Ocular manifestations of multiple sclerosis: an overview

BY ALICE DITCHFIELD

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS), in which there is dissemination of lesions in time (two or more clinical events) and space (multiple lesions seen on brain and spinal imaging). The pathophysiology of this disease is complex and involves a combination of genetic, environmental, and immune factors. MS affects women to men in a 2:1 ratio, and it shows a geographical predilection for Europe and the Americas [1]. Typical age of onset is between 20 and 50 years-old. The disease produces significant sensory, motor, and autonomic effects, among which ocular symptoms are common. Indeed, in a large proportion of patients, the initial presenting symptom may be ocular in nature [2].

This article will provide an overview of the range of ophthalmological manifestations of MS. Given that this disease can affect virtually every portion of the visual system, a considerable breadth of visual effects has been described in the literature. Effects may be split into those residing in the afferent visual pathway (responsible for the production of vision), and those affecting the efferent pathway (that which controls eye movements). This article aims not to provide an exhaustive list of all possible ocular manifestations, but to outline those most common and most pertinent to the clinician when assessing a patient with MS. Prompt symptom recognition and thus diagnosis permits earlier commencement of appropriate treatment regimes, with which comes better disease outcomes and improved quality of life for patients [3].

Afferent pathway manifestations of MS

Optic neuritis

Acute optic neuritis (AON) is the first presenting clinical event of MS in up to 20% of patients. It occurs due to inflammation of the retrobulbar optic nerve. AON usually presents as unilateral visual loss; symptoms develop over hours to days, and typically peak at two weeks. Visual loss often gradually improves over approximately four to 12 months [2]. The nature of the visual loss in AON ranges from a small reduction in visual acuity to loss of light perception [4]. Additionally, visual field defects, most commonly central visual defects, are often seen, although a considerable range of defects have been reported, including ceco-central scotomas, quadrant defects, altitudinal and arcuate patterns and hemianopias [5]. Other symptoms of AON include impaired colour vision (typically red-green), reduced light perception intensity, reduced contrast sensitivity, and painful eye movements. Pain in association with AON may be periorbital or ocular in nature, and may precede or occur alongside visual changes [2].

Optic nerve appearance is usually normal in AON, particularly in adults. Paediatric patients more commonly display anterior optic neuritis, also termed 'papillitis', in which evidence of optic disc swelling may be seen on fundoscopic examination. Performance of the swinging light test may show a relative afferent pupillary defect (RAPD) in the affected eye if AON is unilateral, or in the more severely affected eye if bilateral [6].

While magnetic resonance imaging (MRI) is not necessary to confirm diagnosis of AON (the diagnosis may be purely clinical), MRI brain and spinal cord are required to make a diagnosis of MS, if no diagnosis exists prior to the episode of AON (in order to demonstrate dissemination of demyelinating lesions in time and space) [7]. In AON, MRI usually shows an acute enhancing lesion of the affected optic nerve [5]. Testing of visual evoked potential (VEP) is an investigation that is deemed helpful when there is diagnostic uncertainty about AON. However, abnormal findings are nonspecific to optic neuritis and may also occur secondary to other optic nerve pathology such as compression or inflammation of other aetiologies. Studies have also demonstrated changes on optical coherence tomography (OCT) in AON, namely retinal nerve fibre layer and ganglion cell layer thinning and loss of macular volume [6].

With regards to treatment of AON, there is evidence of short-term symptomatic benefit with a course of high-dose corticosteroid therapy, but this has not been shown to influence the final degree of recovery of vision. Studies have also demonstrated a reduction in rates of development of MS following diagnosis of AON after two years, however there is no change at the three-year mark [6]. With regards to long-term treatment, patients in whom a diagnosis of MS is made will require commencement of disease-modifying therapies (DMT). There is evidence to suggest that even clinically isolated cases of AON deemed at high risk for conversion to MS can benefit from initiation of DMT, due to improved longer-term disease outcomes [8].

