SMGroup

Ocular Involvement in Multiple Sclerosis

Fatih C Gundogan[1]*, Salih Uzun[2], Önder Ayyıldız[1] and Gokhan Ozge[1]

[1]Gulhane Military Medical Academy, Ophthalmology, Turkey

[2]Etimesgut Military Hospital, Ophthalmology, Turkey

***Corresponding author:** Fatih C Gundogan, GATA Medical School, Department of Ophthalmology, Ankara, Turkey, Email: fgundogan@yahoo.com

Published Date: May 10, 2016

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]. **ON**

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].

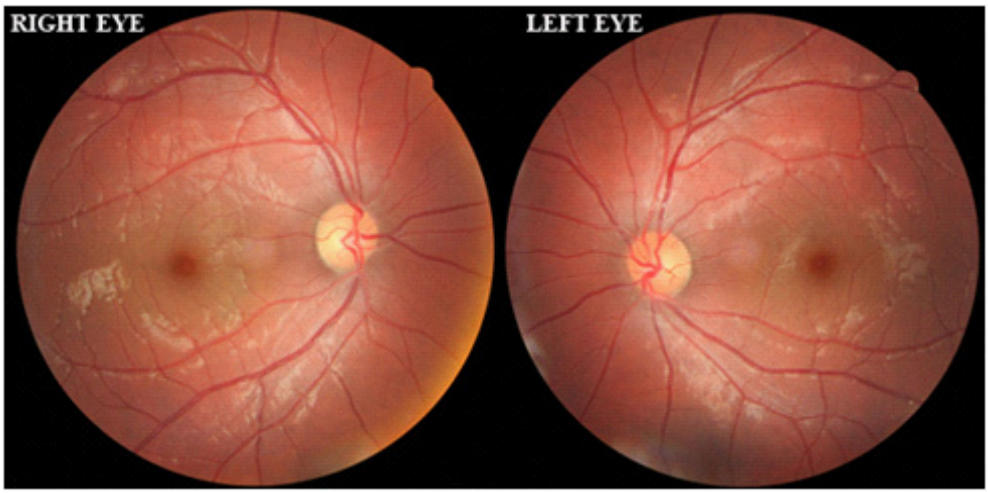

Figure 1: Vague optic disc temporal pallor in the right eye of a multiple sclerosis patient who had an optic neuritis attack 2 months ago. Visual acuities were 0.2/1.0 in the right and left eyes, respectively.

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.

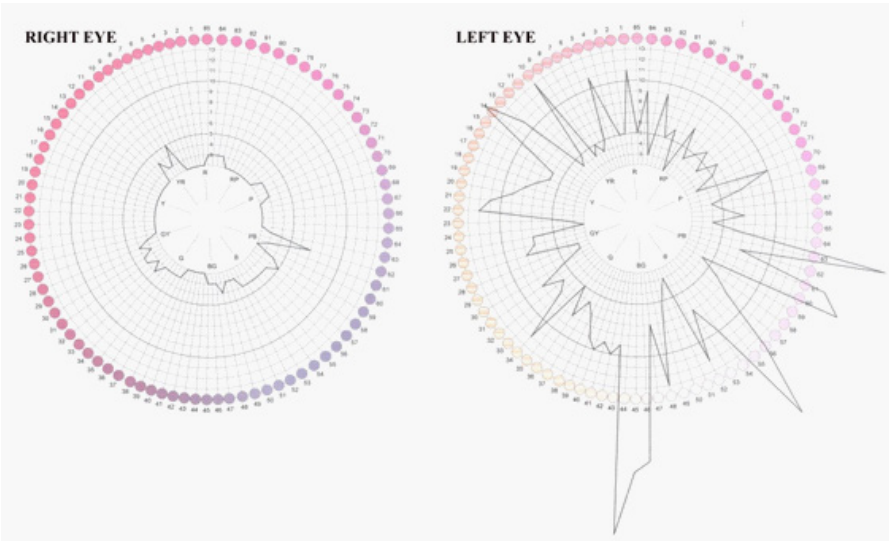

Figure 2: Farnsworth-Munsell 100 Hue test result of a patient with previous optic neuritis attack in the left eye. Total error scores were 64 (average discrimination) in the right eye and 515 (low discrimination) in the left eye.

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 abducting 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 macro-saccadic 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 oscillopsia 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].

