

Atypical Ocular Manifestations of Multiple Sclerosis and Side Effects of Drugs: A Review

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Abstract

Multiple sclerosis (MS) is a chronic, irreversible, and disabling neurodegenerative disease affecting a young and working population. Its debilitating disabilities result in a huge disease burden. Early detection of MS has become possible due to new technologies, in particular early detections of its ocular manifestations. However, MS has both typical and atypical ocular presentations. We review published literature describing different ocular manifestations of MS to enable vigilant primary physicians to correlate systemic signs and symptoms with MS. We also outline some unusual phenomena that can help ophthalmologists suspect atypical MS.

Keywords: *Multiple Sclerosis; Optic Neuritis; Optical Coherence Tomography; Magnetic Resonance Imaging; Neuro-ophthalmology*

Introduction

Multiple sclerosis (MS) is the most common neuro-immunological disorder, with prevalence in 2016 of 2.22 million. There has been a 10% increase in age-standardized prevalence since 1990 [1,2]. Higher altitude, younger age-group, female gender, low serum levels of vitamin D, smoking, childhood obesity, and infection with the Epstein-Barr virus are likely to play roles in disease development [3,4]. Genetic risk for MS has not yet been established; therefore, there is no definite measure or laboratory marker for the diagnosis of MS [5].

According to revised classification, MS can be grouped as relapsing-remitting MS, clinically isolated syndrome, radiologically isolated syndrome, primary-progressive MS and secondary progressive MS [6]. Clinicians are strongly advised to use clinical history and examination, imaging, and other available data to differentiate demyelination related to MS from that related to other ailments [7]. Magnetic Resonance Tomography (MRI) has revolutionized the differential diagnosis of MS from other neurological conditions. MRI and testing of cerebrospinal fluid help to identify different pathological substrates of MS, such as inflammation, demyelination, and neuro-axonal loss [8,9]. Treatment of MS includes pharmacotherapy, diet, and rehabilitation. In the last decade, the FDA has approved 13 new medications, both parenteral and oral, for the treatment of MS, but their use is limited due to their prohibitive costs [10-13]. As MS is a debilitating condition, patients with MS need rehabilitation and changes in diet [14,15].

MS involves myelinated nerves, including motor neuron efferent pathways, sensory nerve fibres, intracranial and autonomous nervous systems, and nerve fibres involving the eyes [16]. In optic neuritis due to MS, a common presentation of MS, the patient presents with an acute, unilateral, ad painful decrease in visual acuity, recovering within a few weeks but with residual stigma [8]. Visual effects are common in patients with MS, and most changes are irreversible, with the disease mainly targeting the afferent visual pathway (retina, optic nerve, chiasma, and tract) [17].

With the advent of Optical Coherence Tomography (OCT) and Magnetic Resonance Imaging (MRI), changes in the eye may be identified at very early stages, which is useful in monitoring overall progress of the disease and management outcomes [18,19].

Since atypical manifestations of MS in the eye are not common, family physicians are often unaware of them. This review aims to describe atypical ocular manifestations of MS as noted in the literature.

Methods

The study was undertaken in 2017-18. Since this secondary research used existing evidence from the literature and did not involve any patients, the need to obtain consent was waived.

We used Medical Subject Headings (MeSH) "Multiple Sclerosis" and "ocular manifestations". PubMed, Cochrane, Google Scholar and Scopus databases were searched using the following keywords: multiple sclerosis, optic neuritis, and ocular changes in MS. As randomized controlled trials in the field are rare, most information is derived from case reports and case series. We grouped these into typical and atypical ocular presentations of MS. The latter had fewer than 20 cases reported in the last 15 years. Articles published before 2000 were excluded. Full articles on those with ocular manifestations of MS were obtained through institutional library access.

The aim of describing these cases was to inform primary physicians of the ocular symptoms, signs, and other systemic manifestations of MS noted in these studies to increase vigilance about presentation of MS with ocular involvement.

The flow chart in figure 1 shows the method we used to select the articles for the present review. The literature review suggested there has been substantial work in the therapeutic field and newer tools for diagnosing MS with ocular involvement in the last five years.

