

REVIEW

The ocular manifestations of multiple sclerosis

2 Abnormalities of eye movements

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"[October 17th, 1827] . . . At Florence I began to suffer from a confusion of sight; about the 6th November the malady increased to the extent of my seeing all objects double. Each eye had its separate vision . . . the malady of my Eyes abated, I again saw all objects actually in their single state."

Augustus d'Esté

The first part of this review described afferent visual disturbances in multiple sclerosis.¹ In this second part we discuss the abnormalities of eye movements that may be encountered. The accurate control of eye movements, authoritatively reviewed by Zee and Pierrot-Deseilligny, depends upon the integration of activity of many separate components of the nervous system, most importantly at the level of the brainstem and cerebellum.^{2,3} The multifocal nature of multiple sclerosis, and its predilection for the posterior fossa explain why patients with this disease are so commonly subject to defects in eye movement control. Diplopia is experienced by one third, nystagmus occurs in two thirds, and some eye movement disorder is present in more than three quarters of multiple sclerosis patients during their illness.⁴⁻⁶

A careful assessments of eye movements in every patient suspected of having multiple sclerosis is necessary, both for deciding whether an abnormality is present (and thus perhaps providing the evidence for a separate lesion crucial to the diagnosis), and defining its nature. The examination must be systematic if abnormalities are not to be missed. It is particularly important to examine the eyes in the primary position to detect spontaneous involuntary movements such as square wave jerks, ocular flutter and second degree nystagmus. Prolonged inspection in conjugate deviation is required to detect periodic alternating nystagmus (see below). Occasionally small amplitude movements are best seen when examining the fundus ophthalmoscopically. Patients with clinically normal eye movements frequently show abnormalities on electroculography (EOG),^{7,8} which is a valuable investigation, complementary to brainstem evoked potentials for detecting subclinical lesions.⁵

The range of symptoms is narrow. Blurring of vision relieved by closure of either eye, diplopia, and oscillopsia are obvious pointers to disorders of ocular motor control, but less clearcut symptoms such as a feeling of unstea-

diness or simply "tired eyes" may be the only complaint, and some patients have no symptoms at all.

With a few exceptions, for example lesions of the medial longitudinal fasciculus (MLF), the clinical examination usually allows only approximate localisation of a lesion responsible for an eye movement disorder. The advent of contrast-enhanced MRI using Gadolinium-DTPA has provided a means of highlighting and accurately delineating the lesion responsible in most multiple sclerosis patients in acute relapse.¹¹ This technique has now been successfully applied to patients with disordered eye movements, allowing precise clinico-anatomical correlation in patients with abnormal horizontal gaze.^{12,13} There are still many abnormalities where the anatomical location of the lesion responsible is uncertain, but with further experience in multiple sclerosis and other diseases, MRI should provide considerable insight into these problems.

Types of eye movement disturbance

Practically all known types of eye movement disorder have been described in multiple sclerosis (table 1), but the commonest are bilateral internuclear ophthalmoplegia (INO), abnormalities compatible with damage to the cerebellum or its connections, and pendular nystagmus.^{14,15} While these disturbances should alert the clinician to the diagnosis of multiple sclerosis, it cannot be too strongly emphasised that no particular clinical pattern is specific to this, or any other disease. In what

Table Simplified classification of eye movement abnormalities in multiple sclerosis

1	Isolated ocular motor nerve palsies
2	Abnormalities of voluntary gaze <ul style="list-style-type: none"> —ocular dysmetria and gaze impersistence —lesions of the medial longitudinal fasciculus —horizontal gaze palsy —one-and-a-half syndrome —dorsal midbrain syndrome —skew deviation
3	Abnormalities of slow phase eye movements
4	Nystagmus <ul style="list-style-type: none"> —horizontal —vertical —pendular —periodic alternating
5	Paroxysmal disorders of eye movements <ul style="list-style-type: none"> —ocular flutter —square wave jerks —opsoclonus

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follows we have tried to indicate the relative frequency with which the various eye movement abnormalities occur in multiple sclerosis.