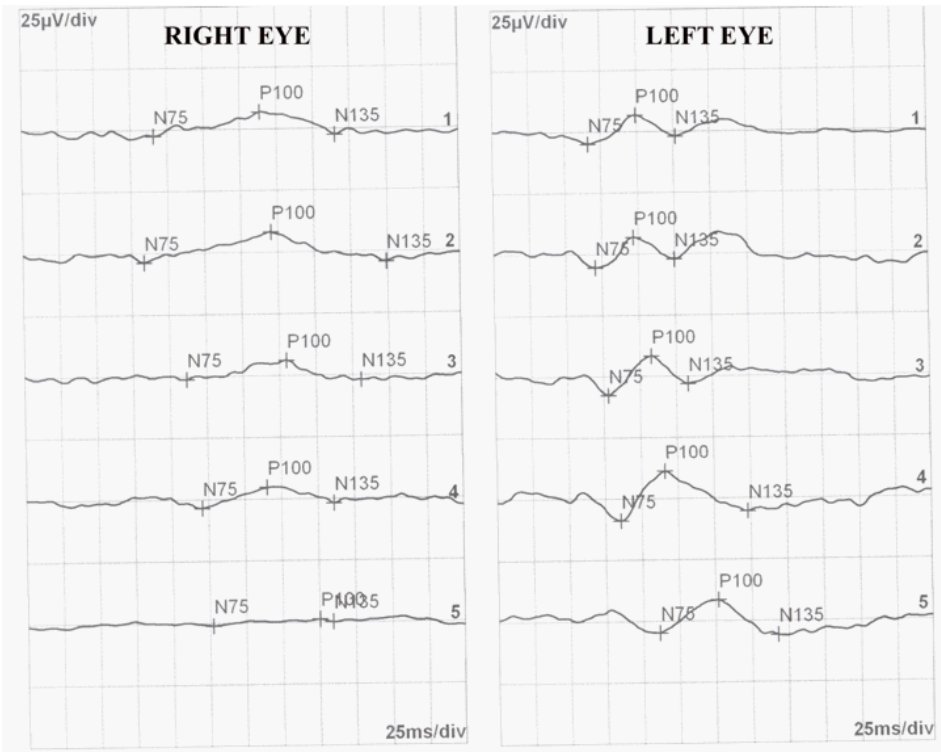

Figure 3: Pattern VEP results of the patient with a history of optic neuritis in the right eye.

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.

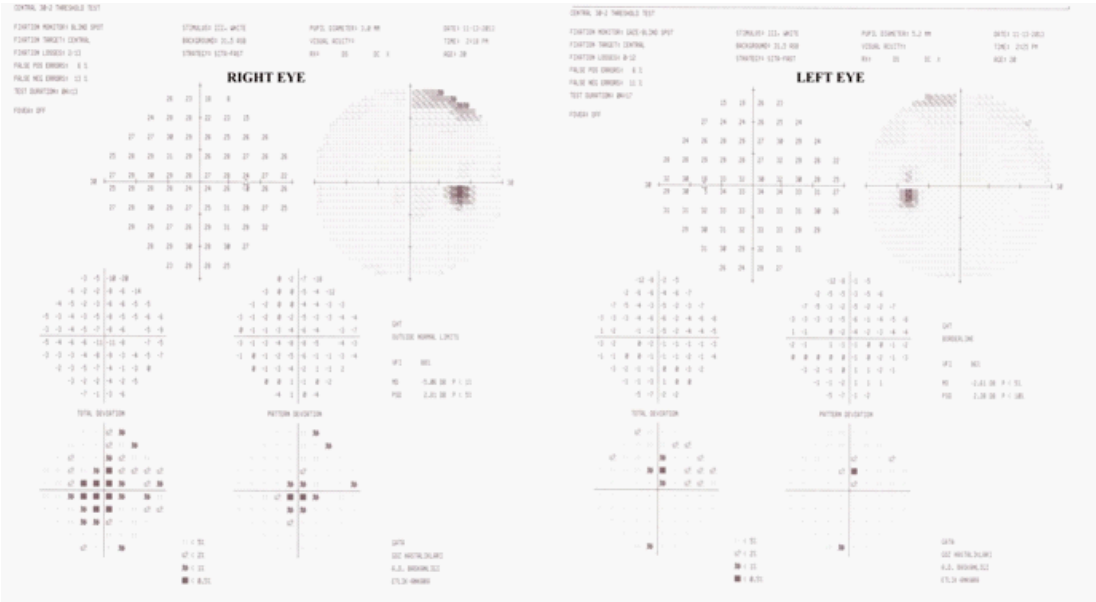

Figure 4: Central scotoma in the right eye of a patient with optic neuritis attack.

