

# Multiple Sclerosis and Neuro-Ophthalmologic Manifestations

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## ABSTRACT

*The authors report clinical features of ocular manifestations in patients with multiple sclerosis (MS), those that affect the visual sensory system and those that affect the ocular motor system. Disturbances of visual sensory function may precede, manifest coincidentally or follow the neurologic manifestations. Visual disturbances are common in MS and often a result of acute demyelinating optic neuropathy. Careful examination of MS patients, who have never suffered optic neuritis, may also reveal asymptomatic visual loss. Asymptomatic visual loss seems to be a universal feature of MS. Patients with multiple sclerosis may develop disorders of fixation, ocular motility and ocular alignment. Disorders of ocular motor system are frequently the initial sign of multiple sclerosis and occur as its presenting sign weeks, month, or years before other neurologic symptoms and signs develop.*

**Key words:** multiple sclerosis, neuro-ophthalmology

## Introduction

Multiple sclerosis is one of the most common causes of neurologic and visual disability. In general, multiple sclerosis (MS) manifests itself in the third and fourth decades, affecting women almost twice as frequently as men. It has a distinctive geographic and ethnic distribution that is more likely the result of a genetic predisposition in Caucasians of northern European descent than a still completely unknown but indubitable environmental factor.<sup>1</sup>

For many years, the diagnosis was based exclusively on the clinical history and physical examination. Progressively, what has been termed paraclinical and laboratory tests have been increasingly used. Starting with the examination of the cerebrospinal fluid and culminating in the different techniques of magnetic resonance imaging (MRI), the process has been extended and refined. Unfortunately, none of the diagnostic procedures is specific for MS, and in some respects, they make the task more difficult by extending the boundaries of differential diagnosis. For instance, the MRI of many disease of the CNS are indistinguishable from those frequently seen in MS.<sup>1,2</sup>

The symptoms and signs caused by MS are many and varied. They are similar in both sporadic and familial MS and include neurologic, psychiatric and neuro-ophthalmologic manifestations, alone or in combination. The neuro-ophthalmologic manifestations of multiple sclerosis can be divided into two main categories: those that affect the visual sensory system and those that affect the ocular motor system.

## Visual Sensory Manifestations

Disturbances of visual sensory function caused by disease of the retina and optic nerve in prechiasmal, chiasmal and postchiasmal locations. These lesions may precede, manifests coincidentally or follow the neurologic manifestations. In some cases, disturbances of the visual sensory system are themselves asymptomatic but may be important findings that establish the diagnosis of MS. Visual disturbances occurs in the great percent of patients with MS.<sup>3</sup> A brief review of the various visual sensory manifestations of multiple sclerosis follows.

*Choroidal and retinal lesions and uveitis*

Some authors reported individual cases or series of periphlebitis, occasionally associated with posterior uveitis, branch retinal occlusion, neovascularization, retinal venous sheathing (included focal venous sheathing, diffuse venous sheathing and sheathing centered on sites of arteriovenous crossings) and pars planitis.<sup>4,5</sup>

Katsimpris et al. (2002) presented the case of a 32-year-old man suffering from MS who had developed bilateral peripheral neovascularization of the retina.<sup>6</sup> The main disease had been diagnosed 10 years before, whereas in his ophthalmic history the patient reported an incident of retrobulbar optic neuritis in his left eye occurring 3 years before. Ophthalmic examination and fluorescein angiography revealed the presence of a bilateral peripheral retinal neovascularization with an intravitreal hemorrhage in the left eye. Systemic clinical and laboratory investigation were negative for other causes of retinal neovascularization except MS, which is associated with periphlebitis in 10% of cases. Chronic retinal ischemia may lead to retinal neovascularization.

Hochwarter et al. (2004) noted vitreoretinal tractions in 2 of 89 patients with MS with signs of periphlebitis before clinical-neurological manifestation of multiple sclerosis.<sup>7</sup> The third patient, in whom the disease had been known for years, showed distinct neovascularizations, vasculitis, and recurrent vitreous hemorrhages. High-dose steroid therapy resulted in stabilization of the retinal situation in one patient, but the tractions remained unchanged. Additional laser coagulation in the second patient achieved stabilization and reduction of the tractions. A pars plana vitrectomy led to stabilization of the retinal proliferation in the third patient. Authors concluded that the vitreoretinal traction syndrome is associated with MS and can precede its clinical-neurological manifestation. The good results after argon laser coagulation and vitreoretinal surgery suggest a vascular pathogenesis of these tractions.

