Original Article

The Effect of Intravenous Prednisolone Treatment on the Retinal Nerve Fiber Layer in Multiple Sclerosis Patients with Optic Neuritis

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Abstract

Objectives: The aim of this study was to investigate the potential impact of intravenous (IV) prednisolone treatment on the retinal nerve fiber layer (RNFL) in multiple sclerosis (MS) patients with optic neuritis (ON).

Methods: The demographic features, systemic illnesses, laboratory results, ophthalmological examination findings and RNFL measurements of 28 MS patients who had IV prednisolone treatment for ON and of 24 MS patients with ON that was not treated were retrieved and reviewed retrospectively.

Results: Of the 52 patients included in the study, 31 were women and 21 were men. The average age in the prednisolone group was 32 ± 7.15 years (range: 28-40 years) and it was $34\pm.2$ years (range: 30-42 years) in patients who did not receive treatment. The initial RNFL in the treatment group was $116.81\pm5.41\mu m$ and it was 78.13 ± 3.94 µm at the third month, while it was 118.2 ± 6.07 µm initially and 80.09 ± 5.18 µm at the third month in the untreated group. There was no statistically significant difference between the groups in the RNLF evaluation ($p>0.05$).

Conclusion: Treatment with IV prednisolone had no distinct effect on RNFL.

Keywords: Multiple sclerosis, optic neuritis, prednisolone, retinal nerve fiber layer.

Introduction

Optic neuritis (ON) is inflammation that damages the optic nerve and is characterized by a sudden onset of vision loss and dyschromatopsia. Visual symptoms typically progress for a few weeks and then begin to improve on their own within the first month. ON is often associated with existing or future multiple sclerosis (MS), and is frequently the first symptom. According to data provided by the Optic Neuritis Study Group (ONSG), the 10-year risk of developing MS after an episode of ON was 38%, and 56% in those with 1 or more demyelinating lesions observed with magnetic resonance imaging (1).

MS is a demyelinating disease in which inflammation affects the central nervous system. It most frequently develops in young adults. In a histopathological review of MS patients, partially preserved axons, numerous demyelinated areas, and loss of oligodendrocyte and astroglial scarring were observed (2). Thinning of nerve fibers without myelin was significant in identifying the axonal loss.

The retinal nerve fiber layer (RNFL) comprises nonmyelinated retinal ganglion cell axons and is the most proximal region of the afferent visual pathway. Changes in the thickness of the RNLF reflect alteration in the axonal integrity of

the optic nerve. Retrobulbar damage due to axonal degeneration is identified by optic nerve pallor and RNFL defect (3).

Optical Coherence Tomography (OCT) is now used in a variety of neuro-ophthalmic cases. Among them are anterior ischemic optic neuropathy, toxic and other inflammatory optic neuropathies, MS, optic-spinal MS, pseudotumor cerebri, migraine, optic nerve head drusen, Leber's hereditary optic neuropathy, Alzheimer's disease, and Friedrich's ataxia (4). In studies conducted with MS patients, there was demonstrated RNFL thinning. Such variations in the RNFL were correlated with the activity of the disease and the size of the demyelinating plate identified in MRG (4, 5).

OCT is a noninvasive and easy-to-use medical imaging system which provides a cross-sectional image of the retina using the reflection and absorption of light waves (6). It can provide a high resolution assessment of the anatomical structure of the retina, and is also used in the examination of the optic nerve and peripapillary RSLT.

More than 50% of MS patients have ON at some point (7). Thinning of the RNFL has also been demonstrated in MS patients who have never had ON (7, 8). The purpose of this study was to assess the impact of IV methylprednisolone treatment on the thickness of RNFL in MS patients.

Methods

The files of patients diagnosed with ON in January 2013 through May 2015 were reviewed and examined retrospectively. Approval of the study protocol was obtained from the institutional review board. The study and data collection protocols complied with all local laws and the principles of the Declaration of Helsinki.

A total of 52 eyes of 52 patients complying with the study criteria were included in the study. The patients were divided into 2 groups: those with ON that was treated and those with ON that was not treated. Of the 28 patients incorporated in the treatment group, 17 were women (61%) and 11 were men (39%). Of the 24 patients who were not treated, 14 were women (58%) and 10 were men (42%).

The treatment protocol was 250 mg intravenous (IV) methylprednisolone; 1 mg/kg/day oral prednisone was administered to the patients in the treatment group for 3 days, 4 times a day. The non-treatment patients were those who refused the treatment or had vital contraindications for treatment.

Inclusion Criteria

- Those who were clinically and definitively diagnosed with MS,
- Those with a visual acuity level that was suitable for OCT measurement, and
- Those who had suffered an attack of ON at least 3 months previously.