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].

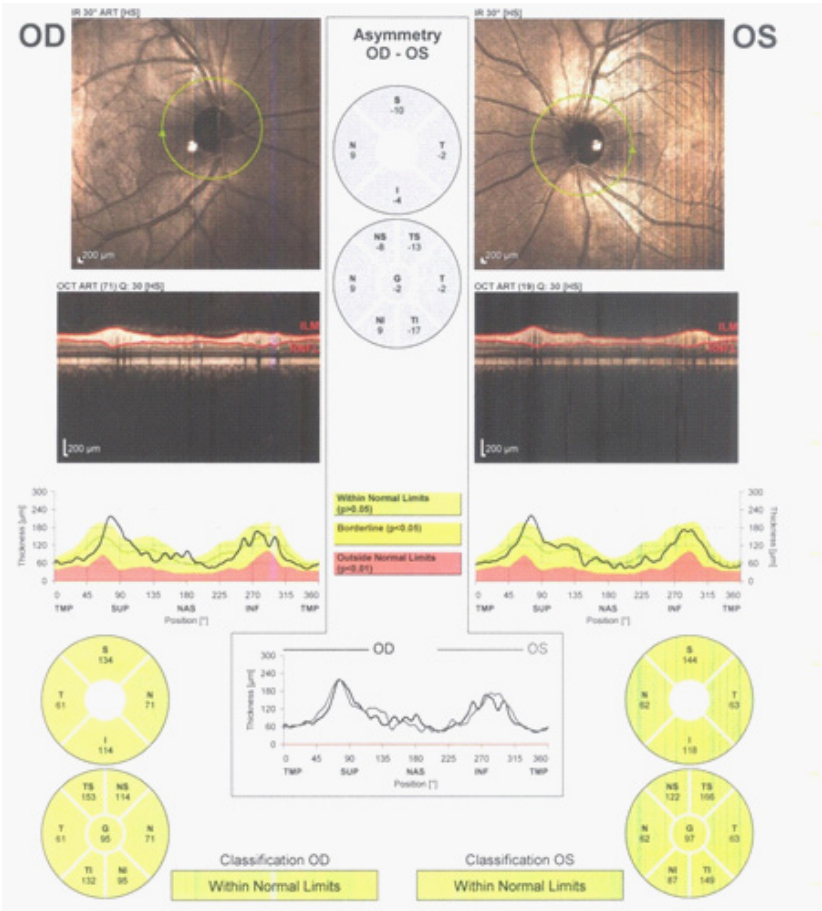

Figure 5: Significantly thinned retinal nerve fiber layer in both eyes of a patient with bilateral previous multiple optic neuritis attacks.

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].

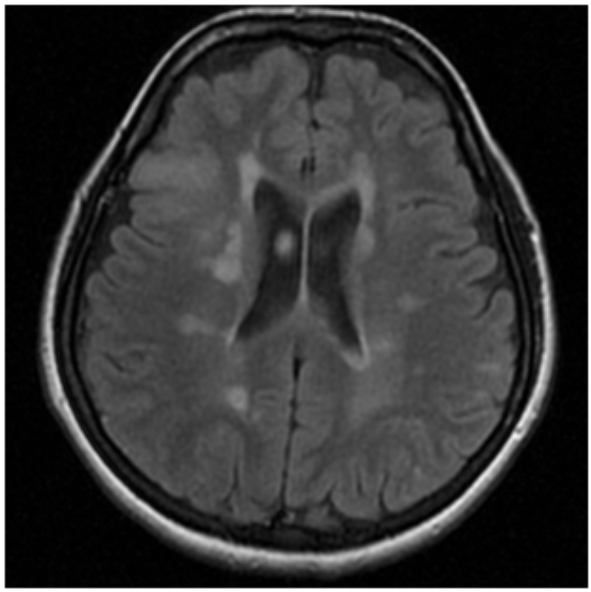

Figure 6: Periventricular, subcortical, juxtacortical ovoid hyper intense demyelinization lesions in a patient with multiple sclerosis.

