Eye Movement Abnormalities in Multiple Sclerosis

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Multiple sclerosis (MS) is an inflammatory condition that affects the central nervous system myelin and is capable of causing a host of neurologic deficits. Eye movement abnormalities are a common manifestation either at the onset or during the course of the disease.1 In fact, eye movement abnormalities in MS often correlate with overall disability from the disease.2 In this article, the authors discuss the disturbances of gaze shifting, gaze holding, and ocular alignment that occur in MS, with an emphasis on underlying neuroanatomic principles and pathologic findings on examination.

Modern neuroimaging has revolutionized the ability to diagnose MS at its earliest stages and to monitor subclinical, silent disease progression. Although MRI has become an indispensable tool in the management of patients with MS, it is not completely sensitive in detecting lesions and therefore does not replace a careful neurologic examination. For example, small lesions in the brainstem may produce overt clinical abnormalities yet fall below the threshold for detection by MRI. This potential dissociation between clinical and radiographic findings further emphasizes the importance of careful clinic-anatomic localization. The proper assessment of subtle visual disturbances often critically impacts rational clinical decisions in the management of patients with MS.

INTERNUCLEAR OPHTHALMOPLEGIA

Internuclear ophthalmoplegia (INO) refers to disruption of rapid, coordinated, horizontal saccades by slowed or limited adduction.3-6 Conjugate adduction in normal

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doi:10.1016/j.ncl.2010.03.006
neurologic.theclinics.com
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horizontal saccades is facilitated by a subset of interneurons within the abducens nucleus. These fibers cross the midline to travel through the contralateral medial longitudinal fasciculus (MLF) from the pons to the medial rectus subnucleus of the ocular motor complex in the midbrain (Fig. 1). The MLF is highly myelinated to support the rapid neural transmission necessary for abduction of one eye and adduction of the fellow eye to be nearly synchronous. Even slight impairment of the transmission speeds through the MLF produces symptoms by compromising this synchronicity, causing ocular misalignment during horizontal saccades. Unlike other myelinated tracts in which slight impairment may produce no overt clinical deficits, the system for coordinated horizontal saccades is extremely sensitive to transmission speeds, making INO a frequent manifestation of MS.

The adduction deficit in INO may manifest as slowing during the horizontal duction (adduction lag, ultimately with a full excursion of the eye) or as incomplete adduction producing an incomitant exotropia (Fig. 2). Normally, a rapid horizontal saccade is produced by pulse discharges originating in the paramedian pontine reticular formation (PPRF) (see Fig. 1). Eccentric gaze following the saccade is maintained by a step function based on inputs from the medial vestibular nucleus and the nucleus prepositus hypoglossus. The step function is derived from velocity information by the process of neural integration, and it serves to maintain gaze holding by overcoming the elastic forces of orbital tissues. Demyelination of the MLF may have greater impact upon the high frequency discharges necessary to produce the rapid saccadic pulse, whereas there may be sparing of the lower frequency discharges required for the step function that ultimately determines the range of adduction. Alternatively, the range of adduction may be spared because of pathways apart from the MLF that possibly mediate a full adducting excursion.

Despite deficient adduction during horizontal saccades, the normal function of the medial rectus in INO can typically be demonstrated by testing convergence of the eyes (Fig. 3). Convergence is mediated by separate inputs to the medial rectus subnucleus that are distinct from the inputs arriving via the MLF. The dissociation between limited adduction on horizontal saccades and spared adduction during convergence highlights the supranuclear nature of the adduction deficit in INO, with intact nuclear function of the midbrain.
and infranuclear components of adduction. In some cases, however, dysfunction of the MLF is sufficiently rostral that the medial rectus subnucleus itself is impaired; therefore, impaired convergence will accompany impaired adduction on horizontal saccades. In this setting, referred to as the anterior INO of Cogan, the distinction is blurred between INO and partial third nerve palsy.9

Patients with unilateral INO typically do not have significant exotropia in primary gaze, likely because of intact convergence tone. In contrast, bilateral MLF lesions often cause exotropia (see Fig. 3). This clinical presentation is described as the WEBINO (wall-eyed bilateral INO) syndrome.