In addition to MS, neuromyelitis optica spectrum disorder (NMOSD) represents another form of inflammatory demyelinating disease which must be borne in mind in the differential for AON. NMOSD has a predilection for the optic nerves and spinal cord. In 75% of cases, it is mediated by antibodies which target a water channel widely expressed in the CNS, called aquaporin-4 (AQP4-Abs) [9]. In contrast to MS, bilateral attacks of AON are more commonly seen in NMOSD than unilateral cases, and transverse myelitis is a common feature [10]. Of the remaining 25% of cases of NMOSD who are seronegative for AQP4-Abs, 40% are positive for myelin oligodendrocyte glycoprotein (MOG) antibodies. AON is a common feature of MOG-antibody positive NMOSD in adults, whilst children most commonly present with acute disseminated encephalomyelitis (ADEM). Although less common than MS, thorough workup in order to exclude these alternative diagnoses is imperative, as the approach to treatment significantly differs. Indeed, the initiation of DMT can worsen NMOSD [9].

Other afferent visual pathway effects

Some patients display a more chronic form of optic neuritis in which there is a more gradual visual change noted over time, contrasting with the rapid visual loss and pain of AON, and the swift resolution of visual defects.

Additionally, MS can affect the rest of the afferent visual pathway, from optic

nerve through chiasm, optic tracts, optic radiations, to the striate cortex, resulting in visual field defects which vary depending on lesion location(s) [11]. For example, retrochiasmatic and retrogeniculate lesions may cause homonymous scotomas or other homonymous visual field defects. The presentation of such lesions may be mistaken for optic neuritis, but the absence of pain helps to distinguish it from AON [6].

Uveitis

Uveitis refers to inflammation of the uveal tract, which consists of the iris, ciliary body, and choroid. It occurs in approximately one percent of cases of MS, and is 10 times more common in this patient group than in the general population [6]. Intermediate uveitis and panuveitis most commonly forms in MS [2]. Symptoms include blurred vision, floaters, photophobia, eye pain, and eye redness. Uveitis can be effectively treated with topical or systemic steroids [6].

Efferent pathway manifestations of MS

Disease of the efferent visual pathways affects 40-76% of patients with MS [12]. Such lesions can manifest in the form of ocular motility disorders, which may be split into disorders of ocular alignment, and disorders of ocular stability. The former typically present with diplopia, while ocular instability may produce oscillopsia (the appearance of the viewed environment to 'quiver' or oscillate). Ocular dysmotility disorders may occur as part of an acute relapse, or as a result of the chronic disease course [13]. While acute optic neuritis often resolves with good recovery from symptoms, symptoms that result from ocular motility disorders often persist chronically [4].

Disorders of ocular alignment may be paralytic or nonparalytic. Paralytic causes include internuclear ophthalmoplegia and ocular motor nuclear and nerve palsies. The most notable nonparalytic cause is skew deviation.

Internuclear ophthalmoplegia

Internuclear ophthalmoplegia (INO) is the most frequent acute efferent pathway manifestation of MS. It can also occur as a more chronic manifestation [13]. Furthermore, the most common aetiology of INO is MS. It occurs due to the presence of a demyelinating plaque in the medial longitudinal fasciculus (MLF). This structure usually functions to connect the contralateral abducens nucleus to the subnucleus of the ipsilateral medial rectus. This pathway coordinates horizontal gaze [11].

The MLF lesion results in loss or weakness of ipsilateral eye adduction, which may be associated with contralateral horizontal gaze-evoked nystagmus (GEN) on abduction [11]. Sometimes the only visible feature may be the slowing of adducting saccade. Given its subtlety on clinical examination, recording of eye-movement may help to detect slowed eye adduction [13]. INO may be asymptomatic or cause diplopia on lateral gaze.

INO can occur bilaterally in MS. In addition to bilateral weakness of eye adduction and GEN on eye abduction, bilateral INO can also cause vertical gaze defects such as gaze-evoked upbeating nystagmus and weakness of holding vertical gaze.

Wall-eyed bilateral INO or 'WEBINO' is a syndrome in which there is bilateral INO, and patients appear 'wall-eyed' due to an associated exotropia, the precise cause of which is unknown [13].

One-and-a-half syndrome refers to a condition in which there is INO and additionally an ipsilateral horizontal gaze palsy. As a result, contralateral eye abduction is the only preserved horizontal eye movement. It is caused by a lesion of the MLF and either ipsilateral abducens nucleus or the paramedian pontine reticular formation. As a feature of MS, it typically occurs as a result of an acute relapse [13].

