Review Article

Ophthalmic Manifestations of Multiple Sclerosis: A Brief Review

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Abstract

Multiple sclerosis (MS) frequently affects visual system, leading to complications such as contrast sensitivity deficits, visual field abnormalities, pupillary reflex disturbances, and efferent pathway dysfunction. These visual deficits may occur even without a history of optic neuritis. Uveitis and periphlebitis, observed in a subset of MS patients, further contribute to disability and require careful monitoring. Given the high prevalence of visual involvement, a comprehensive ophthalmic evaluation, including visual evoked potential (VEP) and optical coherence tomography (OCT), is essential for early diagnosis and disease monitoring.

Steroids remain the primary treatment for acute MS exacerbations, but they offer no long-term visual benefits and may lead to complications such as central serous retinopathy. Disease-modifying therapies, including natalizumab, fingolimod, and alemtuzumab, are associated with retinal vascular complications and increased susceptibility to opportunistic infections. Early recognition and continuous monitoring of ophthalmic complications in MS are critical for preserving visual function.

Keywords: Multiple Sclerosis; Ophthalmic; Manifestations; Review.

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Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease characterized by demyelination within the central nervous system, leading to a wide range of neurological impairments, including visual dysfunction [1]. This review provides a brief analysis of different MS ophthalmic manifestations, with a focus on visual acuity changes, contrast sensitivity deficiencies, pupillary reflex abnormalities, and efferent pathway involvement. Additionally, we explore the role of paraclinical assessments, such as visual evoked potentials (VEP) and optical coherence tomography (OCT), in diagnosing and monitoring MS-related visual impairments. Understanding these visual dysfunctions is crucial for early detection, accurate diagnosis, and optimizing patient care among individuals with MS.

Visual Acuity and Contrast Sensitivity Deficiencies among Patients with MS

In a study of 18 MS patients with 20/20 vision, 9 patients (50 %) exhibited abnormal contrast sensitivity, despite none having a history of optic neuritis [2]. Another study found contrast sensitivity abnormalities in 98.2 % of MS patients [3]. In some cases, progressive visual loss occurs following chronic optic neuritis [4-5]. In some cases, patients are prescribed high-dose steroids by their neurologists without a confirmed diagnosis of optic neuritis, either due to severe vision loss or at the patient's insistence. We consider this an instance of optic neuritis overdiagnosis. Notably, Stunkel et al., [6] reported optic neuritis overdiagnosis in 60 % of their patients. It is important to note that high-dose steroids provide no long-term visual benefits and are not always the best treatment option for neuro-ophthalmic complaints.

There are also transient and acute manifestations of previous optic nerve lesions, known as Uhthoff and Pulfrich phenomena [7,8]. Uhthoff's phenomenon refers to visual impairment triggered by physical exercise, stress, or heat due to impaired impulse conduction [7]. Pulfrich phenomenon occurs when there is a difference in impulse conduction between the two optic nerves, making it difficult to perceive a moving object correctly [8].

Similar mechanisms among MS patients can affect other sensory and motor pathways throughout the body, leading to various neurological symptoms. Higher cortical dysfunction may result from demyelination in the frontal and parietal lobes as well as the thalamus, and cortical atrophy can also be observed [9]. These neurological impairments contribute to deficits in visual perception [9].

Impact of MS on Visual Field

Typical lesions in MS patients often involve retrochiasmal pathways, leading to visual field defects even in the absence of decreased visual acuity [1]. Since all parts of the visual pathways may be affected in multiple sclerosis (MS), performing both monocular and binocular visual field tests within the central 30 degrees is essential.

The type and severity of visual field defects vary depending on the location and extent of demyelination. These defects may or may not impact visual acuity [1,10]. In one study, visual field defects were reported in 97.5 % of cases [11]. When interpreting visual field results, factors such as patient cooperation, the operator's learning curve, and the precision of the instrument should be taken into account.