The misalignment produced by INO may cause a variety of ophthalmic symptoms, including visual blurring, diplopia, loss of stereopsis, and asthenopia (eye fatigue).10 Normally there is cortical sensory suppression during saccades to eliminate blur from retinal slippage, but in INO visual blurring may occur because this mechanism fails to fully suppress inputs from the eye with slowed saccades.9 Visual symptoms are often proportional to the degree of INO, and patients with mild INO may be essentially asymptomatic. Because use-related fatigue and Uhtoff’s phenomenon (worsening symptoms with elevated body temperature) are common in patients with MS, the symptoms caused by INO may fluctuate over the course of the day.

Many patients with INO have normal horizontal pursuit, optokinetic, and vestibulocular responses.11 These functions may be preserved because they are mediated by lower-frequency neural signals with transmission that is spared despite demyelination of the MLF, or because they are also mediated by alternate connections between the abducens and oculomotor nuclei.

INO is often associated with a dissociated horizontal nystagmus most prominent in the abducting eye (Fig. 4). The slow phase of nystagmus is opposite the direction of attempted gaze, with quick saccades in the direction of attempted gaze. The
nystagmus has a unique slow phase with an exponentially decaying wave form. With greater excursions, the amplitude or frequency of the nystagmus may increase.

Several mechanisms may account for the abducting nystagmus in INO, and the explanations are not necessarily mutually exclusive. One possibility is that there is a central adaptive response to reduce visual blurring. To attempt to overcome adduction weakness, a compensatory increased saccadic pulse and step could occur (and would affect both eyes by Hering’s law of dual innervation). Although the adaptive response may improve the adduction of the paretic eye, it would disturb the abduction of the non-paretic eye in two ways. First, amplification of the pulse would lead to saccadic hypermetria; second, pulse-step mismatch would lead to slow post-saccadic drift with exponential decay. According to this account, the phenomenon of abducting nystagmus in unilateral INO is expected to be greatest if patients habitually fixate with the paretic eye, leading to higher demands for central adaptation. On the other hand, if patients fixate with the non-paretic eye, the abducting nystagmus may not be present. In keeping with these predictions, Zee and colleagues demonstrated that in some (but not all) patients with INO, prolonged patching (1–5 days) of the paretic eye reduces the abducting nystagmus, whereas patching of the non-paretic eye increases it. On the other hand, temporary patching of one eye (or the performance of horizontal saccades in total darkness) does not mitigate the abducting

Fig. 3. Bilateral INO. A 47-year-old woman presented with horizontal diplopia. Examination revealed large-angle exotropia and bilateral INO. (A) Limited adduction of the left eye on right gaze. (B) Limited adduction of the right eye on left gaze. (C) Spared convergence of the eyes. (D) Axial FLAIR MRI revealed numerous areas of white matter hyper-intensity (for example, arrow). (E) However, no signal abnormality was detected in the region of the MLF in the pons or midbrain. (F) Improvement of INO after 2 months. Improved right eye adduction. (G) Full left gaze.
nystagmus, suggesting that the nystagmus is generated not by online target-position error signals but by a stored, long-term adaptive mechanism.\(^3\)

A central adaptive mechanism, however, does not fully account for abducting nystagmus, because not all patients demonstrate the predicted changes following patching.\(^{13}\) An alternate explanation proposes the disruption of inhibitory fibers that travel in the MLF and are postulated to cross in the midbrain to arrive at the antagonist medial rectus of the contralateral eye.\(^{14}\) By this account, impaired inhibition of these medial rectus motoneurons reduces the abducting step function in that eye and causes a slow movement back from the abducted position. A corrective abducting saccade follows, and the repeating cycle generates abducting nystagmus. This explanation, however, would predict hypometric abducting saccades, rather than the hypermetric abducting saccades commonly seen.\(^3\)

Yet another explanation for abducting nystagmus in INO is that injury to additional structures outside the MLF may directly lead to an asymmetric gaze-holding disturbance, which would manifest with greater severity in the non-paretic eye. By this account, however, the abducting nystagmus would have a typical saw-tooth waveform (in which the slow component has constant velocity directly relating to insufficient gaze-holding mechanisms), rather than the exponentially decaying waveform that is seen.\(^3\)

