Ocular Involvement in Multiple Sclerosis

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ABSTRACT

Ocular involvement in patients with multiple sclerosis may be observed as acute or chronic optic neuritis, anterior uveitis, intermediate uveitis, colour vision abnormalities, macular edema, etc. Acute optic neuritis is possibly the most common manifestation. Acute optic neuritis presents as visual loss generally associated with pain with ocular movements. Systemic corticosteroid use shortens the duration of attacks. The patients may have multiple optic neuritis attacks during the course of the disease. Some patients may have fluctuating vision with subclinical disease activity. Subclinical disease activity may be diagnosed with pattern visual evoked potential testing. Colour vision tests, magnetic resonance imaging, ocular electrophysiology and optical coherence tomography are generally used in clinical settings in the diagnosis and follow-up of the disease activity.
INTRODUCTION

Multiple Sclerosis (MS) may affect vision in a number of ways, including Optic Neuritis (ON), chronic optic neuropathy, retrochiasmal visual field defects, double vision, and nystagmus [1,2]. It may also be related to ocular conditions such as uveitis, glaucoma, cataract and a combination of those, which may have an additive effect to impair vision [1].

MS patients report that vision is second most important body function [3,4]. In a population-based study on morbidity of MS, 33% of MS patients reported blurred vision, and 26% reported diplopia [5]. Approximately, 67% of the patients reported some visual disability, and 14% of them reported moderate, severe or total visual disability [6].

This chapter will discuss ocular involvement types of MS in a clinical point of view.

Clinic Measures of Visual Function in MS

Clinically visual function in patients with ON is generally monitored by Visual Acuity (VA) however it is known that contrast sensitivity and low-contrast letter acuity [7,8] are also sensitive measures for this purpose. Specifically low contrast loan letter charts have been shown to be sensitive for detecting visual dysfunction due to MS [9]. Therefore, low contrast acuity measurements are currently used in clinical trials in MS.

MS patients describe their visual problems as blurry vision, unclear vision, fuzzy vision, difficulty of reading, trouble of focusing, difficulty in the following of moving objects, difficulty in driving, double vision, difficulty with vision when eyes are tired and difficulty with vision at night [10].

Vision in MS patients may get worse with heat or exercise. This is called as Uhthoff’s phenomenon, and it is due to the heat that shortens the action potential duration, and thereby reducing the safety factor for successful conduction of nerve impulses in the demyelinated axons [11].

If there is a relative conduction delay between two optic nerves, the patient may experience Pulfrich’s phenomenon, which is the misperception of the trajectory of moving objects [12].

Optic Neuritis

Acute ON due to inflammatory demyelinating lesions of the optic nerve is the most common ocular manifestation and a frequent cause of visual impairment in MS [1,3]. In one series, isolated ON was the first presenting attack of MS in 21% of the cases, and in another series, it was reported that 46% of MS patients had an attack of ON [6,13].

ON is characterized by acute onset of blurring or visual loss, visual field loss, colour vision abnormalities and eye pain exacerbated with eye movements [6,13]. In two-thirds of the patients, optic disc appears normal on funduscopic examination. In the remaining one-third of cases, the optic nerve appears swollen [14]. A relative afferent papillary defect is usually present [15].
in patients with MS may sometimes be subclinical that may be explored by the pattern VEP and/or colour vision abnormalities [1,3,16,17]. Patients may sometimes report fluctuating vision that possibly means ongoing low-intensity optic nerve involvement.

Clinical features which are typical for inflammatory ON should raise concern that the acute optic neuropathy may not be due to MS. Those include a completely painless syndrome, complete visual loss, hyperacute onset, bilateral involvement, neuroretinitis, fever, and poor clinical recovery in one month or more following the onset of clinical symptoms [2,13,18].

In acute ON, Magnetic Resonance Imaging (MRI) usually demonstrates a hyperintense optic nerve on T2-weighted images as well as contrast enhancement within the nerve, best appreciated on fat-saturated sequences of the orbit [18-20]. Full-field Pattern-Reversal Visual Evoked Potentials (VEPs) typically exhibit a prolongation in the latency of a well-formed P100 potential following stimulation of the affected eye [19].