Exclusion Criteria

- History of glaucoma or with intraocular pressure (IOP) exceeding 21mmHg,
- Existence of ocular trauma or history of other ocular surgery,
- Diabetic retinopathy identified by ophthalmoscopy,
- History of neurological disease,
- Existence of accompanying ocular disease (glaucoma, uveitis, etc.),
- Explicit refractive defect (a spherical defect of more than 4 diopters or an astigmatic defect of more than 3 diopters),
- Any vascular and autoimmune disease (diabetes mellitus, hypertension, Buerger's disease, vasculitis, etc.), or
- Opacities impeding retinal tomographic imaging.

A definitive clinical and laboratory diagnosis was made based on patient files. All demographic data, records of systemic disease present, initial ophthalmological examination results, and OCT results from both eyes were recorded. All participants underwent full ophthalmological examination. Reactive defects were measured using an automated refractometer. The best corrected visual acuity was identified for each eye using a Snellen chart. The anterior segment was evaluated through biomicroscopic examination. IOP was measured and indirect ophthalmoscopy examination was conducted with non-contact fundus lens (SuperField; Volk Optical, Inc., Mentor, OH, USA) after having achieved mydriasis.

RNFL thickness analysis was performed using a Stratus OCT device, version 6.0.2 (Carl Zeiss Meditec AG, Jena, Germany). The fast RNFL thickness protocol of 3 consecutive 360° scans with a diameter of 3.4 mm centered on the optic disc was performed. The OCT cross-section was fixed such that the center of the measurement circle was the center of the optic disc. RNFL results were recorded in the temporal, superior, and inferior quadrants. The video was monitored during the measurement and the imaging was repeated if required, in order to maintain the fixation point.

SPSS for Windows, Version 15.0 software (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis. An independent samples t-test was used for the comparison of measurements between groups. Comparisons within each group were conducted using a paired t-test. Statistical significance was determined to be $p < 0.05$.

Results

The mean age of the 52 patients recruited for the study was 35±6.4 years (range: 28-42 years); the mean age was 32±7.15 years (range: 28-40 years) in the treatment group and 34±8.2 years (range: 30-42 years) in the non-treatment group. The age difference between the 2 groups was not statistically significant (p>0.05).

Table 1. Retina nerve fiber layer thickness measurements

	Untreated group Initial measurement	Treated group Initial measurement	P	Untreated group 3rd month	Treated group 3rd month	P
Mean RNFL	118.12±6.07	116.81±5.41	>0.05	80.09±5.18	78.13±3.94	>0.05
Temporal RNF	72.03±8.19	70.11±3.19	>0.05	50.19±7.12	49.21±6.74	>0.05
Superior RNFL	133.89±5.02	130.12±7.72	>0.05	116.15±3.73	113.12±2.05	>0.05
Nasal RNFL	89.15±7.08	87.31±6.96	>0.05	72.52±4.94	71.44±7.06	>0.05
Inferior RNFL	136.51±6.12	131.37±4.65	>0.05	119.45±7.69	117.83±8.12	>0.05

RNFL: Retinal nerve fiber layer.

In all, 31 of the patients were women (59.6%) and 21 were men (40.4%); 17 of the 22 patients were women (61%) and 11 were men (39%) and 14 of 24 patients in the treatment group were women (58%) and 10 were men (42%). The gender difference between the 2 groups was not statistically significant (p>0.05).

Initially, the mean RNFL thickness was 116.81±5.41μm in the treated group and 118.12±6.07 μm in the untreated group. The RNFL in the treated group was 1.31 μm thinner than that of the other group; however, the difference was not statistically significant (p>0.05). The difference between the RNFL measurements of the 2 groups conducted in 4 quadrants was not statistically significant (Table 1).

At the third month, the mean RNFL thickness was 78.13±3.94 μm in the treated group and 80.09±5.18 μm in the untreated group. The difference of 1.86 μm was not statistically significant (p>0.05). The difference between the groups in RNFL thickness conducted in 4 quadrants was not statistically significant (Table 1).

Superior quadrant RNFL thickness had decreased by 17.00 μm in the treated group and 17.74 μm in the untreated group at the third month compared to the initial measurement; however, the difference between the 2 groups was not statistically significant (p>0.05). In the inferior quadrant, RNFL thickness had decreased by 13.54 μm in the treated group and by 17.06 μm in the untreated group after 3 months when compared with the initial measurement. The difference between the groups was not statistically significant (p>0.05). RNFL thickness in the temporal quadrant had decreased by 20.90 μm in the treated group and by 21.84 μm in the untreated group at the third month. The differ-

ence between the 2 groups was not statistically significant (p>0.05). It was also seen that RNFL thickness of the nasal quadrant had decreased by 15.87 μm in the treated group and by 16.63 μm in the untreated group after 3 months. The decrease in μm was greater in the untreated group than in the treated group, but the difference between the groups was not statistically significant (p>0.05) (Table 1).

