3 mg edrophonium resulted in improvement of ptosis or an ocular motility defect, thereby minimizing test risk. The ice pack test is an alternative to the edrophonium test; an ice pack is lightly placed over a closed ptotic eye for 2 minutes, followed by observation for improvement of ptosis. The premise of this test is that neuromuscular transmission is improved by cold temperatures. Sensitivity is as high as 80% when partial ptosis is present but may be lower with complete ptosis.

Acetylcholine receptor antibodies consist of three types: binding, blocking, and modulating. In generalized MG, binding and modulating antibodies have a prevalence of 89% and blocking antibodies of 52%; in ocular MG it is lower at 50%. Although anti-muscle specific receptor tyrosine kinase (anti-MuSK)

Figure 13–4  Enhanced ptosis. A, At rest, the left eyelid exhibits significant ptosis. B, Manual elevation of the left eyelid results in increased ptosis of the right eyelid.
antibodies are positive in some patients previously considered to have seronegative generalized MG, they are only rarely associated with ocular MG. A 20% or greater decrement of the compound muscle action potential with repetitive suprathreshold stimulation has a sensitivity of only 42% in ocular MG, but the diagnostic yield is increased with single-fiber electromyogram, with up to 100% sensitivity.

Standard treatments for MG include the long-acting acetylcholinesterase inhibitor pyridostigmine, corticosteroids, and steroid-sparing immunosuppressive agents such as azathioprine and mycophenolate mofetil. Pyridostigmine is primarily used for symptom relief, whereas the others provide treatment of the underlying disease process. In ocular MG, pyridostigmine is more effective for ptosis than for diplopia. Corticosteroids are highly effective for both ptosis and diplopia and may successfully render the patient asymptomatic. There is some evidence that they may also diminish the risk of progression of ocular MG to generalized MG.

Botulism results from exposure to an anticholinergic toxin produced by Clostridium botulinum. Exposure is acquired by ingestion of toxin in contaminated food; from wound infections; and, in infants, from gastrointestinal production of toxin. The clinical features are of a subacute ophthalmoparesis with pupillary involvement, particularly paralysis of accommodation, and muscle weakness without sensory loss elsewhere. It is said to be difficult to distinguish from ophthalmoplegia from MG; however, pupillary light-near dissociation and impaired accommodation are common with botulism.

Ocular motility is rarely affected with the Lambert-Eaton myasthenic syndrome, a presynaptic neuromuscular junction disorder caused by voltage-gated calcium channel antibodies. The clinical features are of autonomic disturbances, ptosis, and pupillary light-near dissociation in association with weakness elsewhere. The disorder may be paraneoplastic but can also occur independently.
**CRANIAL NERVE PALSY**

**Third Nerve Palsy (Oculomotor Nerve)**

The oculomotor nerve innervates the medial, inferior, and superior recti muscles; the inferior oblique muscle; the levator palpebrae superioris; the pupillary sphincter muscle; and the ciliary body. Identification of a complete third nerve palsy is typically straightforward on examination, when there is ptosis, an eye that is deviated “down and out,” and a dilated pupil. Elevation, depression, and adduction of the eye are impaired. Identification of a partial third nerve palsy can be more challenging, especially if the pupil is spared.

Although a lesion anywhere along the oculomotor nerve pathway may result in third nerve dysfunction, the two most common causes are compression of the nerve by a posterior communicating artery aneurysm within the subarachnoid space and microvascular ischemia. Lesions of the third nerve fascicle in the brainstem, cavernous sinus, and superior orbital apex are readily localized when nearby structures are also involved. Meningeal infiltration of the cavernous sinus or superior orbital apex by infectious, neoplastic, or autoimmune processes and compression of the third nerve by an internal carotid artery aneurysm within the cavernous sinus are common diagnostic considerations. Hemorrhage into a pituitary adenoma (pituitary apoplexy) may cause sudden onset unilateral or bilateral third nerve dysfunction, often accompanied by vision loss, nausea, or headache. Onset of a third nerve palsy following minor trauma should prompt investigation for an underlying posterior communicating artery aneurysm, although one may not always be found. Third nerve palsies may also arise in raised intracranial pressure, when the nerve is stretched as it passes across the tentorial edge.