In some studies, retinal vascular sheathing correlates with severity of neurologic dysfunction in patients with MS; in others, there is no such correlation.<sup>4,8</sup> Pathologic evidence of retinal phlebitis is present in higher percentage of cases than those with ophthalmoscopically visible abnormalities. Kerrison et al. (1994) examined the eyes obtained postmortem from 25 patients with definite MS, one patient with possible MS, and three patients with neuromyelitis optica. These investigators found evidence of retinal in only one of 49 eyes examined using routine processing. However, when the retinal vessels were examined after trypsin digestion, seven of 39 eyes (17,9% of eyes) showed evidence of retinal phlebitis.<sup>9</sup> Rodrigues et al. (1995) also found retinal sheathing to be associated with an increased likelihood of developing MS in their cohort of 156 patients with optic neuritis.<sup>10</sup> Thus, retinal venous sheathing may be a prognostic indicator of early development of MS.

The frequency of uveitis among patients with MS is many times that of general population. The uveitis may

be posterior, anterior, or both. In addition, pathologic evidence of uveitis may be found in the eyes of patients who were never noted to have clinical evidence of intraocular inflammation during life<sup>9</sup>. However, only a minority of patients with idiopathic retinal vasculitis have disseminated CNS lesions characteristic of MS<sup>11</sup>. Posterior and anterior uveitis occurs in minority of patients with MS. In some cases, anterior granulomatous uveitis occurs before clinical signs and symptoms of demyelinating disease are evident. MS should be considered in the differential diagnosis of a patient (although disease such a sarcoidosis, tuberculosis, Lyme disease, and syphilis), particularly a young woman, who develops unilateral or bilateral granulomatous iridocyclitis.<sup>12</sup>

Pars planitis is a condition of unknown etiology characterized by intraocular inflammation consisting of cells and debris in the vitreous, condensation of the vitreous along the pars plana, and varying degrees of periphlebitis. There is usually little or no inflammation in the anterior chamber. The condition can have numerous sequelae that may threaten vision, including cataract formation, development of epiretinal membrane in the macula, and cystoid macular edema. Malinowski et al. (1993) found that 16,2% ± 6,2% risk of patients with pars planitis developing MS. Malinowski et al. also found a strong association of pars planitis with HLA-DR2 and the temporal development of MS.<sup>13,14</sup> Genetic predisposition in MS has always been a critical concern in aetiology and progress of the disease. Kheradvar et al. (2004) presented relations between human leukocyte antigen (HLA), optic neuritis (ON) and MS in the Iranian population. These study strongly suggests the association among DR2, A23 and B21 allele and the evolution of ON to MS. High prevalence of A23 and DR2 alleles in clinically definite MS patients compared with the normal population may suggest an important role for these alleles in the development of MS. The study suggests B51 as a protective factor against development of ON in the normal population.<sup>15</sup>

Zein et al. (2004) described the clinical characteristic and course of 16 patients with uveitis associated with MS. Most patients with MS-associated uveitis were white females between 20 and 50 years of age. The diagnosis of MS preceded the onset of uveitis in 56%, followed it in 25%, and was made concurrently in 19% of the cases. In 94%, the uveitis was bilateral. Pars planitis was the most frequent form of uveitis in their study population (81%); concomitant anterior chamber inflammation was common and was granulomatous in nature 56% of the time. Forty-one percent of the eyes with MS-associated uveitis had 20/30 or better initial visual acuity was uncommon. In view of this, MS-associated uveitis should be suspected in female patients with bilateral uveitis, especially if pars planitis is present. These patients often retain useful vision for many years if treated.<sup>16</sup>

