ORIGINAL ARTICLE

Comparison of Visual Field Parameters in Early and Advanced Stages of Multiple Sclerosis Patients Without a History of Optic Neuritis

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ABSTRACT

This study compared the visual field parameters of multiple sclerosis patients without optic neuritis in early versus advanced stage of the disease. Patients were divided into two groups: group 1 (early stage, $n=14$) constituted of patients with Expanded Disability Status Scale scores <3 and group 2 (advanced stage, $n=13$) constituted of patients with Expanded Disability Status Scale scores ≥ 3 . Mean visual acuities in both groups were similar ($p=0.674$). Mean sensitivity, mean defect, loss of variance, reliability factor parameters (Octopus 101 perimeter) of groups 1 and 2 were 24.17 ± 3.62 , 21.81 ± 3.04 ; 4.14 ± 3.05 , 6.49 ± 2.58 ; 21.61 ± 22.17 , 33.31 ± 18.67 ; and 1.57 ± 2.79 , 2.59 ± 3.09 , respectively. Compared with group 1, mean sensitivity was significantly lower in group 2 ($p=0.013$). Mean defect ($p=0.004$) and loss of variance ($p=0.042$) parameters in group 2 were significantly higher than in group 1. Mean reliability factor was similar between two groups ($p=0.211$). Multiple sclerosis may alter visual field parameters without severe loss of visual acuity by possibly involving optic pathways other than optic nerve.

Keywords: Expanded disability status scale, loss variance, mean defect, mean sensitivity, multiple sclerosis, optic neuritis, visual field

INTRODUCTION

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system and the leading cause of disability in young adults. Afferent pregeniculate visual pathways (retina, optic nerves, chiasm, and tracts) are preferential targets of inflammation, demyelization, and axonal degeneration.¹ Acute idiopathic demyelinating optic neuritis (ON) is frequently the initial clinical manifestation of multiple sclerosis and nearly half of the MS patients develop this entity.^{2,3} Apart from ON, current investigations have reported subtle visual impairments (e.g., worse scores

on low-contrast acuity and colour-sensitivity testing) in MS patients without history of ON when compared with age-matched controls.^{4,5} With the advent of newer technology, structural information about optic nerve disease is attainable, it has been shown that MS patients with and without a history of ON demonstrate loss of axons in the retinal nerve fibre layer (RNFL).^{6,7}

The Expanded Disability Status Scale (EDSS) is a method of quantifying disability in MS and monitoring changes in the level of disability over time. The EDSS quantifies disability in eight functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and

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bladder, visual, cerebral, and other).⁸ EDSS has been used successfully to assess impairment for natural history and treatment studies in patients with MS.⁹

The aim of this study is to compare the visual field parameters of MS patients without ON in early versus advanced stage of the disease as graded by EDSS.

MATERIALS AND METHODS

The study adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. Patients seen in the outpatient neurology clinics were invited to participate in the study and enrolled after inclusion criteria were met and informed consent obtained. Enrolled patients were divided into two groups: group 1 ($n=14$): patients with EDSS scores <3 (early stage) and group 2 ($n=13$): patients with EDSS scores ≥ 3 (advanced stage of the disease).¹⁰ Octopus 101 perimeter and dG2 program was used for visual field assessment. To eliminate the learning effect, the second visual field of each eye was included in the statistical analysis. Outputs with reliability factor $>15\%$ were excluded from the study. Visual acuities (va) in logMAR, mean sensitivities (ms), mean defects (md), loss of variance (lv), and reliability factor (rf) parameters from both eyes of patients were compared between the two groups.

Statistical analysis was performed with Statistical Package for the Social Sciences software version 13.0 (SPSS Inc., Chicago, IL, USA). Differences between groups were analysed by independent-samples t tests and p value lower than 0.05 was considered statistically significant.

RESULTS

In group 1, 8 patients were female and 6 were male. In group 2, 8 patients were female and 5 were male. The mean ages of groups 1 and 2 were 33.92 ± 6.97 (23–48) and 37.46 ± 9.15 (22–52) years, respectively ($p=0.115$). The mean EDSS scores of groups 1 and 2 were 1.25 ± 0.37 and 4.61 ± 1.79 , respectively ($p<0.001$).

Mean va, ms, md, lv, and rf parameters of groups 1 and 2 were 0.029 ± 0.092 , 0.021 ± 0.032 ; 24.17 ± 3.62 , 21.81 ± 3.04 ; 4.14 ± 3.05 , 6.49 ± 2.58 ; 21.61 ± 22.17 , 33.31 ± 18.67 ; and 1.57 ± 2.79 , 2.59 ± 3.09 , respectively (Table 1).

Mean ms ($p=0.013$) parameter in group 2 was significantly lower than group 1 (Figure 1). Mean md ($p=0.004$) (Figure 2) and lv ($p=0.042$) (Figure 3) parameters in group 2 were significantly higher than in group 1. Mean va ($p=0.674$) and rf ($p=0.211$) parameters were similar between two groups.

TABLE 1. The mean and the standard deviation of EDSS, va, ms, md, lv, and rf values.