Elevation of the eyelid or constriction of the pupil during adduction or depression of the eye is suggestive of aberrant regeneration (anomalous axon innervation) (Fig. 13-6). When aberrant regeneration develops following an acute third nerve palsy, a compressive posterior communicating artery aneurysm or traumatic etiology should be considered. When aberrant regeneration occurs spontaneously, without a preexisting acute third nerve palsy, a cavernous sinus meningioma, or an internal carotid artery aneurysm is likely, although an unruptured posterior communicating artery aneurysm may also be responsible.

**Fourth Nerve Palsy (Trochlear Nerve)**

Cranial nerve IV innervates the superior oblique, which depresses the adducted eye and intorts the eye. Each trochlear nerve innervates the superior oblique contralateral to its nucleus. With a fourth nerve palsy, the affected eye is higher than the contralateral eye (hypertropia) and vertical diplopia increases with downgaze and adduction of the affected eye and reduces when a contralateral head tilt places the affected eye in an extorted position. There may be a resting head tilt in the direction away from the paretic eye. It is helpful to examine old photographs of the patient to determine if a head tilt is present, which suggests long-standing misalignment such as that seen with congenital fourth nerve dysfunction. Congenital fourth nerve palsies are relatively common and neuroimaging may not be necessary if a long-standing nature can be confirmed by history.
The dorsal location of the brainstem exit near the tentorium makes the trochlear nerves particularly prone to traumatic injury, which may cause unilateral or bilateral trochlear dysfunction. Microvascular fourth nerve palsies are less common than microvascular third and sixth nerve palsies. Schwannomas of the fourth nerve, although very rare, are more common than those of the third and sixth nerves (Fig. 13–7).
Sixth Nerve Palsy (Abducens Nerve)

Cranial nerve VI innervates the lateral rectus. A sixth nerve palsy results in paresis of abduction of the ipsilateral eye and esotropia. The amount of esotropia is greatest in the direction of action of the weak muscle. The patient usually complains of binocular horizontal diplopia.

As the nerve passes through Dorello’s canal,\textsuperscript{50,51} it is prone to become affected, often bilaterally, by elevations in intracranial pressure. Relatively minor head trauma may result in sixth nerve dysfunction.\textsuperscript{48} MG and restrictive medial rectus involvement in thyroid eye disease often mimic the sign of a sixth nerve palsy.

Investigation of Cranial Neuropathy Causing Diplopia

Intracranial magnetic resonance angiography (MRA) or CT angiogram (CTA) is commonly obtained to evaluate for an intracranial aneurysm in the setting, for example, of an acute onset, pupil-involving third nerve palsy. Ninety-two percent of posterior communicating artery aneurysms causing third nerve palsies are larger than 5 mm.\textsuperscript{52} MRI detects aneurysms larger than 5 mm with 97% sensitivity and aneurysms smaller than 5 mm with 54% sensitivity. The rupture risk of an aneurysm less than 10 mm is 0.05% per year.\textsuperscript{33,54} Approximately 1.5% of third nerve palsy-causing aneurysms that eventually rupture may not be detected by MRA. It is often prudent to proceed with conventional intracranial angiogram to exclude an aneurysm definitively if MRA or CTA are equivocal. Gadolinium-enhanced MRI with high resolution, thin cuts through the brainstem increases diagnostic yield, especially after an aneurysm is excluded by MRA or CTA. If MRI is unremarkable, lumbar puncture may be required to assess for cerebrospinal fluid abnormalities. Acute onset of a painful, pupilsparing third nerve palsy and sixth nerve palsy may represent microvascular ischemia to the nerve, especially in older patients with vascular risk factors.\textsuperscript{55} Spontaneous resolution over 8 to 12 weeks is typical. Investigation of the other causes noted in the table should also be undertaken.