In severe INO, the affected eye may demonstrate abduction slowing in addition to adduction slowing. A potential explanation for reduced abduction velocity is that normal abduction depends upon appropriate inhibition of the antagonist medial rectus of the same eye, which could be compromised by an MLF lesion.\(^{15}\) An alternative explanation, however, is that patients with INO and abduction slowing in fact have more extensive pontine lesions not limited to the MLF, but also potentially involving the abducens nucleus, fascicle, or other structures.\(^6,16\)

Impaired horizontal saccades are not the only manifestation of an MLF lesion. The MLF also contains fibers mediating many vertical eye movements (pursuit, vestibular, and otolithic pathways); corresponding impairments of vertical gaze therefore frequently accompany INO.\(^{11,17,18}\) Impaired vertical pursuit may manifest as “staircasing” ductions interrupted by horizontal movements. Patients with bilateral INO may have marked impairment of vertical gaze holding, resulting in primary-position or gaze-evoked vertical nystagmus. In contrast to the exponentially decaying slow waveform of abducting nystagmus, vertical nystagmus in INO has a typical saw-tooth waveform.
pattern caused by insufficient gaze-holding mechanisms. Impairment of the utricular pathways within the MLF may additionally lead to vertical misalignment of the eyes, in the form of skew deviation or the full ocular tilt reaction (Fig. 5).

The precise measurement of eye movements, using methods, such as infrared oculography, allows highly accurate detection and quantification of INO. Furthermore, these methods serve as a gold standard by which the accuracy of the bedside examination can be assessed.19 Using this method, Frohman and colleagues found that severe INO was accurately detected by virtually all physician observers (regardless of level of training), but that milder INO was missed by many physicians other than trained neuro-ophthalmologists.

Various metrics from eye movement recordings have been used to quantify INO. These include the versional dysconjugacy index (VDI), which compares the peak velocities for abduction in one eye to adduction in the other.20,21 This measure has the benefit of cancelling intra- and interindividual variations of absolute saccade velocities (caused by fatigue, for example). The VDI has also been assessed by a Z score and histogram analysis, which is a statistical method to better distinguish normal and abnormal results.22 VDI measures use velocity rather than final amplitude because the extent of final amplitude in INO is often normal. The first-pass amplitude, on the other hand, evaluates the ratio of abducting and adducting eye position at the time that the abducting eye has initially completed its saccade.23 Finally, recent studies have employed a phase-plane analysis, which plots eye velocity directly as a function of position, removing the effects of temporal variation that arise, for example, from onset latency.24 Quantified measures of INO may provide a useful way to index the clinical effects of fatigue and Uhtoff’s phenomenon, and ultimately may provide a method to objectively assess potential symptomatic treatments.25

Patients with INO frequently have a corresponding abnormality in the pons or midbrain that is detectable by MRI.26 Frohman and colleagues studied 58 subjects with MS and INO and found that the sensitivity of proton density imaging, T2-weighted imaging, and fluid-attenuated inversion recovery (FLAIR) imaging was 100%, 88%, and 48%, respectively. It is not clear from this study, however, how the severity of INO relates to these MRI findings; cases of mild INO may have a higher rate of normal imaging. Furthermore, because patients with MS without INO were not included in this study, the exact specificity of these MRI abnormalities is not known. In some cases, MRI signal abnormality in this region may not have a clinical correlate. Another MRI measure that has been studied in INO is diffusion tensor imaging (DTI), in which the spatial constraints of water diffusion allow assessment of the integrity of white-matter tracts.27 Fox and colleagues found a modest correlation between INO severity (graded by VDI) and mean white matter diffusivity in the MLF, showing that DTI measures may serve as a surrogate marker of brain-tissue integrity.