1 ISOLATED OCULAR MOTOR NERVE PALSIES

Truly isolated ocular motor palsies are uncommon in multiple sclerosis; careful examination often reveals other defects such as nystagmus on upgaze. When they do occur, the VIth and IIIrd nerves are most commonly involved. We have only seen one patient with isolated involvement of the trochlear nerve. Partial IIIrd nerve palsies, either fascicular or nuclear, may occur, and precise lesion localisation is often possible by careful analysis of the clinical signs.¹⁶ More uncommonly, brainstem demyelination can cause an upper or lower divisional IIIrd nerve palsy usually associated with more distal lesions.¹⁷ Ivers and Goldstein found only two cases of isolated lateral rectus palsy in 144 multiple sclerosis patients reviewed at the Mayo Clinic.¹⁸ Similarly, in a study of 1000 cases of isolated ocular motor palsies, Rush and Younge found only 27 (2.7%) to be due to multiple sclerosis: involvement of the IIIrd alone occurred in eight patients, the IVth in none, the VIth in 18, and multiple nerves were affected in one patient.¹⁹ Moster *et al*, however, examined 49 patients under the age of 50 with isolated lateral rectus palsies and found demyelination to be the cause in 12%, the third commonest aetiology.²⁰ Furthermore, in most studies about 1/4 of cases remain undiagnosed,^{19,21} and it is possible that some of these patients may have had an episode of demyelination.

In one multiple sclerosis patient with an isolated lateral rectus palsy, MRI showed a lesion corresponding to the site where the VIth nerve emerges from the ventral paramedian pons.²² Similarly, in the series of Bronstein *et al*,¹² isolated lateral rectus palsy in multiple sclerosis was shown by MRI to be associated with lesions involving the fascicular portion of the nerve: if the nucleus was involved an ipsilateral gaze palsy, more marked in the abducting eye, was seen. Thus while isolated palsies are relatively uncommon in multiple sclerosis, this diagnosis should be borne in mind in a young patient with no other obvious cause.

2 ABNORMALITIES OF VOLUNTARY GAZE

Disturbances of conjugate gaze, either voluntary saccades or, as described below, smooth pursuit, are the commonest eye movement abnormalities caused by multiple sclerosis, although they are frequently subclinical. Their detection often provides evidence of dissemination of lesions in the nervous system, allowing a definite diagnosis to be made. In a detailed EOG study of saccades and smooth pursuit in 84 patients with definite, probable or possible multiple sclerosis, Reulen *et al* found abnormalities in 85%, 77% and 60% of cases respectively.⁴ Similar studies have confirmed the high incidence of saccadic and pursuit eye movement defects: they are present in about two-thirds of patients in whom the diagnosis is

not yet definite, but are frequently sub-clinical.^{23,24} Several authors emphasise the importance of measuring as many separate parameters of saccades as possible for lesion localisation, as for example, a prolonged saccadic initiation time alone can result from delay in any part of the afferent or efferent visual system.²⁵ The findings of these studies emphasise that, in experienced hands, EOG is often helpful in the evaluation of patients with possible multiple sclerosis.

Lesions of the medial longitudinal fasciculus (MLF)

The best known clinical eye movement abnormality in multiple sclerosis is the INO. The cardinal feature of an INO is slow, or less commonly, incomplete adduction of the eye ipsilateral to the affected MLF. Slowing of adducting saccades may become more obvious during rapidly repeated lateral gaze movements (with the examiner looking at the glabella). Although INOs are most commonly due to multiple sclerosis, it is important to remember that they may be seen in other disorders such as brainstem infarction, gliomas and anticonvulsant toxicity.²⁶ An INO is present in 34–53% of patients, and is often bilateral, especially later in the course of the disease.^{4,6} Dysconjugation of the two eyes is often compounded by overshooting of the contralateral abducting eye (followed by a few beats of “ataxic” nystagmus in about 50% of patients), and also by overshoot on recentering of the abducted eye. Ataxic nystagmus is rarely sustained, and its mechanism is unclear, although Zee *et al* showed that in three out of four patients, it represented an adaptive response to weak adduction in the affected eye, as predicted by Hering’s law of equal innervation.²⁷