Multiple Cranial Neuropathies

Lesions at the cavernous sinus are associated with third, fourth, and sixth nerve pareses in combination with signs of involvement of the first and second divisions of the trigeminal nerve and sympathetic fibers. Primary tumors such as parasellar meningiomas, lymphoma, and pituitary adenomas and secondary tumors including nasopharyngeal carcinoma and myeloma; vascular disorders such as carotid-cavernous fistula and intracavernous internal carotid artery aneurysm; and inflammatory disorders such as Tolosa Hunt syndrome, Wegener’s granulomatosis, Rosai-Dorfman syndrome, and hypertrophic pachymeningitis may all cause cavernous sinus syndromes (Table 13-1). Lesions at the orbital apex may affect the oculomotor, trochlear, and abducens nerves in combination with the first division of the trigeminal nerve and the optic nerve. Proptosis, chemosis, and conjunctival injection are often present. Inflammation, including orbital pseudotumor and those noted previously, infection from the sphenoid and ethmoid sinuses, particularly aspergillosis and mucormycosis, and primary and secondary neoplastic disease may all cause orbital apex syndromes.
Multiple ocular motor nerves may be affected in Guillain-Barré syndrome or in the Miller-Fisher variant of Guillain-Barré. The classic triad of Miller-Fisher syndrome is ophthalmoplegia, ataxia, and areflexia. In addition to ophthalmoplegia, pupillary light-near dissociation is common. Anti-GQ1b antibodies are present in greater than 90% of patients with Miller-Fisher syndrome and are associated with Campylobacter jejuni infections. Treatment if required is with plasma exchange or intravenous immunoglobulin, as for Guillain-Barré syndrome.

**BRAINSTEM DISORDERS**

**Cranial Nerve Nuclei**

As has been noted in Chapter 1, nuclear lesions differ in clinical appearance from their corresponding cranial neuropathies. A third nerve nuclear lesion causes bilateral impairment of ocular elevation (resulting from contralateral innervation of the superior rectus) and bilateral ptosis (resulting from a single midline levator palpebrae subnucleus that innervates both levator muscles). Very rarely, a third nerve nuclear lesion may result in isolated weakness of a single muscle such as the inferior or superior rectus.

A fourth nerve nuclear lesion causes a superior oblique palsy clinically similar to a fourth nerve lesion; however, the superior oblique weakness is *contralateral* to
the nuclear lesion because of the fourth nerve decussation after dorsal emergence from the midbrain. In addition, a fourth nerve nuclear lesion is almost invariably accompanied by a Horner's syndrome ipsilateral to the lesion because of the proximity of the preganglionic sympathetic fibers to the dorsally placed fourth nerve nucleus.60

A sixth nerve nuclear lesion causes an ipsilateral horizontal gaze palsy.61–63 Although rare cases of isolated horizontal gaze palsy are reported,63 it is nearly always accompanied by an ipsilateral seventh cranial nerve palsy with lower motor neuron facial weakness (because of the anatomic proximity of the seventh cranial nerve fascicle to the sixth nerve nucleus, which it wraps around).

**SUPRANUCLEAR OCULAR MOTILITY CONTROL**

Supranuclear eye movement abnormalities result from dysfunctional cerebral, cerebellar, and brainstem afferent connections to the ocular motor cranial nerve nuclei. Because of the excessive demands that saccadic eye movements place on the neural network, a clinical hallmark of supranuclear eye movement disorders is disproportionate involvement of saccadic eye movements relative to smooth pursuit. Vestibular eye movements are typically intact. In contrast, a nuclear or infranuclear process impairs saccades, smooth pursuit, and vestibular eye movements to the same extent.

Burst neurons in the brainstem provide the sudden, intense neural discharge required to initiate a high velocity saccade and to overcome dampening, orbital elastic forces. Burst neurons for horizontal saccades are located in the paramedian pontine reticular formation (PPRF) and, for vertical saccades, in the rostral interstitial medial longitudinal fasciculus (riMLF) in the midbrain (Chapter 1). A lesion of the PPRF causes slow or absent horizontal saccades and a lesion of the riMLF causes slow or absent vertical saccades. Burst neurons must be inhibited; otherwise constant saccades would occur and disrupt vision. This is provided to both the horizontal and vertical burst neurons by omnipause neurons located in the pons. Dysfunction of these neurons results in excessive back-to-back saccades in either the horizontal directions (ocular flutter) or in all directions (opsoclonus) (see later).