Discussion

Typical presentations of MS in the eye

The typical presentation of ocular manifestations of MS includes optic neuritis, nystagmus and diplopia.

Optic neuritis: Optic neuritis with underlying etiology of MS occurs in people 20 to 50 years of age. Women have three times higher risk of optic neuritis. It presents as uniocular loss of vision, diminished color vision and field of vision, relative afferent pupillary defect, and typical papillitis. MRI T2 hyper-intensities suggestive of demyelination confirm optic neuritis with MS. Patients may have past history of episodes involving vision, auditory, or neurological signs suggestive of MS [20-22].

Nystagmus: Nystagmus in MS is mainly due to the involvement of the cerebellum and resultant ocular motor neuron disorders. Presenting signs also include gaze-evoked nystagmus, saccadic hypermetric, and lack of vestibulo-ocular reflex inhibition. Pendular nystagmus is the most disabling ocular manifestation of MS [23,24].

Diplopia: MS can affect the efferent visual pathway, impair ocular movement, especially synchronization of the two eyes [25]. Internuclear ophthalmoplegia is another effect of MS that results in ocular muscle imbalance [26].

Atypical ocular manifestations in patients with multiple sclerosis

Atypical manifestations can be divided into three subgroups, as follows:

- B1: Afferent nerve pathway-related atypical presentation.
- B2: Efferent nerve pathway-related atypical presentation.
- B3: Autonomous nervous system effects.

B1: Afferent nerve pathway-related atypical presentation

Atypical optic neuritis: In contrast to the common presentation, bilateral simultaneous vision loss, non-response to corticosteroid therapy, and hemorrhage on the optic nerve head or peripapillary area are atypical presentations. Detailed clinical assessment supported by OCT and MRI could support optic neuritis due to cause other than MS as an underlying cause [25,27].

Central retinal artery occlusion: (CRAO) in the eye of a patient with multiple sclerosis.

A young female patient known to have MS was on oral contraceptive and presented with unilateral loss of vision. On examination, CRAO was noted. Retinal vasculitis secondary to the demyelinating process was noted as the underlying cause of this atypical presentation [28].

Retinal vasculitis: Secondary to multiple sclerosis was reported by Abu el-Asar, *et al* [29]. Perivascular sheathing and Keratic precipitates (Kps) in an eye of a patient with MS at presentation confirmed intermediate uveitis.

Pars planitis or intermediate uveitis: Cases without optic neuritis but with history of MS and with pars planitis have been found to not respond to steroid therapy [30,31]. Another presentation involved an acute hypertensive uveitis [32], presenting as acute loss of vision, high intraocular pressure, and evidence of inflammation in the posterior segment. MRI confirmed intracranial lesions, suggesting MS.

Optic chiasma: Optic chiasma is a posterior extension of the optic nerve and isolated lesion of chiasma, both reported in MS. A patient presented with bilateral vision loss and defects in the visual field (bi-temporal hemianopia) typical of MS. An MRI of the base of the brain confirmed abnormal enhancement of the optic chiasm. The patient responded to corticosteroid treatment [33].

Effect on the temporal part of the optic radiation due to MS was noted by diffusion tensor imaging (DTI) and on ophthalmic evaluation by OCT. It was noted that the thickness of the relevant temporal retinal nerve fiber layer (tRNFL) was reduced, and the patient had reduced low-contrast visual acuity [34].

Progressive visual loss: Progressive visual loss is less frequent in MS, although progression of systemic manifestation is noted in as many as 10% of MS cases [35]. OCT showing progressive thinning of the retinal nerve fiber layer (RNFL) and newer demyelinating intracranial changes shown by MRI suggest the progression of MS [36]. In cases of MS, late-onset progressive vision loss could be due to additional diseases, such as Harding's disease or ischemic optic neuropathies [37]. It could also be due to natalizumab-related progressive multifocal leukoencephalopathy (PML). In such cases, investigations and monitoring of PML are recommended, along with immediate halt to ongoing natalizumab treatment [38].