Other abnormalities which may be found with an MLF lesion include vertical gaze-evoked nystagmus, impairment of vertical gaze, hypertropia most commonly ipsilateral (skew deviation—see below), and unilateral or bilateral slowing of abduction.²⁸ The vertical gaze disorders probably reflect disruption of connections with the rostral interstitial nucleus of the MLF. Convergence is usually spared, but in those patients in whom it is impaired there is a correlation with the clinical severity of the INO suggesting a more extensive (particularly rostral) lesion. Furthermore, INOs are frequently associated with an increase in saccadic latency suggesting that the lesion responsible extends beyond the MLF to other brainstem structures involved in the programming of saccades.⁴ This impression was confirmed by Bronstein *et al* who studied 28 patients (14 had multiple sclerosis) with an INO by MRI, and found that in all patients the lesions showed similar MRI appearances, and frequently extended beyond the MLF to involve neighbouring pontine or mid-brain structures.¹³ Interestingly, the anatomical extent of the MRI abnormalities did not correlate with the presence of associated abduction and convergence defects, although patients with these features tended to have

more severe INOs clinically. In some patients with bilateral INOs, fixation is disrupted by occasional abducting saccadic bursts in one or other eye, the adduction deficit preventing conjugate movement of the fellow eye. This phenomenon is thought to signify a lesion extending beyond the MLF, and disrupting the supranuclear control of omnipause cells in the nucleus raphe interpositus.^{29 30}

Other less common clinical eye movement disorders are now described which may result from demyelinating lesions in the pontomesencephalic region: conjugate gaze palsy,^{31 32} the "one-and-a-half" syndrome,^{33 34} gaze-alternating skew deviation³⁵ and the dorsal midbrain syndrome³⁶ all occur, but are uncommon in isolation.

Horizontal gaze palsy

Horizontal gaze palsies may theoretically result from lesions of: (1) the ipsilateral paramedian pontine reticular formation (PPRF) rostral to the abducens nucleus; (2) the abducens nucleus; (3) both one and two, and (4) both the Vth nerve fascicle and contralateral MLF. The first three of these possibilities were documented by Bronstein *et al* in their MRI study.¹³ Functionally, the abducens nucleus may be the caudal end of the PPRF. Complete gaze palsies which result from lesions of the PPRF alone may be distinguished clinically from those involving the nucleus because in the former, the eyes can still be driven to the side of the palsy by oculocephalic stimulation (Doll's eye manoeuvre) because the vestibulo-ocular reflex (VOR) does not rely on an intact PPRF. Incomplete palsies, however, are less easy to differentiate.

Isolated gaze palsies do occasionally occur in multiple sclerosis, but are more commonly associated with other defects such as an INO. When isolated, they are assumed to be due to lesions confined to the PPRF-abducens complex, and this assumption has so far been borne out by a small number of MRI studies.^{12 13 22 32} Although gaze palsies are usually partial, they may be complete. For example, a patient recently presented to us with bilateral INOs that developed into complete horizontal gaze palsies over one week, and other similar patients are reported.^{31 32} In patients with bilateral gaze palsies, MRI consistently shows a single midline lesion in the pons, probably damaging both PPRFs and the ventral raphe area.^{13 32}

The "one-and-a-half" syndrome

The "one-and-a-half" syndrome was first described with pathological correlation by Miller Fisher in 1967.³⁷ It is the combination of a horizontal gaze palsy with an ipsilateral INO due to a lesion involving both the PPRF-abducens complex and MLF on the same side: thus the patient has a gaze palsy to the side of the lesion ("one") with impaired adduction on attempted contralateral gaze ("and-a-half"). As with an isolated INO, there may be associated abnormalities of vertical gaze. Martyn and Kean described a patient with multiple sclerosis and a "one-and-a-half" syndrome in