An association between MS during childhood and uveitis is exceptionally rare. Jordan et al. (2003) reported a female patient who presented at the age of 8

years with bilateral intermediate uveitis and whose final diagnosis of multiple sclerosis was made at age 21 years. Over 10 years these patient was treated systemically and underwent bilateral vitrectomy to reduce permanent side effects. Owing to good visual function and low inflammatory signs, systemic therapy was stopped. MS was diagnosed at the age of 21, after a 13-year history of uveitis and after 3 years without medication. In the constellation of uveitis in childhood and later diagnosis of multiple sclerosis, the outlined therapy provided good functional results. Moreover, it may have delayed the manifestation of the underlying disease for 13 years.<sup>17</sup>

### *Optic neuritis*

The term optic neuritis (ON) most often refers to the optic neuropathy associated with demyelinating disease (MS). ON is often the initial presentation of MS. Demyelinating optic neuritis can be considered in three categories: acute, chronic or asymptomatic (subclinical). Acute optic neuritis is the most common form of optic neuritis. Acute optic neuritis is characterized clinically by sudden loss of vision, usually in one eye but sometimes in both eyes, and is associated with pain or discomfort around the orbit or with eye movement. Pain may precede or occur concurrently with the visual loss. Decreased acuity is the rule. The degree of visual loss varies widely and is usually monocular, although a small subgroup, particularly children, often have both eyes affected simultaneously. Patients with unilateral acute ON invariably have a relative afferent pupillary defect (RAPD) in the affected eye (if the process is unilateral or asymmetric) unless they have some type of related or unrelated organic visual disturbance in the contralateral eye.<sup>3,18,19</sup>

Acquired dyschromatopsia with the color deficit often being greater than the degree of visual acuity loss and is of mixed red-green and blue-yellow type.<sup>20</sup> Flanagan and Zele (2004) reported that colour thresholds for the observers with MS/ON were higher in the red-green direction than blue-yellow direction, indicating greater levels of red-green loss than blue-yellow loss. Achromatic thresholds were raised less than either red-green or blue-yellow thresholds, showing less luminance-contrast loss than chromatic loss. These findings indicate that demyelinating disease selectively reduces sensitivity to colour vision over luminance vision and red-green colours over blue-yellow colours.<sup>21</sup>

Virtually any type of optic nerve visual field loss can occur in optic neuritis, including altitudinal, arcuate, central or cecentral, diffuse, and even unilateral hemianopic visual field defects or asymmetric upper nasal quadrantanopsia.<sup>22,23</sup> Visual field defects are often found in the contralateral eye. Contrast sensitivity impairment is found in virtually all patients with optic neuritis, usually parallels the severity of visual loss.<sup>24</sup> The optic disc appears normal (retrobulbar ON) in about two-thirds of patients. Optic disc swelling will be present in 20 to 40% of cases or, if the patient has experi-

enced a previous clinical or subclinical attack of optic neuritis, pale. Both the swelling and the pallor are non-specific findings in ON, and neither is useful in distinguishing demyelinating ON from the ON that may accompany other inflammatory or infectious diseases. The degree of swelling does not correlate with the severity of optic nerve dysfunction. Optic disc or peripapillary hemorrhages are uncommon.

Magnetic resonance imaging (MRI) is the modality of choice for investigating optic neuritis. MRI scanning of the brain should be undertaken in all cases of acute ON for diagnostic and prognostic purposes. The brain lesions of MS are commonly seen as T2 ovoid high-signal white matter lesions on MR scans of the brain located in periventricular regions perpendicular to ventricles with variable enhancement.<sup>25</sup> If the patient has a typical presentation of ON, an MRI need not be performed to exclude a compressive lesion or to confirm the diagnosis. An MRI can be performed to detect subclinical demyelinating plaques to assist in determining the prognosis for developing MS.

Beck et al. (2003) reported finding for the 10-year risk of MS following an initial episode of acute ON is significantly higher if there is a single brain MRI lesion. Higher numbers of lesions do not appreciably increase that risk. However, even when brain lesions are seen on MRI, more than 40% of the patients will not develop clinical MS after 10 years. In the absence of MRI lesions, certain demographic and clinical features seem to predict a very low likelihood of developing multiple sclerosis. This natural history information is a critical input for estimating a patient's 10-year multiple sclerosis risk and for weighing the benefit of initiating prophylactic treatment at the time of optic neuritis.<sup>26</sup>

For atypical presentations of optic neuritis, additional laboratory test, such as a cerebrospinal fluid analysis, serologic tests, and visual evoked potentials, prove to be useful in the diagnosis and subsequent management of the patient.<sup>25</sup> For typical presentation of ON, no serologic tests or cerebrospinal studies need to be performed. Visual evoked potentials (VEP) are almost always abnormal, showing a prolonged latency on the side of the affected optic nerve.<sup>27</sup> Prolonged VEP latency is quite a common but neither mandatory nor pathognomonic finding in optic neuritis. The clinical importance of VEP relies on its usefulness as a relatively objective determinant of the visual pathway integrity, however, clinical approach requires a combined diagnostic procedure.