B2: Efferent nerve pathway-related atypical presentation

In as many as 70% of MS cases, ocular movement is affected [39]. The involvement of the efferent system in MS can be due to effects on the supranuclear, internuclear, nuclear, and gaze-holding systems [40]. Supranuclear effects in MS result in lateral and up-gaze uncoordinated movement and paresis. Unusual presentations include tonic gaze deviation, smooth pursuit disorders, and vergence abnormalities [41]. In addition to OCT and MRI, electrophysiological testing is crucial to locate MS lesions in the supranuclear visual pathways [42].

B3: Autonomous nervous system effects in MS and ocular changes

There is a significantly higher rate of autonomous nervous system involvement in patients with MS compared to age- and sex-matched healthy persons [43]. MS also influences the sympathetic and parasympathetic ocular nerves. Pupillometric parameters were significantly impaired in 60% of MS patients [44]. Sleep disorders, like rapid eye movement (REM) sleep behavior disorders, insomnia and muscle fatigue have been documented in patients with MS involving the brain stem [45].

Systemic phenomenon can help ophthalmologists suspect MS as an underlying cause of optic neuritis. A few systemic tests, symptoms or patient complaints can suggest that clinicians should suspect MS at first presentation. Family physicians and primary eye care professionals should be aware of these [46]. They are described herewith.

Lhermitte's sign: (LS) is characterized by an electric shock-like sensation spreading along the spine in the cervical to caudal direction and to arms and legs when the patient is asked to flex the neck [47]. This sign in MS is so consistent that Gafson, *et al.* recommended including it in the diagnostic criteria [48].

Pulfrich phenomenon

Patients with MS-related unilateral optic neuropathy have delayed transmission of retinal responses to light from one eye to the brain. This affects their perception of motion and depth, resulting in clumsy behavior and accidents. Such a phenomenon, as described by Pulfrich, can be elicited in clinic. Patients may have difficulty describing their problem, but physicians who know about this issue in MS can help to delay impulse transmission in the normal eye using filter glasses, relieving patient symptoms [49].

Side effects related to MS medications

In the past decade, a number of FDA-approved medications have become available to treat MS, albeit at high cost. Much new information in neuro-ophthalmology has been gained through research on the clinical management of ocular manifestations of MS [50]. Medications have helped to reduce the relapse and severity of MS manifestations [51]. Treatment mainly includes management of the acute effects on ocular and visual pathways and long-term management using steroids and antioxidants. However, long-term use of medication has some demonstrated side effects, which often lead to their discontinuation [52]. The side effects of these drugs also confuse clinicians attempting to differentiate reactivation of lesions and iatrogenic presentations [53]. The following are a few documented ocular manifestations of the drugs used to treat MS.

Acute anterior uveitis was reported by Mack, *et al.* following the use of Fingolimod (FTY720) to treat MS. Discontinuation of this medication and treatment of MS with alternative medication improved uveitis and MS [54]. A large series of MS cases treated with Fingolimod subsequently developed Macular edema [55]. Discontinuation of this drug resolved edema and improved vision. Thus, the side effect of macular edema with or without uveitis should be monitored in MS cases treated with this medication.

Alemtuzumab is used to treat relapsing-remitting MS. It helps to improve disability up to five years. Autoimmunity against thyroid gland tissue following administration of this drug has been reported. Careful monitoring and, if required, treatment of this side effect in the early stages is recommended [51,56].

Mitoxantrone (MTZ) is used to treat aggressive forms of MS. Therapy-related acute leukemia has been reported in a few cases [57].

Progressive multifocal leukoencephalopathy (PML) in an MS patient being treated with natalizumab presented as subacute bilateral blindness [38].

Opportunistic infections: There are low risks of adverse events related to immune suppression, such as opportunistic infections and secondary malignancies managed with Immune reconstitution therapy (IRTs). Cryptococcal meningitis in patients with MS being treated with Fingolimod has been reported [58].

Conclusion

Family physicians have limited resources to undertake detailed clinical assessment and investigations for a neurological case. Clinicians suspecting multiple sclerosis should note the atypical presentations of MS listed in this review, as they do not fit in the standard

signs and symptoms of MS. They should also be aware of newer modalities of MS treatment now available and their possible side effects. Any early signs and symptoms mentioned here should raise alarm if noticed, and they should promptly refer cases to their attending neurologist or ophthalmologist, as appropriate.

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