Figure T2-weighted axial MRI showing a right sided dorsal pontine and cerebellar lesion in a patient with multiple sclerosis and a right "one-and-a-half" syndrome. (Ormerod *et al*. *Brain* 1987;110:1597. By permission of Oxford University Press).

whom MRI confirmed that the lesion was situated on the appropriate side of the dorsal pons (figure).³⁸ This syndrome was well reviewed by Pierrot-Deseilligny *et al* with descriptions of five cases of their own and a review of the 17 previously reported cases: of these 22 patients, the majority had vascular disease and only two had multiple sclerosis.³³ In 1983, however, Wall and Wray added a further 20 cases to the literature, of whom 12 had definite, and two suspected multiple sclerosis.³⁴ Of these 14 patients, 12 had visual symptoms, most commonly diplopia, but blurring, oscillopsia and difficulty looking to one side were also noticed. Associated findings included gaze-evoked upbeat nystagmus in 13, downbeat nystagmus in two, and skew deviation in five (ipsilateral hypertropia in only three). From this report it seems that, in keeping with our own experience, the "one-and-a-half" syndrome may be a more common manifestation of demyelination than was previously thought.

The dorsal midbrain syndrome

The dorsal midbrain syndrome describes a constellation of eye signs. Upward gaze is affected most consistently, but eyelid retraction or ptosis, near-light dissociation of the pupils, accommodation paralysis or spasm, convergence paralysis or spasm, convergence-retraction nystagmus, skew deviation (see below) and paresis of downgaze are also characteristic. Clinically, it is usually incomplete, but its recognition has considerable localising value. It is most commonly due to masses in the pineal region or vascular disease.³⁷ There are a few reported cases in multiple sclerosis, however, and this diagnosis should be considered in young patients without an alternative cause.³⁶

Skew deviation

Skew deviation refers to a supranuclear vertical dissociation of the eyes, and the first clue to its

presence may be a head tilt. In midbrain lesions, the hyperdeviated eye is usually ipsilateral, whereas with more caudal lesions it is contralateral, although exceptions do occur. The degree of dissociation may vary with eye position. When the higher eye reverses with gaze to either side, it is called gaze-alternating skew (hyper-) deviation. This abnormality is most commonly associated with lesions in the pretectal region and craniocervical junction,^{40,41} but has no precise localising value. While acute lesions of the posterior fossa (for example, hydrocephalus and strokes) are usually responsible,⁴⁰ it is not uncommon in multiple sclerosis, particularly in association with INO. Clinically, alternating skew may be confused with some childhood squints, and with bilateral lesions of the IVth or, less commonly, IIIrd nerves.

Lesions of the cerebellum and its connections

Lesions of the cerebellum or its connections are extremely common in multiple sclerosis, and produce characteristic eye movement abnormalities, often in association with other symptoms and signs of cerebellar dysfunction. A cerebellar eye movement disorder is present in about one-third of patients; saccadic undershoot or overshoot dysmetria, pendular nystagmus (see below) and fixation instability being the commonest. Saccadic dysmetria is most easily seen by asking the patient to centre quickly from a position of lateral deviation, and when it is the sole eye movement abnormality it indicates a lesion in the cerebellar vermis. Truncal or limb ataxia or both frequently coexist.⁴²

Gaze-paretic, rebound (recentring after 15–30 seconds of lateral gaze produces a few beats of nystagmus in the opposite direction) and less commonly centripetal (fast phase towards the position of primary gaze on lateral gaze) nystagmus are typical of lesions in the vestibulo-cerebellum, and represent attempts to compensate for defective cerebellar fixation mechanisms. Leech *et al* described the further abnormalities of failure to maintain lateral gaze in darkness, and slow drifting of the eyes away from the primary position in the absence of fixation, attributing both to cerebellar disease on the basis of observations in cerebellectomised animals.⁴³ These deficits may be more common than suspected in multiple sclerosis, but are difficult to detect clinically.