Ocular motor nuclear and nerve palsies

Nuclear palsies occur because of demyelinating brainstem lesions that damage the abducens, trochlear or oculomotor nuclei (or combinations thereof). Oculomotor or trochlear nuclear damage is rare in MS, and if seen, is usually in combination with other neurological features rather than in isolation. Ocular motor nerve palsies may occur in MS due to demyelinating lesions of the fascicular portion of the implicated cranial nerve(s) within the brainstem. This usually occurs in the context of a clinical relapse of MS [13]. As with nuclear palsies, the most commonly affected ocular motor nerve in MS is the abducens nerve, while oculomotor is seen less frequently, and trochlear nerve involvement is virtually never seen. Trochlear nerve palsies are particularly rare due to a relatively small proportion of the nerve being intra-axial, meaning it is exposed to minimal white matter to be subject to demyelination [14].

Lesions of the abducens nucleus result in a horizontal gaze palsy with weakness of ipsilateral eye abduction, and associated weakness of contralateral eye adduction [7]. It also commonly produces disruption of smooth pursuit and impaired saccadic and vestibular eye movements [11]. In contrast, damage to the abducens nerve fascicle causes impaired abduction of the ipsilateral eye, without an associated contralateral adduction deficit. Oculomotor nucleus lesions will result in bilateral paresis of the superior rectus muscles, an ipsilateral fixed dilated pupil, and weakness of ipsilateral eye elevation, depression, and adduction. It will also cause bilateral ptosis. Third nerve fascicle lesions cause ipsilateral weakness of elevation, depression and adduction, and ipsilateral pupil and lid elevation defects [7]. Trochlear nucleus or fascicle lesions cause partial or complete paresis of superior oblique muscle, and hypertropia and excyclotorsion [15].

Skew deviation

Skew deviation is a non-paralytic cause of ocular misalignment, while INO and ocular motor nerve and nuclear palsies represent the commonest paralytic causes. Skew deviation refers to vertical misalignment of the eyes in all directions of gaze. It occurs due to disturbance of the central graviceptive vestibular pathways, within which the cerebellum is included [13]. In MS, skew deviation is often seen in association with contralateral INO.

With regards to the management of disorders of ocular alignment, administration of corticosteroids improves clinical outcomes in the context of an acute flare or relapse. Temporary ocular occlusion may help to improve symptoms. Strabismus surgery, botulinum toxin injection, and Fresnel prism glasses represent additional available options but are rarely used in clinical practice [13].

This article will now discuss disorders of ocular stability and oscillopsia described in MS.

Nystagmus

Nystagmus most typically occurs in the context of acute attacks in MS [13]. It is due to demyelination in the cerebellum or tracts between the cerebellum and brainstem [4].

There are different forms of nystagmus which may be seen as part of the clinical manifestation of MS. It can be split into jerk nystagmus, which encompasses GEN and primary position nystagmus, and pendular nystagmus.

The most common form of nystagmus in MS is seen in association with INO, whereby the contralateral abducting eye exhibits horizontal gaze-evoked nystagmus (as discussed above).

Sixteen percent of patients with MS have some form of GEN. It rarely causes symptoms and typically occurs in a chronic disease pattern.

Demyelinating lesions affecting the cervicomedullary junction or cerebellum can produce downbeat nystagmus [11].

Patients may exhibit upbeat GEN the presence of bilateral INOs [11].

Pendular nystagmus is rare, however is the most troublesome form of nystagmus symptomatically. It is defined as nystagmus in a sinusoidal or pendular trajectory, in which there are rhythmic, slow-phase oscillations [16]. Acquired pendular nystagmus is most commonly caused by MS, and it occurs as a chronic disorder. It is the result of a lesion in Mollaret's triangle, which refers to the connection between the red nucleus, inferior olive, and dentate nucleus [11]. Pendular nystagmus in primary gaze causing troubling symptoms of oscillopsia and disruption to visual acuity [16]. Oculopalatal myoclonus can develop in this condition, in which eye movements occur synchronously with movements of the palate [11].

Saccadic intrusions and dysmetria

Saccadic intrusions are rapid, involuntary conjugate eye movements that result in disturbance of visual fixation [17]. Although a degree of saccadic intrusions is seen in healthy individuals, they occur at greater frequencies and amplitudes when associated with a pathological process. Saccadic intrusions can be seen as a feature of an acute relapse or as chronic disease in MS. Square-wave jerks and square wave pulses are the most common types of saccadic intrusion seen in MS. Square wave jerks are back and forth jerky movements with pauses, or intervals, between each eye movement. Square wave pulses are similar but with a higher frequency and shorter intervals. They occur due to demyelinating cerebellar lesions [18].