Recovery after ON may last until the 6 months after onset. Optic neuritis attacks generally results in optic disc pallor. Optic disc pallor may sometimes be in the form of temporal pallor (Figure 1). The long-term prognosis for vision following ON is generally good from the patients’ view. Optic Neuritis Treatment Trial followed up 294 of the original cohort of 454 patients for at least 15 years following their initial presentation with the first episode of acute ON [21]. Seventy-two percent of the originally affected eyes had a VA of ≥20/20, and 66% of the patients had ≥20/20 acuity in their both eyes. Poor visual outcome was usually related to recurrent attacks of ON [21].

![Image of optic disc pallor](https://www.smgebooks.com)

**Figure 1:** Vague optic disc temporal pallor in the right eye of a multiple sclerosis patient who had an optic neuritis attack 2 months ago. Visual acuities were 0.2/1.0 in the right and left eyes, respectively.
Chronic Optic Neuropathy

The most classical manifestation of chronic optic neuropathy is a transient worsening of vision in an eye previously affected by ON [18,20]. This is generally related to an increase in body temperature and stress. Most cases occur in females, although the non-optic nerve features of the disease are typical for MS with relapses and remissions; they develop severe irreversible bilateral visual loss due to bilateral optic neuropathy [18,20].

Colour Vision Abnormalities

Colour vision abnormalities may be seen in 32.5-42.5% of MS patients even in the absence of previous ON [22]. Colour vision dysfunction is detected in both red-green and blue-yellow axes, implying impairment in both parvocellular and koniocellular systems [23]. Gundogan et al. found that colour vision abnormalities as assessed by Farnsworth-Munsell 100- Hue test is a more sensitive parameter than pattern visual evoked potentials in the assessment of subclinical optic pathway involvement in MS patients [16]. Figure 2 shows abnormal colour vision function of a patient with a history of optic neuritis.

![Figure 2: Farnsworth-Munsell 100 Hue test result of a patient with previous optic neuritis attack in the left eye. Total error scores were 64 (average discrimination) in the right eye and 515 (low discrimination) in the left eye.](image)

Retinal Changes

It has been demonstrated that MS causes primary retinopathy, which may reflect central nervous system atrophy [24]. Macular edema, mostly affecting the Inner Nuclear Layer (INL), was reported in about 5% of patients with MS [25]. It was found to be more common in the eyes with higher Multiple Sclerosis Severity Scores. The presence of macular edema suggests that there may be a breakdown of the tight junction integrity, and blood-retinal barrier [25,26].
Trip et al. demonstrated the correlation between reduced Retinal Nerve Fiber Layer (RNFL) thickness and reduced macular volume in eyes with and without ON [27]. The authors suggested that there was a retrograde axonal degeneration in MS with the loss of retinal ganglion cells, and consequent macular volume reduction. Costello et al. suggested that the reduction of RNFL thickness was about 10-40 μm within 6 months after ON [28]. Pulicken et al. demonstrated that the RNFL thickness decreased more in patients with secondary progressive MS when compared to relapsing-remitting MS [29]. This suggested that RNFL thickness could represent a marker of progression of the disease. Green et al. demonstrated reduction of both Ganglion Cell Complex (GCC) and Inner Plexiform Layer (IPL) thickness in 82 patients with MS [30]. They also found a complete absence of inflammatory cells in INL and supposed that it was related to the effect of retrograde transsynaptic degeneration. Tátrai et al. found reduced RNFL, GCC, and IPL thickness in the eyes of MS patients regardless of previous ON, and underlined the important role of this pathology in the diagnosis and follow-up of the disease [31]. In a recent study, Cennamo et al. documented a significant reduction of GCC thickness, RNFL thickness, and macular volume when compared to the control group [32]. They also found a significant reduction of macular sensitivity in patients with MS and ON. They demonstrated strong correlations between macular sensitivity and macular volume, and among macular sensitivity, GCC and RNFL thickness.

Uveitis

Anterior, intermediate, posterior and panuveitis were documented in patients with MS [33]. MS is also associated with pars planitis [3]. It was hypothesized that uveitis in MS was secondary to an inflammatory event in the Central Nervous System (CNS), which sensitized the immune system to antigens that were co-expressed in the uvea and CNS [34]. Myelin basic protein and myelin oligodendrocyte glycoproteins are shown to induce demyelinating disease and uveitis in rodent models.