3) ABNORMALITIES OF SLOW PHASE EYE MOVEMENTS

Disordered smooth pursuit and a correspondingly abnormality of optokinetic nystagmus (OKN) are found in more than 50% of patients. It must be borne in mind, however, that smooth pursuit is likely to be abnormal in any tired, visually handicapped or uncooperative subject, or in one taking sedative drugs. These caveats limit the usefulness of testing smooth pursuit clinically,⁴⁴ but when the examination is unequivocally abnormal, and these complicating factors are absent, it remains a valuable diagnostic sign. The VOR, which maintains target fixation during head

movement, can be voluntarily suppressed when tracking a moving target. VOR suppression is related to, but not entirely dependent on smooth pursuit, and may be easily tested clinically by asking the patient to turn the head from side to side while watching an object such as the thumb held fixed relative to the face. It is abnormal in up to 75% of patients, and usually parallels disturbances of smooth pursuit, but has no precise localising value. In a few patients, however, VOR suppression may be abnormal in the absence of a defect in pursuit, and this finding suggests a cerebellar lesion.⁴⁵

4) NYSTAGMUS

Limitation of eye movements in multiple sclerosis is commonly associated with saccadic instability, manifested clinically as involuntary movements such as nystagmus or spontaneous jerks. Such movements may also be seen in isolation, and some have enough localising value to be helpful in making the diagnosis. EOG examination is invaluable for characterising these abnormalities when there is doubt at the bedside. Nystagmus of various types is very common in multiple sclerosis; it may be apparent only on attempted gaze, or be present in the primary position. In the latter case it may only be detected during ophthalmoscopy, when the retinal vessels will appear to oscillate.

Pendular nystagmus

Acquired pendular nystagmus occurs frequently in multiple sclerosis^{46,47} and is characterised by sinusoidal involuntary oscillations of one or both eyes: if both eyes are involved, the movements may be conjugate or dysconjugate. Oscillations may occur in any plane, and result in linear, elliptical, circular or torsional movements of the globe. Pendular nystagmus is sometimes associated with rhythmical movements of other parts of the body, such as the limbs or palate, at a similar frequency. In the study of Gresty *et al* 12 out of 16 patients with acquired pendular nystagmus had multiple sclerosis.⁴⁷ In each, there was an associated defect of convergence, and half had bilateral INOs. Traditionally, the lesion responsible for pendular nystagmus has been thought to involve the dentato-rubro-olivary (Guillain-Mollaret) triangle. Gresty argued that this ascription is incorrect in demyelination, first, because stimulation of the cerebellum results in binocular eye movements whereas pendular nystagmus may be monocular, secondly because less than half of his patients had unequivocal evidence of truncal or limb ataxia, and thirdly because the association with INOs places the lesion in the brainstem. In a multifocal disease like multiple sclerosis, the possibility that neurological abnormalities associated with pendular nystagmus, such as cerebellar ataxia, are due to separate lesions cannot be excluded until MRI studies are available. The prognosis for suppressing oscillopsia due to pendular nystagmus is poor.

Vertical nystagmus

Both upbeating and downbeating nystagmus

can occur in multiple sclerosis, although they are more commonly seen in other diseases. Primary position upbeating nystagmus is associated with abnormal vertical gaze, particularly upwards, and attempted convergence and lateral gaze may enhance or attenuate the nystagmus. Fisher *et al* described 11 patients with primary position upbeating nystagmus, of whom two had multiple sclerosis: in the four patients with a discrete lesion, two were situated in the ponto-medullary, and two in the ponto-mesencephalic junction.⁴⁸