The dorsal midbrain syndrome is comprised of a supranuclear upgaze palsy, convergence-retraction nystagmus, lid retraction (Collier's sign), and pupillary light-near dissociation. The most common etiologies are a pineal gland cyst or hemorrhage and hydrocephalus. A supranuclear upgaze palsy with forced downward deviation of the eyes (“peering at the tip of the nose”) may result from a thalamic lesion that extends into the midbrain.64 Thalamic esotropia, in which the eyes are deviated medially on both sides, arises because of excessive convergence tone with compression or involvement of the dorsal midbrain.65

Gaze deviation is a common manifestation of a supranuclear disorder. The frontal eye fields (FEF) project to the contralateral PPRF; a destructive lesion of the FEF, for example, following cerebral infarction, results in ipsiversive bilateral gaze deviation; the patient “looks at the lesion.” With an irritative lesion, for example, seizure or hemorrhage, there is contraversive deviation; the patient “looks away from the lesion.” A thalamic lesion, however, may cause “wrong way eyes” in which the patient “looks away” from a destructive lesion.66

Degenerative brainstem diseases such as progressive supranuclear palsy, Parkinson's disease, spinocerebellar degenerations, and Huntington's disease
and metabolic disorders such as Wilson's disease and lipid storage diseases may all show distinctive abnormalities of supranuclear ocular motility control.

Internuclear ophthalmoparesis (INO) results from a lesion of the medial longitudinal fasciculus (MLF), which carries signals from the abducens nucleus to the contralateral medial rectus subnucleus of the oculomotor nucleus. These signals allow conjugate horizontal eye movements with co-contraction of the ipsilateral lateral rectus and contralateral medial rectus muscles. A unilateral INO leads to impaired adduction of the eye ipsilateral to the MLF lesion and dissociated nystagmus of the contralateral abducting eye. Despite adduction weakness on direct horizontal motility testing, adduction of the eye ipsilateral to the MLF lesion is intact with convergence eye movements because direct vergence signals to the medial rectus motor neurons do not pass through the MLF. The eye movements may appear normal with bedside smooth pursuit testing and the presence of an INO diagnosed only by the identification of a decreased velocity of the adducting eye compared with the abducting eye during saccadic testing, known as adduction lag. Multiple sclerosis; vascular lesions such as infarction, hemorrhage, and arteriovenous malformations; and tumors are the most common causes of INO. Bilateral INO is usually because of multiple sclerosis and may be associated with a marked exotropia; the “walled eyed” bilateral INO.

Because the PPRF and MLF lie in close proximity within the brainstem on each side, lesions in this region may affect both structures, leading to the “one and a half syndrome” coined by Miller-Fisher. The coexistence of an INO and an ipsilateral horizontal gaze palsy results in there being only abduction in the contralateral eye and no other horizontal eye movement.

Skew deviation is a vertical misalignment of the visual axes. Patients have a hypertropia, which may be concomitant (the same in all directions of gaze), or incomitant. It may be difficult to differentiate incomitant skews from other ocular motility problems such as ophthalmoparesis because of dysfunction of cranial nerves III or IV, but there should be other signs of brainstem or cerebellar dysfunction. It occurs when a disorder causes a mismatch between inputs to the brainstem from the otoliths on both sides.

Some patients may have an INO as well. Others may show the ocular tilt reaction (OTR), in which there is a tilt of the head to the side contralateral to the lesion. It is assumed that this reflects a compensation by the brainstem for the loss of vestibular input; the patient’s position of center of gravity has been shifted. The OTR may be paroxysmal or sustained. Skew deviation with or without the OTR may arise with lesions in the cerebellum, midbrain (particularly lesions of the dorsal midbrain which include the interstitial nucleus of Cahal), and pons.