Natural history of acute ON is to worsen over several days to 2 weeks and then to improve. Improvement initially is rapid and starts approximately 3 weeks after onset. Recovery of vision is nearly complete by 5 weeks after onset. Improvement continues up to 1 year. Lana-Peixoto and Andrade reported (2001) that the clinical features of childhood ON differ from those observed in adults. In children is a better visual outcome and a lower conversion rate to multiple sclerosis than in adults.<sup>28</sup>

There is no known treatment for acute demyelinating optic neuritis. The use of a short course of intravenous corticosteroids (1g/day) for 3 days followed by a 2-week course of oral prednisone is associated with an increase in the speed of recovery of vision, but the ultimate visual function at 1 year and 5 years is the same as it would be if no treatment were given.<sup>29,30</sup> Oral prednisone alone, without prior treatment with high doses methylprednisolone, may increase the risk for recurrent ON and should be avoided.<sup>31</sup>

While it is clear that many patients with ON suffer from a generalized disease of the central nervous system that will go on to clinically definite MS, it is also clear that others do not. As patients become increasingly wellinformed and with the development of effective pharmacotherapy for MS, the distinction between those patients with ON who have MS and those who do not has become ever more important. Recent randomized clinical trials in patients with ON and evidence of prior subclinical demyelination on MRI of the brain found that treatment with recombinant interferon-beta-1a is beneficial in reducing the development of clinically definite MS. Ophthalmologists should refer patients with acute ON suggestive of MS to a neurologist for MS directed investigation.<sup>32,33</sup> Chronic optic neuritis is common. There is numerous MS patients who have no history of acute visual loss, but who, nevertheless, complain that the vision in one or both eyes is not normal and who have evidence of unilateral or bilateral nerve dysfunction. Such patients may complain of a slowly progressive loss of vision in one or both eyes or, complain of blurred or distorted vision even though visual acuity is 1.0 in both eyes. Such patients have evidence of chronic ON by clinical testing (e.g., visual fields, color vision, contrast sensitivity) or electrophysiologic testing (VEPs). Sometimes, slowly progressive visual loss are the first symptom of the underlying MS.<sup>34</sup>

Asymptomatic or subclinical optic neuritis reported in numerous patients with apparently unilateral ON in their asymptomatic fellow eye. Many of these eyes also had impairment of visual acuity, visual fields, color vision, and contrast sensitivity. It is important to note that some of the subclinical findings in the contralateral eye of a patient with acute ON may reflect concurrent bilateral involvement. In the ONTT, visual fields followed longitudinally showed new and different patterns of defects over time, occasionally in both eyes.<sup>35</sup> Asymptomatic visual loss seems to be a universal feature of MS and has a substantial impact on the visual pathways, that it is present already at the time of clinical onset of the disease, and that any progression thereafter is slow enough to elude detection during several years of follow-up.<sup>36,37</sup>

### *Optic chiasmal and postchiasmal demyelinating optic neuritis.*

Demyelinating of the optic chiasm may produce optic chiasmal syndrome characterized by a bitemporal visual field defect associated with varying degrees of loss

of visual acuity and color vision during the course of well-documented MS, or it may be the initial manifestation of MS, preceding other neurologic signs and symptoms by weeks, months or even years.<sup>38</sup> Demyelination can occur anywhere along optic pathway, including the optic tract, optic radiations, and striate cortex. Some patients with MS develop homonymous visual field defects from demyelinating lesions of the postchiasmal visual sensory pathways. The defect may be quadrantic or hemianopic, complete or incomplete.<sup>39</sup>