Overall, downbeating nystagmus is more common than upbeating nystagmus, and is usually associated with an Arnold-Chiari malformation or cerebellar degeneration.⁴⁹ Downbeating nystagmus is usually accentuated by horizontal deviation of the eyes on downgaze, and may be associated with impaired downward pursuit, directional preponderance of OKN downwards and impaired VOR suppression. In the Arnold-Chiari malformation, a torsional component to the nystagmus indicates the presence of an associated syrinx.⁵⁰

Downbeating nystagmus is very uncommon in multiple sclerosis, although two patients were described by Masucci and Kirtzke.⁵¹ In one series of 62 patients, none were thought to have multiple sclerosis, although the cause was not established in 27.⁴⁹ Following the advent of MRI, however, the diagnostic precision in patients with downbeating nystagmus has improved, and in a recent series of 24 cases from the National Hospital, a definite diagnosis was made in 18.⁵⁰ In this series two patients with multiple sclerosis were identified, both of whom had unusually extensive cerebellar abnormalities, especially subjacent to the flocculus and paraflocculus. If such widespread damage to the cerebellum is required to produce downbeating nystagmus, this finding probably accounts for its rarity in multiple sclerosis.

Other types of nystagmus

A number of other types of nystagmus are occasionally encountered, such as horizontal periodic alternating nystagmus. On forward gaze this disorder is manifested as beats of increasing then decreasing amplitude to one side, followed after a pause by a similar cycle to the other side. The periodicity is constant and usually between one and six minutes, with a quiescent interval of 20 seconds between periods: it may therefore be missed without prolonged observation.⁵² The periodicity may be shorter, however, as in the atypical example described by Rudge and Leech in whom it was only 10 seconds.⁵³ The anatomical site of damage in periodic alternating nystagmus has not been determined with certainty, although it is likely that a bilateral disturbance of the inhibitory connections between the cerebellum and vestibular nuclei is required.⁵⁴ In keeping with this localisation, Keane described a patient with multiple sclerosis and a combination of periodic alternating and downbeating nystagmus who, at necropsy, showed symmetrical lesions involving the inferior vestibular nuclei and inferior cerebellar peduncles.⁵⁸

Affected patients complaining of oscillopsia often respond to baclofen.⁵⁶

Positional nystagmus, usually of the "central" type (immediate onset, non-fatiguable with fast phase beating upwards), is not uncommon in patients complaining of vertigo,⁵⁷ but a mass lesion in the region of the IVth ventricle should always be excluded, particularly if the patient complains of headache.

5) PAROXYSMAL DISORDERS OF EYE MOVEMENTS

Sometimes, more obtrusive and disturbing involuntary eye movements can interfere with vision, and some may represent paroxysmal disorders of the type well recognised in multiple sclerosis. A number of case reports have described paroxysmal diplopia, with or without associated neurological deficits. For example, Todman reported on a 24 year old woman whose first symptom of multiple sclerosis was paroxysmal diplopia and hemiplegia.⁵⁸ Each attack lasted 20 seconds and recurred every three minutes. Her symptoms resolved after five days of anticonvulsant therapy.

Ocular flutter, opsoclonus and square wave jerks are also occasionally seen in multiple sclerosis. Ocular flutter consists of brief bursts of uniplanar saccades which are not separated by a saccadic interval, and may be exacerbated by voluntary eye movement. Francis and Heron observed repetitive bursts of ocular flutter in a 23 year old girl with probable multiple sclerosis, and her symptoms and signs responded favourably to carbamazepine.⁵⁹ Gresty *et al* described a variant of ocular flutter in a patient in whom horizontal and vertical flutter movements were temporally linked to produce sporadic bursts of rotatory nystagmus.⁶⁰ Unlike ocular flutter, opsoclonus is characterised by chaotic multiplanar conjugate saccades. It is also occasionally caused by multiple sclerosis, though is much more commonly paraneoplastic or follows viral infections. Finally, we have seen a few patients with square wave jerks, in which the involuntary eye movements away from, and back to, the intended position of gaze are separated by a saccadic interval.

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