### Abnormal Spontaneous Eye Movements

#### NYSTAGMUS

Nystagmus is a repetitive to-and-fro movement of the eyes that can be congenital or acquired, physiologic or pathologic. Physiologic nystagmus is sometimes evident at a bedside motility examination and consists of low-amplitude, high-frequency gaze-evoked nystagmus present only in extremes of horizontal gaze. The nystagmus will resolve when the eyes are moved to a slightly less eccentric gaze position.
Pathologic acquired nystagmus is described as jerk or pendular; jerk nystagmus is characterized by a to-and-fro oscillation whose phases are of unequal velocity, termed the slow and fast phases, whereas in pendular nystagmus the phases have equal velocity. Although the direction of jerk nystagmus is named after the direction of the fast phase, the underlying mechanism generating the abnormal eye movement is the slow phase, or slow drift of the eyes away from the desired position. The fast phase is a rapid, corrective movement in the opposite direction. There are three primary mechanisms by which an image is maintained on the fovea: fixation, the vestibulo-ocular reflex, and eccentric gaze holding. Nystagmus may result from disruption of any one of these mechanisms.

Nystagmus Associated with Visual Loss

Visual loss of any cause may disrupt fixation and be associated with nystagmus; that resulting from optic nerve disease is more commonly pendular and that resulting from retinal disease more commonly of jerk type. In the Heimann-Bielchowsky phenomenon, the nystagmus is more prominent in the eye with the greater visual loss or may arise when the visual loss is only in one eye. This is usually pendular and is more prominent in the vertical direction.

Acquired Pendular Nystagmus

Acquired pendular nystagmus (APN) is one of the most visually disabling types of nystagmus. It is a pendular nystagmus that may have horizontal, vertical, or torsional components. APN may occur in the setting of visual loss because of optic neuritis, but it is more commonly seen in brainstem lesions, for example, because of multiple sclerosis; Pelizaeus-Merzbacher disease; lysosomal storage diseases; brainstem infarction; Whipple’s disease (when it is associated with oculomasticatory myorhythmia); spinocerebellar degenerations; toluene abuse; or as a component of oculopalatal myoclonus (oculopalatal tremor), in which pendular nystagmus with a prominent vertical component associated with a synchronous palatal tremor develops months after brainstem or cerebellar infarction. Others brainstem signs are invariably present, such as INO and skew deviation.

Treatment of APN

A double-blind, placebo-controlled, cross-over study comparing gabapentin and baclofen found gabapentin to be highly effective in minimizing oscillopsia and ocular oscillations in patients with APN. The known role of gamma-aminobutyric acid (GABA)-ergic neural transmission in control of the neural integrator, which functions to maintain stability of the eyes in eccentric gaze positions, suggests altered GABA transmission as a mechanism for APN. Memantine, clonazepam, valproate, and scopolamine may also be tried. Patients with oculopalatal tremor may respond to carbamazepine.

Nystagmus from Vestibular Imbalance

Nystagmus from vestibular imbalance may be caused by disease of peripheral or central vestibular pathways. With peripheral vestibular disease, asymmetric vestibular inputs result in jerk nystagmus because the unaffected and unopposed
contralateral vestibular nucleus drives the eyes slowly toward the side of the lesion, and hence the direction of the nystagmus is away from the lesion. An important feature of peripheral vestibular nystagmus is that it is accentuated by, and indeed may only be detected with, elimination of fixation, for example, with Frenzel goggles. The nystagmus is usually of mixed torsional and horizontal direction. Most nystagmus from acute peripheral vestibular impairment such as benign paroxysmal positional vertigo or acute labyrinthitis resolves spontaneously; however, if oscillopsia or vertigo are significantly debilitating, acute management with pharmacologic agents such as diphenhydramine or promethazine may be beneficial.

Imbalance of central vestibular connections may result in vertical or torsional nystagmus. Elimination of fixation tends not to influence the severity of the nystagmus appreciably. Downbeat nystagmus, in which the slow phase is in an upward direction and which is accentuated looking down and to either side, may arise because calcium channel-rich cerebellar Purkinje cells inhibit the vestibular nucleus mediating downward, but not upward, eye movements. This causes a relative decrease in inhibition of upward eye movements, with a resultant slow drifting of the eyes upward and fast corrective downward eye movements. Other signs of cerebellar dysfunction, such as abnormal vestibulo-ocular reflex, are also seen.