Uveitis may be seen in approximately 0.65-1% of the patients with MS [34]. The onset of uveitis may precede, coincides with, or come after the diagnosis of MS. It may cause significant visual impairment. In one MS series with uveitis, Biousse et al. found that 21 out of 50 affected eyes had a VA of 20/50 or worse after a mean follow-up period of 13.4 years [35].

Intermediate Uveitis (IU) associated with MS is characterized by the presence of pars planitis, and peripheral retinal vasculitis in the form of periphlebitis in 6-26% of patients [36]. Pars planitis affects vision less than other forms of uveitis, but it may lead to cataract, epiretinal membrane formation or cystoid macular edema [36].

Raja et al. published a retrospective series in 1999 and reported that 11% of patients with IU had MS [37]. Patients with retinal vascular sheathing were found to be more likely to develop MS compared to those without retinal vascular sheathing. In 2009, Jakob et al. reported that 10.3% of their 438 MS patients with IU went on to be diagnosed with MS [38].
Although present in the majority of patients, the retinal vascular changes seen in MS patients are generally asymptomatic. Numerous publications demonstrated a spectrum ranging from simple peripheral retinal periphlebitis to the presence of peripheral occlusive retinal vasculitis in 6.5% of patients [33,34]. This condition leads to other complications such as retinal ischemia, neovascularization, retinal detachment, vitreous hemorrhage, or neovascular glaucoma [33,34].

**Cataract and Glaucoma**

The prevalence of cataract was reported between 0.74% and 12.1% and the prevalence of glaucoma between 1.24% - 3.5% in MS patients [1,6]. A population-based cohort study conducted in England on 5576 MS patients revealed that the risks for cataracts (HR 2.45; 95% CI: 1.56-3.86) and glaucoma (HR 1.70; 95% CI: 1.01-2.86) were higher in MS patients younger than 50 years of age, and particularly in men [39]. That study reported that two frequently administered medications, anticonvulsants and corticosteroids, were associated with increased risks of cataracts while corticosteroid use was also associated with an increased risk of glaucoma.

**Eye Movement and Nystagmus**

One of the major causes of visual problems in MS is damage to the eye movement centres of the brainstem [40]. The range of eye movement abnormalities has been described. They may occur in relation with relapse of the disease, or persist in progressive forms of the disease [40].

One of the most common eye movement abnormalities seen in MS is Inter Nuclear Ophthalmoplegia (INO). In one series, 53% of the patients with clinically definite MS had detectable INO [41]. An INO is characterized by limitation or slowing of the adducting eye relative to the abducted eye during conjugate horizontal eye movements. INOs are usually asymptomatic, but they can cause visual disorientation, transient oscillopsia, diplopia, reading fatigue, and loss of stereopsis [42]. INOs may be associated with a contra lateral gaze palsy (the one-and-a-half syndrome) if the lesion also affects the paramedian pontine reticular formation, and/or the sixth nerve nucleus [43].

Nystagmus has been reported in 15-48% of cases of MS patients [5]. Nystagmus may include diverse forms of ocular movements such as gaze-evoked, multidirectional, upbeat or downbeat, vestibular or peripheral, dysconjugate, rebound, pendular, jerk, occult, or periodic alternating nystagmus [44].

Double vision has been reported in 19.1-38.6% of MS patients at some point in their course of the disease [6]. Diplopia attacks may also be paroxysmal, lasting for less than a minute, probably due to axonal hyperexcitability [45].

MS affects just the intra-axial structures, but isolated third, fourth and sixth cranial nerve palsies may occur due to both nuclear and fascicular lesions [42]. Primary gaze could also be affected by saccadic intrusions including square wave jerks, opsoclonus and micro- and macrosaccadic oscillations. They may be asymptomatic although opsoclonus may be visually quite disabling causing jiggling, himmering, or wavy vision [42].
Ocular Blood Flow

Various techniques have been used to evaluate the ocular blood perfusion in patients with MS with conflicting reports [46-48]. Modrzejewska et al. found reduced systolic and mean velocities in the Central Retinal Artery (CRA) and Posterior Ciliary Artery (PCA) in MS eyes with past ON, and also in the contralateral unaffected eyes [47]. However, Akcam et al. recently reported no change of blood flow velocity in patients with significant RNFL thinning [48]. Those conflicting results have indicated that vascular dysfunction in MS is mainly located in the retinal microvasculature.