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

1. Beisse C. Eye and multiple sclerosis. Ophthalmologe. 2014; 111: 708.
2. Roodhooft JM. Summary of eye examinations of 284 patients with multiple sclerosis. Int J MS Care. 2012; 14: 31-38.
3. Palau AE, Morgan ML, Yalamanchili S, Lee AG. Neuro-Ophthalmology Annual Review. Asia Pac J Ophthalmol (Phila). 2014; 3: 104-125.
4. Nikpoor N, Gregori N, Chang JS. More than just multiple sclerosis. JAMA Ophthalmol. 2014; 132: 885-886.
5. Swingler RJ, Compston DA. The morbidity of multiple sclerosis. Q J Med. 1992; 83: 325-337.
6. Salter AR, Tyry T, Vollmer T, Cutter GR, Marrie RA. "Seeing" in NARCOMS: a look at vision-related quality of life in the NARCOMS registry. Mult Scler. 2013; 19: 953-960.
7. Torres-Torres R, Sanchez-Dalmau BF. Treatment of acute optic neuritis and vision complaints in multiple sclerosis. Curr Treat Options Neurol. 2015; 17: 328.
8. Narayanan D, Cheng H, Tang RA, Frishman LJ. Longitudinal Evaluation of Visual Function in Multiple Sclerosis. Optom Vis Sci. 2015; 92: 976-985.
9. Kotov SV, Kuchina NV, Lapitan DG, Milanich AI, Rogatkin DA, Iakushina TI, et al. Low contrast non-color vision in patients with multiple sclerosis. Zh Nevrol Psikhiatr Im S S Korsakova. 2015; 115: 16-20.
10. Ma SL, Shea JA, Galetta SL, Jacobs DA, Markowitz CE, Maguire MG, et al. Self-reported visual dysfunction in multiple sclerosis: new data from the VFQ-25 and development of an MS-specific vision questionnaire. Am J Ophthalmol. 2002; 133: 686-692.

11. Smith KJ, McDonald WI. The pathophysiology of multiple sclerosis: the mechanisms underlying the production of symptoms and the natural history of the disease. Philos Trans R Soc Lond B Biol Sci. 1999; 354: 1649-1673.

12. O'Doherty M, Flitcroft DI. An unusual presentation of optic neuritis and the Pulfrich phenomenon. J Neurol Neurosurg Psychiatry. 2007; 78: 906-907.

13. Confavreux C, Vukusic S. The clinical course of multiple sclerosis. Handb Clin Neurol. 2014; 122: 343-369.

14. [No authors listed]. The clinical profile of optic neuritis. Experience of the Optic Neuritis Treatment Trial. Optic Neuritis Study Group. Arch Ophthalmol. 1991; 109: 1673-1678.

15. Balcer LJ. Clinical practice. Optic neuritis. N Engl J Med. 2006; 354: 1273-1280.

16. Gundogan FC, Tas A, Altun S, Oz O, Erdem U, Sobaci G. Color vision versus pattern visual evoked potentials in the assessment of subclinical optic pathway involvement in multiple sclerosis. Indian J Ophthalmol. 2013; 61: 100-103.

17. Gundogan FC, Demirkaya S, Sobaci G. Is optical coherence tomography really a new biomarker candidate in multiple sclerosis? - A structural and functional evaluation. Invest Ophthalmol Vis Sci. 2007; 48: 5773-5781.

18. Zhang Y, Liang X, Wei S, Li H. Differential Diagnosis for Multiple Sclerosis-related Optic Neuritis. Eye Sci. 2015; 30: 23-28.

19. Wilhelm H, Schabet M. The Diagnosis and Treatment of Optic Neuritis. Dtsch Arztebl Int. 2015; 112: 616-625.

20. Golnik KC. Neuro-Ophthalmology Annual Review. Asia Pac J Ophthalmol (Phila). 2015; 4: 307-315.

21. Optic Neuritis Study Group. Visual function 15 years after optic neuritis: a final follow-up report from the Optic Neuritis Treatment Trial. Ophthalmology. 2008; 115: 1079-1082.

22. Vleugels L, Lafosse C, van Nunen A, Nachtergaele S, Ketelaer P, Charlier M, et al. Visuoperceptual impairment in multiple sclerosis patients diagnosed with neuropsychological tasks. Mult Scler. 2000; 6: 241-254.