	Group 1	Group 2	p Value
EDSS	1.25 ± 0.37	4.61 ± 1.79	0.001*
va	0.029 ± 0.092	0.021 ± 0.032	0.674
ms	24.17 ± 3.62	21.81 ± 3.04	0.013*
md	4.14 ± 3.05	6.49 ± 2.58	0.004*
lv	21.61 ± 22.17	33.31 ± 18.67	0.042*
rf	1.57 ± 2.79	2.59 ± 3.09	0.211

EDSS=Expanded Disability Status Scale; va=visual acuity; ms=mean sensitivity; md=mean defect; lv=loss variance, rf=reliability factor.

DISCUSSION

Recent findings in MS patients have raised the question of whether primary neurodegenerative changes can occur in the retina independent of optic nerve inflammation. A plethora of studies have implicated early axonal loss in MS patients even in the absence of clinically evident optic neuritis. Fairless et al. reported that before manifestation of ON, degeneration of retinal ganglion cell bodies had already begun and ultrastructural signs of axon degeneration could be detected in a rat model.¹¹ Reis et al. have found evidence for independent damage of retinocortical parallel pathways in patients with MS without previous ON, in distinction to the post-ON group in their study.¹² Gelfand et al. performed spectral-domain optical coherence tomography (OCT) in eyes without ON and demonstrated that retinal axonal thinning begins early in the course of MS and independently of the occurrence of symptomatic ON.¹³ Serbecic et al. analysed MS patients with and without ON prospectively with the high resolution spectral-domain OCT device and determined significantly reduced RNFL globally, and in at least one of the peripapillary sectors, compared with age- or sex-matched healthy controls.¹⁴ Additionally, recent studies have shown that macular thickness and volume are decreased in the eyes of MS patients with or without ON.^{15,16} Siger et al. suggested that measurement of RNFL by OCT in MS patients without ON might be used as a structural surrogate marker of axonal destruction in brain tissue injury.¹⁷

Previous studies that have evaluated correlations between EDSS scores, RNFL thickness, and visual field parameters in MS patients without ON have noted different results. Pueyo et al. found no significant correlation between RNFL thickness and the neurological impairment evaluated by the EDSS scale.¹⁸ Siepmann et al. reported that EDSS scores correlated with md, visual field-pattern standard deviation, RNFL thickness, and macular volume in MS patients without previous ON.¹⁹ In another study, RNFL thickness and perimetric scores were significantly lower in MS group without a history of ON and

FIGURE 1. Box-plot graph showing the distribution of mean sensitivity values in two groups. The black lines in diagram show the median values of the groups.

FIGURE 2. Box-plot graph illustrates the distribution of mean defect in two groups. The black lines in diagram indicate the median values of the groups.

in the unaffected eyes of MS patients with unilateral ON, compared with controls.²⁰ Cheng *et al.* made a topographic comparison between standard automated perimetry (SAP) and RNFL thickness measurements in eyes of patients with MS, with and without a history of ON. They found good agreement between

SAP and RNFL thickness in ON eyes but not in non-ON eyes.²¹

Congruent with current literature, our results indicate that there is chronic and progressive functional visual field deterioration in MS, even in the absence of ON. MS values in group 2 were

FIGURE 3. Box-plot demonstrating the distribution of loss variance values in two groups. The black lines in diagram show the median values of the groups.

significantly lower compared with group 1. We believe that MS related loss of nerve fibres is the main reason for the decrement of ms in this group. Patients with advanced stage MS had higher mean md and lv values compared with patients with early stage MS. Our results support the findings that MS causes diffuse and focal visual field defects and progressively damages the uniformity of the visual field. Contrary to other findings, va was not significantly impaired in either group. Retinal ganglion cells located near the fovea have smaller cell bodies and comparatively smaller axons compared with those located peripherally because ganglion cell size increases with eccentricity.²² Cells with small axons may have resistance to the subclinical demyelination, and axonal degeneration process in MS. Although the number of patients in our study was relatively small, mean EDSS scores between groups were significantly different (1.25 ± 0.37 in group 1 and 4.61 ± 1.79 in group 2; $p < 0.001$). We think that this wide EDSS difference between the groups strengthens the reliability of our data. Visual field testing results may be influenced by other factors. Persons with MS may have poor reaction speed, cognition, and testing abilities. These non-visual factors may worsen scoring of visual field testing. However the reliability factors in our study were statistically similar between the two groups (1.57 ± 2.79 and 2.59 ± 3.09 in groups 1 and 2, respectively; $p = 0.211$).

In summary, MS may damage visual fields progressively and insidiously without decreasing va

dramatically in patients without ON. The significantly deteriorated perimetric scores in advanced stage patients, compared with early-stage patients, implies chronic damage of retinocortical pathways in MS patients without a history of ON. The deteriorated perimetric scores could be the result of chronic axonal loss due to the disease process of MS or subclinical, painless episodes of ON. Multiple sclerosis may primarily target the retina or retina may be affected by retrograde degeneration of nerve cells from sub-clinical post-chiasmal lesions.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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