TREATMENT

When the visual symptoms occur as part of an MS relapse, high dose glucocorticoids will speed up the recovery [42]. They are usually given as 1g per day intravenous methylprednisolone for three days, or 500 mg per day oral methylprednisolone for five days, either with or without an oral prednisolone taper. A second course of IV methylprednisolone or a trial of plasmapheresis can be considered as rescue measures in resistant cases [7,19].

Becker et al. demonstrated improvement of VA in 17 of 24 eyes with MS and uveitis with interferon β treatment [49]. Although corticosteroids remain the preferred treatment modality for the initial uveitis flare, there is a growing evidence for the role of immunomodulation therapy in the treatment of a subset of patients with uveitis [34].

Results from a small trial in chronic optic neuropathy in MS indicated that 4-aminopyridine improved VEP P100 latency compared to placebo, and led to improvements in low-contrast VA in a subset of patients [50].

The NICE guidelines suggest that gabapentin may be tried for oscillospia due to pendular nystagmus as an unlicensed indication [51]. There is a class B evidence to recommend treatment with doses up to 2400 mg per day. Second-line treatment could be tried with memantine at doses up to 40 mg per day.

Downbeat nystagmus could respond to clonazepam, 3,4- diaminopyridine or 4-aminopyridine [52]. Upbeat nystagmus may be treated with baclofen or one of the aminopyridines. Carbamazepine or acetazolamide may suppress some paroxysmal forms of nystagmus [52].

An approach of vertical Kestenbaum-type procedure to move the patient’s acquired pendular nystagmus null point combined with gabapentin has been reported to be successful in an MS patient with a compensatory abnormal head posture [53].

There may be a role for strabismus surgery or botulinum toxin injections to the extra-ocular muscles in the management of symptomatic INOs [54].

TREATMENT COMPLICATIONS

The sphingosine-1-phosphate (S1P) receptor plays a role in regulating vascular permeability, and enhancing endothelial barrier integrity. Fingolimod is the first oral agent used for the treatment of relapsing-remitting MS. Fingolimod, a structural analogue of S1P, inhibits this barrier
action and leads to increased vascular permeability [55]. This may be the pathophysiological mechanism involving fingolimod-associated macular edema [54]. Based on data from 2,564 MS patients, macular edema occurred in a dose-dependent manner with an incidence of 0.3% among patients taking 0.5 mg dose, and with an incidence of 1.2% among patients on 1.25 mg dose [56]. The macular edema occurs most frequently 3 to 4 months after initiation of fingolimod, but it may occur later (after 12 months) in a small percentage of patients. Most cases of FAME are unilateral, and the most frequent presenting symptoms include blurry vision, decreased VA, or eye pain [56].

**DIAGNOSTIC TESTS**

**Visual evoked potentials**

**VEP** is the most common electrophysiologic test utilized in the diagnosis of MS.

Multifocal VEP (mfVEP) may be helpful in identifying segmental latency delay when the full-field VEP is normal, and it may be particularly relevant in cases in which the optic neuropathy or injury to the visual pathway spares central vision [3,42].

The prolonged latency of the P100 response is typically interpreted as evidence of demyelinating injury (Figure 3). In clinical practice, VEPs are usually read in a binary fashion, as either normal or abnormal, based on the P100 latency exceeding 2.5 or 3 standard deviations from normal, or based on having a similarly excessive difference in latency between eyes [1,2,42].

![Pattern VEP results](image)

**Figure 3**: Pattern VEP results of the patient with a history of optic neuritis in the right eye.
Optic disc appearances are shown in Figure 1. It is apparently seen that P100 latencies are significantly delayed in the right eye. P100 latencies are almost 180 ms in the right eye and around 100 ms in the left eye.

In the pre-MRI era, the latency on full-field pattern reversal VEP was abnormal in about 60-90% of patients with MS [19,20]. The proportion of the patients with relapsing MS with abnormal VEP in the present era appears to be far lower, probably due to earlier detection of disease.

The accuracy of VEP test results is highly dependent on a cooperative patient, a reliable lab with adequate technical experience, and a trained/experienced reader.