Fig. 5. A 30-year-old woman with MS developed horizontal, vertical, and torsional diplopia. Examination revealed right INO (with incomitant exotropia greatest in left gaze) and skew deviation (with comitant right hypertropia in all directions of gaze). A demyelinating lesion of the right MLF accounts for this pattern of misalignment.
NUCLEAR OR FASCICULAR OCULAR MOTOR PALSY

MS may cause acquired strabismus in the form of nuclear or fascicular palsy of one of the three ocular motor nerves. In sixth nerve palsy, a fascicular lesion causes impaired abduction of the ipsilateral eye with spared adduction of the fellow eye (Fig. 6). A lesion of the sixth nerve nucleus, however, causes ipsiversive gaze palsy, consisting of combined deficits of ipsilateral abduction and contralateral adduction. Rarely, a pontine lesion may affect the sixth nerve nucleus (or pontine paramedian reticular formation) and the ipsilateral MLF. The effect of this lesion is a combined ipsiversive gaze palsy and an ipsilateral INO, referred to as a “one-and-a-half” syndrome, and the only spared horizontal eye movement is abduction of the contralateral eye on lateral gaze (see Fig. 6). In third nerve palsy, a fascicular lesion may cause partial deficits of elevation, depression, adduction, or lid elevation in the ipsilateral eye. In rare cases, these lesions may be highly selective and cause weakness of a single muscle. Also, a discrete lesion of the third nerve fascicle may mimic superior or inferior divisional third nerve palsy (which more often localizes to the anterior cavernous sinus or orbit). A nuclear third nerve lesion causes bilateral superior rectus weakness (in addition to the ipsilateral deficits), because the superior rectus subnucleus issues fibers that travel through the contralateral nucleus to join the contralateral nerve. In addition, nuclear third nerve palsy often causes bilateral ptosis, because the unpaired central caudal nucleus supplies both levator palpebrae muscles.

Normal eyelid position is maintained by inputs to the levator palpebrae. The motorneurons to both levator palpebrae muscles arise from the unpaired central caudate subnucleus (CCN) of the ocular motor complex. Lesions affecting these fascicles may cause unilateral ptosis, often in addition to other deficits of partial third nerve

Fig. 6. One-and-a-half syndrome from right pontine lesion in a patient with MS. (A) In addition to a complete right gaze palsy (from involvement of the right abducens nucleus), there was deficient adduction of the right eye on attempted left gaze (from involvement of the right MLF). Left eye abduction is the only spared horizontal eye movement. (B) Axial T2-weighted MRI revealing a right pontine lesion (arrow). (From Frohman TC, Galetta S, Fox R, et al. Pearls & Oy-sters: The medial longitudinal fasciculus in ocular motor physiology. Neurol 2008;70:e57–67; with permission.)
palsy. Rarely, isolated unilateral or bilateral ptosis may occur.\textsuperscript{33} The CCN is under the control of the nearby M-group cells, which receive tonic inhibitory inputs from the nucleus of the posterior commissure. Disruption of these inputs in the dorsal midbrain causes eyelid retraction (Collier’s sign). The M-group cells couple the contractions of the levator palpebrae muscles to those of the vertically acting eye muscles on the basis of inputs from the superior colliculi.\textsuperscript{34} Selective lesions in this location may cause abnormal, dissociated lid and eye movements. Blepharospasm (forceful, involuntary contractions of the orbicularis oculi) may occur following MS lesions of the brainstem, possibly caused by denervation supersensitivity of the facial nucleus or disinhibition of facial nerve reflexes.\textsuperscript{35} Painful, gaze-evoked blepharoclonus that principally involves the orbicularis oculi may also occur in MS, perhaps relating to ephaptic spread of impulses. MRI studies of these patients, however, have not revealed a consistent localization of lesions.\textsuperscript{36,37} A lesion of the fourth nerve nucleus or proximal fascicle causes hyperdeviation of the contralateral eye. Because of the direction of action of the superior oblique muscle, the hyperdeviation of a fourth nerve palsy is greatest in contralateral gaze and with ipsilateral head tilt. Rarely, a solitary lesion may cause combined INO and contralateral fourth nerve palsy, because of the anatomic proximity of the MLF and the fourth nerve nucleus and fascicle (Fig. 7).\textsuperscript{38}

**SK EW DEVIAT ION**

As mentioned earlier, it is possible for skew deviation to accompany INO because the MLF contains utricular pathways maintaining vertical eye position in addition to interneurons from the abducens nucleus to the medial rectus subnucleus (see Fig. 5). In cases where there is selective damage of the utricular pathways, however, skew deviation will occur in the absence of INO. Imbalance of utricular inputs leads to a cyclovertical misalignment of the eyes, typically with a comitant vertical deviation that does not follow a pattern characteristic of third or fourth nerve palsy. With a pontine lesion, the ipsilateral eye is lower, and with a midbrain lesion, the ipsilateral eye is higher. Typically, there is relative intorsion of the higher eye (because intorsion of the higher