23. Moura AL, Teixeira RA, Oiwa NN, Costa MF, Feitosa-Santana C, Callegaro D, et al. Chromatic discrimination losses in multiple sclerosis patients with and without optic neuritis using the Cambridge Colour Test. Vis Neurosci. 2008; 25: 463-468.

24. Saidha S, Sotirchos ES, Oh J, Syc SB, Seigo MA, Shiee N, et al. Relationships between retinal axonal and neuronal measures and global central nervous system pathology in multiple sclerosis. JAMA Neurol. 2013; 70: 34-43.

25. Fernandes DB, Raza AS, Nogueira RG, Wang D, Callegaro D, Hood DC, Monteiro ML. Evaluation of inner retinal layers in patients with multiple sclerosis or neuromyelitis optica using optical coherence tomography. Ophthalmology. 2013; 120: 387-394.

26. Saidha S, Sotirchos ES, Ibrahim MA, Crainiceanu CM, Gelfand JM, Sepah YJ, et al. Microcystic macular oedema, thickness of the inner nuclear layer of the retina, and disease characteristics in multiple sclerosis: a retrospective study. Lancet Neurol. 2012; 11: 963-972.

27. Trip SA, Schlottmann PG, Jones SJ, Altmann DR, Garway-Heath DF, Thompson AJ, et al. Retinal nerve fiber layer axonal loss and visual dysfunction in optic neuritis. Ann Neurol. 2005; 58: 383-391.

28. Costello F, Coupland S, Hodge W, Lorello GR, Koroluk J, Pan YI, et al. Quantifying axonal loss after optic neuritis with optical coherence tomography. Ann Neurol. 2006; 59: 963-969.

29. Pulicken M, Gordon-Lipkin E, Balcer LJ, Frohman E, Cutter G, Calabresi PA. Optical coherence tomography and disease subtype in multiple sclerosis. Neurology. 2007; 69: 2085-2092.

30. Green AJ, McQuaid S, Hauser SL, Allen IV, Lyness R. Ocular pathology in multiple sclerosis: retinal atrophy and inflammation irrespective of disease duration. Brain. 2010; 133: 1591-1601.

31. Tátrai E, Simó M, Iljicsov A, Németh J, Debuc DC, Somfai GM. *In vivo* evaluation of retinal neurodegeneration in patients with multiple sclerosis. PLoS One. 2012; 7: e30922.

32. Cennamo G, Romano MR, Vecchio EC, Minervino C, Della Guardia C, Velotti N, et al. Anatomical and functional retinal changes in multiple sclerosis. Eye (Lond). 2016; 30: 456-462.

33. Gordon LK, Goldstein DA. Gender and uveitis in patients with multiple sclerosis. J Ophthalmol. 2014; 2014: 565262.

34. Hildebrandt AL, Mackensen F. Uveitis in multiple sclerosis: Overview and perspectives. Ophthalmologe. 2014; 111: 733-739.

35. Biousse V, Trichet C, Bloch-Michel E, Roullet E. Multiple sclerosis associated with uveitis in two large clinic-based series. Neurology. 1999; 52: 179-181.

36. Messenger W, Hildebrandt L, Mackensen F, Suhler E, Becker M, Rosenbaum JT. Characterisation of uveitis in association with multiple sclerosis. Br J Ophthalmol. 2015; 99: 205-209.

37. Raja SC, Jabs DA, Dunn JP, Fekrat S, Machan CH, Marsh MJ, et al. Pars planitis: clinical features and class II HLA associations. Ophthalmology. 1999; 106: 594-599.

38. Jakob E, Reuland MS, Mackensen F, Harsch N, Fleckenstein M, Lorenz HM, et al. Uveitis subtypes in a german interdisciplinary uveitis center--analysis of 1916 patients. J Rheumatol. 2009; 36: 127-136.

39. Bazelier MT, Mueller-Schotte S, Leufkens HG, Uitdehaag BM, van Staa T, de Vries F. Risk of cataract and glaucoma in patients with multiple sclerosis. Mult Scler. 2012; 18: 628-638.

40. Downey DL, Stahl JS, Bhidayasiri R, Derwenskus J, Adams NL, Ruff RL, et al. Saccadic and vestibular abnormalities in multiple sclerosis: sensitive clinical signs of brainstem and cerebellar involvement. Ann N Y Acad Sci. 2002; 956: 438-440.