Pupillary Reflex Abnormalities in MS

Although the pupillary reflex is a key indicator of optic neuritis, variations in light response- both in magnitude and speed- are also commonly observed in healthy individuals [12]. This variability makes precise measurement impossible, rendering it a relative rather than an absolute diagnostic sign, so we believe its diagnostic value is limited without a comprehensive ophthalmic examination, including a detailed history and biomicroscopy examination. This is because efferent pathways are also affected in MS, and there is a possibility of pupillary distortion or anterior and posterior synechiae due to uveitis, which is reported to be 10-20 % more prevalent in MS patients than in the general population. Furthermore, conditions such as Adie's pupil and Horner syndrome must also be considered in differential diagnosis.

Ocular Motor Disfunction in MS

Efferent disorders are more common in progressive multiple sclerosis (MS) and are associated with a worse neurological prognosis [13]. Involvement of nerve fibers within the nuclei leads to ocular motility disturbances. While recovery after optic neuritis is common, ocular symptoms such as diplopia often persist [14].

Efferent problems in MS include isolated cranial nerve palsies, which, although rare, may affect the 4th and 6th cranial nerves. Saccadic dysfunction, which causes fixation difficulty, is often accompanied by general fatigue [15]. Nystagmus of various types is seen in at least 20 % of MS patients. Horizontal gaze palsy and skew deviation are also observed. All of these disturbances are caused by lesions in the brainstem and cerebellum [16-18]. Internuclear ophthalmoplegia (INO) is a common ocular motility problem in MS, affecting 15-52 % of cases [19]. It results from lesions in the medial longitudinal fasciculus and presents as impaired adduction of the eye ipsilateral to the lesion during horizontal gaze, along with end-gaze nystagmus in the contralateral abducting eye, while convergence remains intact. In one study of 65 patients, the etiologies of INO were reported as 36.9 % vascular, 32.3 % MS, and 13.8 % infectious [20]. Bilateral involvement strongly favors MS [21]. Serra et al.,[22] and Tsuda et al., [23] suggested that clinically diagnosed INO is present in approximately one-fourth of MS cases.

In a study of 70 MS patients with permanent visual impairment, 59 (84.3 %) had ocular motility deficits, with 39 (55.7 %) exhibiting INO, including bilateral involvement in 22 (31.4 %) [5].

In 2014, Servillo et al., [24] studied ocular movements in 163 MS patients, including 125 females (76.7 %) and 38 males (23.3 %), with a mean age of 45 years and a 10-year history of the disease. They reported at least one motility disturbance in 68.1 % of patients, including smooth pursuit disorders in 42.3 %, saccadic dysmetria in 41.7 %, INO in 14.7 %, followed by nystagmus and skew deviation in 13.5 % [24].

Inflammatory Ocular Manifestations of MS

Uveitis and periphlebitis are reported in 1 - 3 % of MS cases [25,26]. They often increase the risk of disability and may be associated with optic neuritis [26,27]. Uveitis can present in anterior, posterior, and intermediate forms [28]. Pars planitis, particularly when bilateral, should strongly raise suspicion for MS. The risk of uveitis in MS patients is reported to be 10 - 20 % higher than in the general population [25,27, 29, 30].

All studies emphasize the importance of

monitoring patients with uveitis, particularly pars planitis, for potential MS involvement. Zein et al., [31] reported that among 16 uveitis cases, 94 % were bilateral and 81 % were pars planitis, with half of these patients already diagnosed with MS. In many studies, uveitis is diagnosed before or during an MS attack [31]. Decreased vision in an MS patient may be due to uveitis and its complications, such as lens opacity and macular edema.

Inflammation in the form of periphlebitis, reported in 10 % of MS cases, is usually asymptomatic because it primarily affects the peripheral retina [32]. It most commonly occurs during the severe or acute phase of the disease [33,34]. Although fundoscopy is normal in two-thirds of MS patients, it should still be performed to assess macular edema, optic nerve status, and to exclude other diseases.

MS in Children

Ophthalmic manifestations in children under 16 years of age are less common, and there are limited studies on the subject [35]. Optic neuritis is not frequently observed in pediatric cases. A retrospective study by Ghezzi et al., [35] on 3,375 MS patients found that disease onset occurred before the age of 16 in 149 cases (4.4 %), with optic neuritis appearing in 16.5 % of them. Bilateral optic nerve involvement is more common in children and tends to improve more rapidly [36-38]. Steinlin et al.,[39] reported ocular symptoms in 17 children with definite MS. Among them, 16 (94 %) had ophthalmic symptoms, 8 (47 %) experienced disturbed vision, 12 (70 %) had optic neuritis, and 4 (23 %) had efferent pathway impairments, including internuclear ophthalmoplegia, sixth nerve palsy, and one-and-a-half syndrome. One case (5 %) presented with progressive uveitis [39]. Most of these patients achieved good recovery [39].