![Fig. 7](image-url)
eye exceeds extorsion of the lower eye). In the ocular tilt reaction (OTR), the hyperdeviation is accompanied by head tilt away from the higher eye. In addition to diplopia, many patients with skew deviation or OTR describe tilting of the subjective visual vertical.39

NYSTAGMUS

Gaze holding is mediated by velocity-position neural integrators; for horizontal gaze, these critical structures are in the medulla (the medial vestibular nuclei and the nucleus prepositus hypoglossus) and for vertical gaze, they are in the midbrain (the interstitial nuclei of Cajal).40 The superior vestibular nuclei may also influence vertical gaze holding via connections through the MLF. The neural integrators make projections to the cerebellar tonsils (the flocculus and paraflocculus) that function to fine-tune velocity-position coding and maintain normal gaze holding.

Dysfunction of the neural integrators leads to impaired gaze holding and pathologic nystagmus. One common pattern is gaze-evoked nystagmus, which has a jerk waveform in which a slow drift back toward primary position is followed by a quick saccade to re-establish eccentric gaze. More significant gaze-holding impairments lead to primary position jerk nystagmus. Downbeat nystagmus often results from a cerebellar or cervico-medullary lesion that disrupts projections from the posterior semicircular canal, resulting in tonic upward deviation of the eyes with fast downward corrective movements. In contrast, upbeat nystagmus occurs more rarely, following pontomedullary or pontomesencephalic lesions that disrupt projections from the anterior semicircular canal. Rebound nystagmus refers to a transient jerk nystagmus that occurs upon returning from eccentric gaze to primary position, with the fast phase away from the previous direction of lateral gaze. Acquired periodic alternating nystagmus has a shifting null point, with the direction of nystagmus changing every 90 to 120 seconds and an intervening rest period of 5 to 10 seconds.41,42 This condition may result from damage to the cerebellar centers that maintain velocity storage mechanisms and the stability of the vestibulo-ocular reflex (VOR). An asymmetric, jerk form of see-saw nystagmus, in which there is intorsion and elevation of one eye with synchronous extorsion and depression of the other eye, may follow midbrain lesions that disrupt inputs to vertical gaze-holding centers.43,44

Another common pattern is pendular nystagmus, which is often the result of damage to the interconnections between the brainstem neural integrators and the gaze-holding centers of the cerebellar tonsils.45,46 Demyelination and conduction slowing along these pathways, which is common in MS, sufficiently disrupts their normal function and leads to abnormal, spontaneous firing patterns. The onset of nystagmus may follow the lesion by several months, suggesting that neural deaffertation may contribute to the pathophysiology. Combined pendular nystagmus and palatal tremor often result from a lesion in the Guillain-Mollaret triangle (including the dentate nucleus, superior cerebellar peduncle, red nucleus, central tegmental tract, inferior olive, and finally the inferior cerebellar peduncle).47,48 There is often inferior olivary hypertrophy, which may be evident on MRI. Monocular visual loss also may contribute to acquired dissociated pendular nystagmus.49

Several drugs are available to attempt to dampen nystagmus and may provide symptomatic benefit to patients with MS.50 Clonazepam, baclofen, gabapentin, and memantine are reasonably well tolerated and are effective in some patients.51 The aminopyridines have been studied in reducing MS-associated symptoms,52 and may be specifically helpful in reducing nystagmus. Many forms of pathologic nystagmus are thought to be caused by reduced physiologic inhibition of the
vestibular nuclei by cerebellar purkinje fibers, and the aminopyridines are potassium-channel blockers that putatively facilitate action potentials in purkinje cells. Both 4-aminopyridine\textsuperscript{53} and 3,4-diaminopyridine\textsuperscript{54} have shown efficacy in controlled trials, but side effects including nausea, vomiting, and seizures limit the use of these medications.