Saccadic dysmetria refers to failure of saccades to achieve visual fixation on the intended target – either overshooting (hypermetria) or undershooting (hypometria), or an error of saccade direction [18]. It is one of the commonest chronic ocular motor disorders in MS. It occurs secondary to lesions of the dorsal oculomotor vermis and fastigial oculomotor region of the cerebellum. Directional dysmetria and hypermetria are the commonest forms in MS [13].

Conclusion

MS can affect every portion of the visual system and thus produces a wide and varied range of clinical syndromes. The commonest ocular manifestations seen in MS are acute optic neuritis, INO, nystagmus and saccadic disturbances. Some features of ocular disease can be acutely disabling, for example due to acutely reduced visual acuity seen in AON. Ocular dysmotility disorders may demonstrate longer term effects which can significantly impact quality of life. It is important for the clinician to be aware of the hallmark features seen on clinical examination as, if detected promptly, early referral and initiation of treatment leads to improved disease outcomes [3]. Furthermore, improved localisation of disease on clinical examination may shed light on the most appropriate management course and surveillance schedule, thus limiting disease activity and progression [7].

References

1. Walton C, King R, Rechtman L, et al. Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS, third edition. *Multiple Sclerosis Journal* 2020;**26(14)**:1816-21.
2. Chen L, Gordon L. Ocular manifestations of multiple sclerosis. *Current Opinion in Ophthalmology* 2005;**16(5)**:315-20.
3. Landfeldt E, Castelo-Branco A, Svedbom A, et al. The long-term impact of early treatment of multiple sclerosis on the risk of disability pension. *J Neurol* 2018;**265(3)**:701-7.
4. Hoff J, Dhayalan M, Midelfart A, et al. Synsproblemer ved multippel sklerose. *Tidsskr Nor Laegeforen* 2019;**139(11)**:10.
5. Frohman T, Graves J, Balcer L, et al. The neuro-ophthalmology of multiple sclerosis. *Continuum* 2010;**16**:122-46.
6. Costello F. Vision disturbances in multiple sclerosis. *Semin Neurol* 2016;**36(2)**:185-95.
7. O'Riordan JI, Thompson AJ, Kingsley DPE, et al. The prognostic value of brain MRI in clinically isolated syndromes of the CNS a 10-year follow-up. *Brain* 1998;**121(3)**:495-503.
8. Kale N. Optic neuritis as an early sign of multiple sclerosis. *Eye and Brain* 2016;**8**:195-202.
9. Huda S, Whittam D, Bhojak M, et al. Neuromyelitis optica spectrum disorders. *Clin Med* 2019;**19(2)**:169-76.
10. Hoorbakht H. Optic neuritis, its differential diagnosis and management. *Open Ophthalmol J* 2012;**6(1)**:65-72.
11. Jacobs D, Galetta S. Multiple sclerosis and the visual system. *Ophthalmol Clin North Am* 2004;**17(3)**:265-73.
12. Costello F, Burton J, Lee A. Neuro-ophthalmologic manifestations of multiple sclerosis. *Medscape* 2022. Epub ahead of print.
13. Nerrant E, Tilikete C. Ocular motor manifestations of multiple sclerosis. *J Neuroophthalmol* 2017;**37(3)**:332-40.
14. Jacobson D, Moster M, Eggenberger E, et al. Isolated trochlear nerve palsy in patients with multiple sclerosis. *Neurology* 1999;**53(4)**:877-9.
15. Al-Zubidi N, Okla Suleiman A, Harish Bindiganavile S. Cranial Nerve 4 Palsy – EyeWiki. https://eyewiki.aao.org/Cranial_Nerve_4_Palsy Last accessed August 2022.
16. Kang S, Shaikh A. Acquired pendular nystagmus. *J Neurol Sci* 2017;**375**:8-17.
17. Lemos J, Eggenberger E. Saccadic intrusions. *Curr Opin Neurol* 2013;**26(1)**:59-66.
18. Serra A, Chisari C, Matta M. Eye movement abnormalities in multiple sclerosis: pathogenesis, modeling, and treatment. Frontiers in Neurology. 2018;**9**:31.

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