Imaging and Electrophysiology in MS Diagnosis

The most commonly utilized paraclinical examinations in multiple sclerosis (MS) include MRI, visual evoked potential (VEP), and optical coherence tomography (OCT).

MRI of the brain and spinal cord is essential for diagnosing MS, monitoring its progression, and localizing lesions that typically correlate with clinical symptoms.

Visual evoked potential (VEP), particularly pattern VEP, is highly valuable in detecting patients with subclinical visual loss [2]. Some studies have found VEP to be more useful than contrast sensitivity testing. Both amplitude and latency measurements provide important insights [2]. VEP abnormalities often persist even after optic neuritis has resolved. It is considered one of the most specific electrophysiological tests in MS, with abnormalities reported in more than 94 % of patients [40]. Delayed latency is indicative of demyelination, while reduced amplitude suggests conduction block, injury, or axonal loss [30,41].

In 2014, Grecescu [42] studied 28 eyes of 14 patients with definite MS and found delayed VEP latencies. Similarly, Leys et al.,[2] observed delayed VEP latencies in 13 out of 18 MS patients (73 %). Both studies concluded that VEP is the best test for detecting subclinical nerve injury [2,42]. None of the patients in these studies reported visual complaints, and all had visual acuities of 20/20 in both eyes [2,42].

Optical coherence tomography (OCT) of the optic nerve and macula is a structural imaging modality used in MS assessment. Studies have demonstrated greater retinal nerve fiber layer thinning and ganglion cell axon loss in MS patients without a history of optic neuritis

compared to the general population [43-45]. This makes OCT of the optic nerve a valuable tool for evaluating visual dysfunction in MS clinical trials [43, 46, 47]. OCT of the macula reveals microcystic macular edema or inner nuclear layer thickening in approximately 5 % of early MS cases [48]. This phenomenon has been reported in other inflammatory conditions as well, but its occurrence in MS is associated with disease severity and suggests that inflammation extends beyond myelinated central nervous system tissues [49,50]. Another important application of OCT is the detection of medication-related complications, such as central serous chorioretinopathy following high-dose steroid administration and macular edema resulting from fingolimod treatment.

Ocular Side Effects of MS Therapies

Two groups of medications are administered in MS. The first group includes steroids, which are used in the acute phase and may result in central serous retinopathy (CSR). In 90 % of cases, CSR improves within 1-3 months after cessation of steroids, but in cases of relapse, it can lead to retinal atrophy and permanent visual loss [51, 52]. Steroid-related complications, such as lens opacity and glaucoma, are uncommon in pulse therapy [53].

The second group consists of disease-modifying drugs, including interferon, fingolimod, natalizumab, alemtuzumab, and mitoxantrone. The most common complications associated with these medications include ischemic retinopathy, vascular occlusions, macular edema, cortical blindness, and increased susceptibility to viral infections with potential visual complications, such as varicella-zoster virus and John Cunningham virus, particularly with natalizumab [54, 55]. Thyroid-related orbitopathy-like symptoms have been specifically reported with alemtuzumab use [56,57].

Conclusion

All definite or suspected multiple sclerosis (MS) patients should undergo a comprehensive ophthalmic examination before initiating high-dose steroid treatment. This evaluation should include low-contrast visual acuity assessment, refraction, visual field testing, and an assessment of any pre-existing conditions such as amblyopia. It is important to note that high-dose steroids have no effect on long-term visual acuity. In these cases, MRI, VEP and OCT should be performed to confirm the diagnosis of optic neuritis, detect subclinical nerve injuries, and rule out other causes of decreased vision.

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Footnotes and Financial Disclosures

Conflict of interest:

The authors have no conflict of interest with the subject matter of the present manuscript.