**SACCADIC ACCURACY**

The accuracy of saccadic excursions is under the control of inputs from the posterior fastigial nuclei and dorsal vermis in the cerebellum, which calibrate the size of the saccadic pulse. Dysfunction of these pathways leads to saccadic dysmetria; hypermetric saccades result from damage to the deep nuclei and hypometric saccades result from damage to the vermis alone. Furthermore, dysmetric saccades in one direction of gaze can occur from unilateral lesions.\textsuperscript{55} For example, a lesion of the inferior cerebellar peduncle (affecting the climbing fibers) may cause contralateral hypometric saccades, which occurs because of reduced stimulation of the ipsilateral fastigial nucleus, and consequently reduced stimulation of the contralateral PPRF (Fig. 8). In contrast, a lesion of the Hook bundle region near the superior cerebellar peduncle will cause contralateral hypermetric saccades (Fig. 9).\textsuperscript{55} The reason for contralateral hypermetric saccades is that fibers from the fastigial nucleus to the

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**Fig. 8.** Schematic depiction of the pathways controlling saccadic accuracy. Fibers arising from the inferior olive ascend through the contralateral inferior cerebellar peduncle and synapse on the dentate nucleus. Then, fibers ascend to traverse the contralateral superior cerebellar peduncle within the uncinate bundle of Russell and reach the paramedian pontine reticular formation. (Courtesy of Paul Schiffmacher Medical Illustrator, Thomas Jefferson University.)
SACCADIC INTRUSIONS

Stable fixation is maintained by pause-cell neurons, which are located in the pontine raphe between the two abducens nuclei. They prevent the occurrence of unwanted saccadic pulses by tonically inhibiting the saccadic premotor burst neurons in the PPRF and the midbrain. Dysfunction of pause cells leads to extraneous saccades interrupting fixation. A square-wave jerk, for example, is a 1- to 5°-movement away from and back to the primary position, with an inter-saccadic latency of 150 to 200 milliseconds. Saccadic interruptions with a larger excursion (up to 10–40°) and a shorter inter-saccadic latency (up to 80 milliseconds) are termed macro square-wave jerks. When large saccadic intrusions occur across the midline in a to-and-fro pattern, they are termed macro-saccadic oscillations. In ocular flutter, back-to-back horizontal saccades occur without an inter-saccadic latency. If the saccadic movements occur in the horizontal and vertical planes, they are termed opsoclonus. In micro-saccadic flutter, low-amplitude, back-to-back saccades occur but are generally seen only on ophthalmoscopy or eye movement recordings.
IMPAIRED SMOOTH PURSUIT AND IMPAIRED SUPPRESSION OF THE VESTIBULO-OCULAR REFLEX

Smooth pursuit movements function to minimize retinal slippage of a moving foveated target. They are generated by cortical and subcortical areas, including V5/MST, the frontal eye fields, the dorsolateral pontine nucleus, the cerebellar flocculus and dorsal vermis, the vestibular nuclei, and ultimately the ocular motor nuclei. Lesions to these pathways are common in MS and often produce low-gain pursuit, in which eye movements are disproportionately slower than the moving target.\textsuperscript{58,59} Compensatory catch-up saccades are generated to reestablish visual object tracking.

In natural circumstances, head movements often accompany eye movements to maintain fixation of a moving target. In this situation, the vestibulo-ocular reflex must be suppressed to maintain fixation. Lesions of the cerebellar flocculus commonly impair VOR cancellation, resulting in poor fixation of targets during dynamic head and eye movements. Suppression of the VOR can be assessed by having the subject view the thumb on their own outstretched arm while rotating their chair. If VOR cancellation is deficient, the intact VOR causes the eyes to drift opposite the direction of the head movement, and compensatory catch-up saccades will occur.

SUMMARY

Several eye movement abnormalities occur commonly in MS. The demyelinating lesions of MS can occur quite selectively within critical brainstem and cerebellar pathways that mediate coordinated eye movements, gaze holding, and ocular alignment. Delayed neural transmission in these pathways may lead to INO, ocular motor palsy, ocular misalignment, pathologic nystagmus, impaired saccades, saccadic intrusions, or impaired pursuit. Detailed neuro-ophthalmic examination of patients with MS with visual complaints often yields a diagnosis with highly specific neuroanatomic localization. In turn, a thorough evaluation may suggest targeted symptomatic therapies and enhance the ability to monitor disease progression.

REFERENCES