Upbeat nystagmus is usually present in the primary position of gaze and, like downbeat nystagmus, increases when the eye is moved in the direction of the nystagmus. It is not, however, accentuated by looking to either side. Vertical nystagmus is almost always associated with a central cause, although a peripheral vestibular lesion can occasionally be associated with upbeating nystagmus, usually with a torsional component.

Either downbeat or upbeat nystagmus may result from a variety of other brainstem or cerebellar pathologies such as vascular disorders, tumors, encephalitis, inherited and acquired causes of cerebellar degeneration, multiple sclerosis and other inflammatory diseases, and metabolic states such as drug intoxication with lithium and anticonvulsants, Wernicke’s encephalopathy, and vitamin B₁₂ deficiency. Downbeat nystagmus may also be caused by structural lesions of the craniocervical junction, such as Arnold-Chiari malformation (Fig. 13–8), Paget’s disease and basilar invagination, and foramen magnum lesions such as meningo. Pure torsional nystagmus is rare and is associated with the brainstem diseases noted previously.

**Treatment**

The potassium channel blockers 3,4-diaminopyridine and 4 aminopyridine are effective treatments for downbeat nystagmus. Clonazepam, baclofen, and gabapentin may also be useful. Periodic alternating nystagmus (PAN) is a horizontal jerk nystagmus that spontaneously reverses direction every 60 to 90 seconds. It is often missed if the examiner does not watch the eyes for long enough. At the time of direction-reversal, there may be a transition period in which vertical nystagmus or a series of square wave jerks may arise, before the horizontal nystagmus changes direction and
continues. It may occur in multiple sclerosis, cerebellar degenerations or mass lesions, brainstem infarction, anticonvulsant toxicity, meningoencephalitis, and trauma. In an animal model, PAN results from ablation of the cerebellar nodulus and uvula, structures known to use GABA B inhibitory pathways to control rotationally induced nystagmus. Both experimental and clinical PAN respond well to the GABA B agonist baclofen.

**Seesaw Nystagmus**

This is a rare nystagmus in which one eye elevates and intorts while the other moves down and extorts, then the movement reverses. It occurs in patients with chiasmal visual loss due, for example, to pituitary and other parasellar lesions but may also arise in brainstem lesions that involve the interstitial nucleus of Cahal in the midbrain. Treatment of the parasellar lesion usually improves the condition, as do baclofen, clonazepam, and alcohol.

**Gaze-Evoked Nystagmus**

Gaze-evoked nystagmus is the most common type of nystagmus, is absent in central position, and beats in the direction of eccentric gaze. It is the result of impairment in eccentric gaze holding mechanisms from a variety of causes, including anticonvulsant or sedative medications and brainstem lesions that have impaired the function of the diffuse gaze-holding neural network. Because it is absent in central position, it is generally not visually disabling and, therefore, does not require treatment.

**Saccadic Intrusions**

In contrast to nystagmus, in which the initial abnormal movement is a slow drift of the eyes away from their desired position, the initial abnormal eye movement...
with saccadic intrusions is a sudden saccadic movement that abolishes steady fixation. The spectrum of saccadic intrusions ranges from abnormal intrusive single saccades (macrosquare wave jerks) to sustained saccadic oscillations (ocular flutter and opsinclusus). Back-to-back saccades with no saccadic interval in the horizontal plane are termed ocular flutter, whereas similar saccadic intrusions in all directions are termed opsinclusus. Ocular flutter and opsinclusus arise because of disease of pontine omnipause neurons that normally inhibit saccadic burst neurons.92 Many causes of ocular flutter and opsinclusus, such as viral parainfectious encephalitis, meningitis, and medication toxicity, resolve spontaneously. Others, such as paraneoplastic syndromes, stroke, or tumor, may not and clonazepam or gabapentin may be tried but are not very effective.

REFERENCES