## **Disorders of Ocular Motor System**

Patients with multiple sclerosis may develop disorders of fixation, ocular motility and ocular alignment. Nystagmus is the most common disorder of fixation associated with MS, including upbeat nystagmus, downbeat nystagmus, see-saw nystagmus, periodic alternating nystagmus and convergence-induced pendular nystagmus.<sup>40</sup> Jain et al. reported a 40-year-old patient with acquired horizontal and vertical nystagmus and severe oscillopsia secondary to multiple sclerosis had combined treatment with gabapentin and a vertical Kestenbaum type procedure. After gabapentin treatment (3,000 mg orally daily) the horizontal nystagmus was significantly reduced, and the patient developed a marked chin-up position. The vertical nystagmus remained unchanged, dampening on downgaze. A recession of both inferior rectus muscles reduced the nystagmus significantly in primary position, the abnormal head position disappeared, and oscillopsia completely resolved. Treatment increased visual acuity from 6/24 in the right eye and 6/60 in the left eye to 6/9 in both eyes.<sup>41,42</sup>

Various saccadic intrusions – inappropriate saccades that interfere with fixation – may occur in patients with multiple sclerosis, including ocular flutter, opsoclonus, and square-wave jerks. Clinical examination of eye movements, with attention to dynamic properties of saccades and the vestibulo-ocular reflex, takes only a few minutes to perform, but may provide better information concerning the presence of brainstem and cerebellar involvement.<sup>43,44</sup> Prospective studies are required to determine whether the development of abnormalities with ocular motor testing are predictive of disease activity and progressive disability in MS.<sup>45</sup>

Disturbances of ocular motility or alignment may develop during the course of MS, usually result from demyelinating lesions in the brainstem that affect supranuclear, internuclear, nuclear, or fascicular pathways. Frohman et al. compared the accuracy of clinical detection of internuclear ophthalmoparesis (INO) with that of quantitative infrared oculography. Oculographic techniques significantly enhance the precision of INO detection to the clinical exam.<sup>44,46–49</sup>

Reche Sainz et al. (2002) presented a 38-year-old woman with a episode of homonymous horizontal diplopia at distance. She was orthophoric a near but had esotropia at distance. Neurological evaluation was normal but multiple demyelinating lesions were shown in

the magnetic resonance scan, with increased intrathecal IgG production. Double vision improved after corticosteroid mega-doses.<sup>50</sup>

## Conclusion

Patients with MS may develop disturbances of visual sensory function and disorders of ocular motor system. These disturbances may precede, or occur coincidentally with neurologic manifestations. Sometimes, disturbances of the visual sensory system are themselves asymptomatic but may be important findings that establish

the diagnosis of MS in a patient with a single symptomatic neurologic deficit. Visual impairment occurs in numerous patients with MS and may be the presenting symptom. MRI scanning of the brain should be undertaken in all cases of acute ON for diagnostic and prognostic purposes. Disorders of ocular motor system are frequently the initial sign of multiple sclerosis and occur as its presenting sign weeks, month, or years before other neurologic symptoms and signs develop. We emphasize that cooperation of neurologist and ophthalmologist plays an important role for clinical evaluation of MS patients.

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## NEUROOFTALMOŠKE MANIFESTACIJE MULTIPLE SKLEROZE

### SAŽETAK

Autori pregledno prikazuju oftalmološke manifestacije u bolesnika s multiplom sklerozom (MS), kako one koje zahvaćaju vizualni senzorni sustav tako i one koje zahvaćaju očni motorni sustav. Poremećaji vidne funkcije mogu prethoditi, javiti se istodobno ili mogu pratiti neurološke manifestacije. Poremećaji vida nisu rijetki u bolesnika s MS i obično nastaju uslijed akutne demijelinizirajuće optičke neuropatije. Pažljiv pregled bolesnika s MS koji nikada nisu

imali akutni optički neuritis, može otkriti asimptomatska oštećenja vida. Ova asimptomatska oštećenja vida čini se da predstavljaju univerzalno obilježje multiple skleroze. Bolesnici s multiplom sklerozom mogu razviti i poremećaje fiksacije, očne pokretljivosti i poremećaje ravnoteže očnih mišića. Poremećaj očnog motornog sustava nerijetko je inicijalni znak multiple skleroze i može se manifestirati tjednima, mjesecima ili godinama prije drugih neuroloških simptoma i znakova.