41. Kurtzke JF, Hyllested K. Multiple sclerosis in the Faroe Islands: I. Clinical and epidemiological features. Ann Neurol. 1979; 5: 6-21.

42. Frohman EM, Frohman TC, Zee DS, McColl R, Galetta S. The neuro-ophthalmology of multiple sclerosis. Lancet Neurol. 2005; 4: 111-121.

43. Wall M, Wray SH. The one-and-a-half syndrome--a unilateral disorder of the pontine tegmentum: a study of 20 cases and review of the literature. Neurology. 1983; 33: 971-980.

44. Sarvananthan N, Surendran M, Roberts EO, Jain S, Thomas S, Shah N, et al. The prevalence of nystagmus: the Leicestershire nystagmus survey. Invest Ophthalmol Vis Sci. 2009; 50: 5201-5206.

45. Clifford DB, De Luca A, Simpson DM, Arendt G, Giovannoni G, Nath A. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. Lancet Neurol. 2010; 9: 438-446.

46. Jiang H, Delgado S, Tan J, Liu C, Rammohan KW, DeBuc DC, et al. Impaired retinal microcirculation in multiple sclerosis. Mult Scler. 2016; .

47. Modrzejewska M, Karczewicz D, Wilk G. Assessment of blood flow velocity in eyeball arteries in multiple sclerosis patients with past retrobulbar optic neuritis in color Doppler ultrasonography. Klin Oczna. 2007; 109: 183-186.

48. Akçam HT, Capraz IY, Aktas Z, Batur Caglayan HZ, Ozhan Oktar S, Hasanreisoglu M, et al. Multiple sclerosis and optic nerve: an analysis of retinal nerve fiber layer thickness and color Doppler imaging parameters. Eye (Lond). 2014; 28: 1206-1211.

49. Becker CC, Gidal BE, Fleming JO. Immunotherapy in multiple sclerosis, Part 1. Am J Health Syst Pharm. 1995; 52: 1985-2000.

50. Horton L, Conger A, Conger D, Remington G, Frohman T, Frohman E, et al. Effect of 4-aminopyridine on vision in multiple sclerosis patients with optic neuropathy. Neurology. 2013; 80: 1862-1866.

51. Shery T, Proudlock FA, Sarvananthan N, McLean RJ, Gottlob I. The effects of gabapentin and memantine in acquired and congenital nystagmus: a retrospective study. Br J Ophthalmol. 2006; 90: 839-843.

52. Mehta AR, Kennard C. The pharmacological treatment of acquired nystagmus. Pract Neurol. 2012; 12: 147-153.

53. Jain S, Proudlock F, Constantinescu CS, Gottlob I. Combined pharmacologic and surgical approach to acquired nystagmus due to multiple sclerosis. Am J Ophthalmol. 2002; 134: 780-782.

54. Wagner CA, Goverman JM. Novel Insights and Therapeutics in Multiple Sclerosis. F1000Res. 2015; 4: 517.

55. Turaka K, Bryan JS. Does fingolimod in multiple sclerosis patients cause macular edema? J Neurol. 2012; 259: 386-388.

56. Jain N, Bhatti MT. Fingolimod-associated macular edema: incidence, detection, and management. Neurology. 2012; 78: 672-680.

57. Wang X, Jia Y, Spain R, Potsaid B, Liu JJ, Baumann B, et al. Optical coherence tomography angiography of optic nerve head and parafovea in multiple sclerosis. Br J Ophthalmol. 2014; 98: 1368-1373.

58. Kerrison JB, Flynn T, Green WR. Retinal pathologic changes in multiple sclerosis. Retina. 1994; 14: 445-451.

59. Gonzalez-Lopez JJ, Rebolleda G, Leal M, Oblanca N, Muñoz-Negrete FJ, Costa-Frossard L, et al. Comparative Diagnostic Accuracy of Ganglion Cell-Inner Plexiform and Retinal Nerve Fiber Layer Thickness Measures by Cirrus and Spectralis Optical Coherence Tomography in Relapsing-Remitting Multiple Sclerosis. Biomed Res Int. 2014; 2014: 128517.

60. Petzold A, de Boer JF, Schippling S, Vermersch P, Kardon R, Green A, et al. Optical coherence tomography in multiple sclerosis: a systematic review and meta-analysis. Lancet Neurol. 2010; 9: 921-932.