**Visual field defects**

Visual field testing may pick up a retrochiasmal defect, however, most deficits detected are due to optic nerve involvement. ON may lead to any form of visual field defect although diffuse abnormalities (48.2%), altitudinal defects (15%) and central (Figure 4) or centrocaecal scotomata (8.3%) were most commonly seen in the ONTT [21]. In the ONTT, 13.2% of patients had evidence of bitemporal or homonymous hemianopsia on visual field examinations during the 1-year follow-up. Of those patients, 75.7% had an abnormal baseline brain MRI compared with 46% for those without visual field defects [21]. Visual field defects can also be seen in the absence of previous ON. In one study, asymptomatic visual field defects on standard automated perimetric testing were detected in 63.6% of eyes in MS patients without a previous history of ON [21].

Visual field defects in MS are mostly encountered during an episode of ON, and tend to disappear with visual recovery in 67% of the cases.
Optical Coherence Tomography

Optical Coherence Tomography (OCT) is an office-based imaging method that uses near-infrared light to generate high-resolution cross-sectional images. Newer OCT analysis techniques focus on segmentation of individual retinal layers, permitted by the high-resolution spectral domain OCT instruments currently in use.

Large cross-sectional and some longitudinal studies have shown that the RNFL (as well as macular volume and ganglion cell layer) becomes thinned most dramatically after ON, but also during the course of MS in the absence of classic ON [17,19,29]. Measured at the macula, ganglion cell layer analysis provides a way to assess the integrity of the layer of first-order sensory neurons. Therefore, the three measures most commonly in use to monitor MS using OCT are the peripapillary RNFL thickness (Figure 5), total macular volume, and the ganglion cell layer thickness [27,29].

![Significantly thinned retinal nerve fiber layer in both eyes of a patient with bilateral previous multiple optic neuritis attacks.](image)

**Figure 5:** Significantly thinned retinal nerve fiber layer in both eyes of a patient with bilateral previous multiple optic neuritis attacks.
Several investigators studied the relationship between RNFL and VEPs in MS patients and found a correlation between those parameters [3,17,20,32]. Ganglion Cell-Inner Plexiform Layer (GCIPL) thickness was previously reported to represent a better structure-function correlation compared to RNFL, and its relation with functional measures has been of particular interest. Some authors advocated OCT as a useful biomarker of disease activity and recommended that OCT should be the part of routine monitoring in patients with MS [25,32,57].

Previously, the histopathological evidence of qualitative atrophy of nerve fiber and ganglion cell layers was demonstrated in over 70% of the cases with MS in postmortem analysis [58]. Saidha et al. detected RNFL and GCIPL thinning in vivo by OCT, highlighting that inner retinal layer changes were prominent in MS patients [26]. Those findings were consistent with the results of the histopathologic study by Green et al. who observed retinal nerve and ganglion cell-layer atrophy in patients with MS [30]. Reduced RNFL and GCIPL thickness in the absence of acute attacks of ON supports the possibility of subclinical episodes of ON. Apart from optic nerve and optic tract involvement, MS lesions in the posterior visual pathways might cause ganglion cell damage and axonal loss as a result of retrograde transsynaptic degeneration [30].

González-López et al. indicated that GCIPL measurements had significantly better sensitivity than temporal peripapillary RNFL thickness to detect retinal thickness changes in relapsing-remitting MS patients [59]. In a review by Petzold et al., it was suggested that ON could be defined as a value below 20% of the RNFL thickness in the non-ON eye [60].

Magnetic Resonance Imaging

Brain MRI is one of the most important diagnostic utility in patients with acute ON, as the presence or absence of multifocal brain lesions informs about the likelihood of MS, and overall lesion burden on early brain MRI informs about the prognosis of MS (Figure 6) [18,19].

Dedicated imaging sequences focusing on the orbits may be included to either verify the presence of optic nerve swelling and enhancement or evaluate for infiltrative or neoplastic processes if symptoms are progressive. The most useful imaging sequence is coronal, fat-suppressed, T1-weighted image series, acquired after gadolinium contrast administration [19].
CONCLUSIONS

Although severe visual impairment is uncommon in MS, visual symptoms are common. Relapses, causing problems such as ON, will usually recover well, with recovery speeded up by the use of glucocorticoids, if appropriate. Visual symptoms may occur in all stages of the disease. Therefore, it is important to enquire whether they have any trouble with their vision or eyes in MS patients.

References