RNFL thickness was seen to have decreased in all quadrants in the untreated group at the third month compared with the original measurements. The difference between the 2 groups was statistically significant (p<0.05). The comparison of all quadrants with each other yielded the observation that RNFL thickness, especially in the temporal quadrant, was thinner at the end of 3 months and this result was statistically significant (p<0.05). The comparison of thinning in other quadrants in the untreated group did not generate statistically significant results (p>0.05) (Table 1).

RNFL thickness had also decreased in all quadrants in the treated group at the third month compared with the initial measurements. The difference between the groups was statistically significant (p<0.05). The comparison of all quadrants revealed that RNFL thickness, particularly in the temporal quadrant, was thinner at the end of 3 months and that the difference was statistically significant (p<0.05). The comparison of thinning in other quadrants in the treated group did not generate statistically significant results (p>0.05) (Table 2).

Discussion

MS is a demyelinating disease of the central nervous system, the etiology of which is not properly known. Various factors are thought to be responsible for demyelination, and different neurological and systemic symptoms arise as a result of demyelination. Among them are motor deficits, followed by sensorial complaints, and finally, visual impairment. In general, it is a syndrome of multifocal disorders where gliosis is observed with histological demyelination and inflammatory variations in a series of relapses and remissions (5).

Following an episode of ON, inflammation of the optic

Table 2. Variation in retinal nerve fiber layer thickness in the treated and untreated groups

RNFL	Treated group	Untreated group	P
Initial RNFL	116.81±5.41	118.12±6.07	>0.05
3rd month RNFL	78.13±3.94	80.09±5.18	>0.05

RNFL: Retinal nerve fiber layer.

nerve causes axonal degeneration and optic nerve atrophy. In various studies, treatment of 1 g/day of IV methylprednisolone has been applied during an attack of ON to reduce visual loss; however few have assessed the impact of IV methylprednisolone upon RNFL thickness.

Corticosteroids are the initial episode treatment option in cases of ON (9). However, the appropriate dosage is still controversial (10). The use of oral prednisolone as a monotherapy is ineffective and may increase the risk of further attacks (11). ONSG data indicated that the patient group medicated first with 250 mg IV methylprednisolone 4 times for 3 days followed by 1 mg/kg/day oral prednisolone reached definitive visual acuity in shorter period than a placebo group (1). In a study conducted by Yahu et al. (12) on 20 patients diagnosed with ON, it was demonstrated that 11 patients medicated with IV methylprednisolone recovered their visual acuity in an average 13 days, while 9 patients not treated recovered their visual acuity in 18 days. Akyurekli et al. (13) studied 55 patients diagnosed with acute ON and found that 39 patients medicated with IV methylprednisolone improved in 11 days, while 16 patients not treated improved in 41 days. In our study, we observed that visual acuity improved 3 lines in patients treated with IV methylprednisolone in 7 days and in 3 days in the untreated group.

Studies of retinal neurodegeneration in MS have a long history and there has been an increase in the number of such studies in recent years. Voght (14) first demonstrated that there was a clear loss in the retinal nerve fiber layer during his assessment of patients with a history of ON using direct ophthalmoscopy and a green filter in 1913.

RNFL is largely made up of retinal ganglion cell axons. The optic nerves are also an extension of ganglion cells in the retina oriented toward the brain. In the retina, these axons are without myelin, but and they are covered by a myelin sheath formed by oligodendrocytes after exiting the retina. The retinal nerve fibers are the most proximal parts of the visual transmission pathways, and RNFL volume provides information about the axonal integrity of the optic nerve and its structure. That is, any variation in RNFL demonstrates axonal response.

Qualitative variations in RNFL in MS patients were defined for the first time by Frisen and Hoyt (15) in 1974. It was Parisi et al. (16), in 1999, who reported quantitative variations for the first time (16). That study was the first to use OCT in MS. OCT is a relatively new and practical method that allows for quantitative measurement of the retinal fiber layer in MS.

OCT provides cross-sectional imaging of biological tissue through high resolution. The axial resolution of OCT is 8 to 10 microns. It is possible to obtain cross-sectional images similar to those observed under a microscope. The degree of visualization that can be achieved with OCT is sufficient for use as a noninvasive tissue biopsy. OCT not only provides imaging of the optic disc in the retina and anatomical structures such as the macula, but also allows for the examination of intra-retinal structures, such as the retinal nerve fibers, photoreceptors, and retina pigment epithelium. Furthermore, the quantitative retinal measurements obtained provide valuable information for the diagnosis and follow-up of disease. RNFL thickness measured by OCT serves as a good indicator of axonal degeneration and may constitute a good model for neurobiological studies of MS.

Parisi et al. (16) studied RNFL thickness in 14 MS patient 1 year after an ON attack and the results were compared the measurements of 14 healthy controls. The mean RNFL thickness in the eyes of the control group was 111.11±11.42 μm, while it was 82.73±10.73 μm in the unaffected eyes of the patients and 59.79±10.80 μm in the affected eyes. The RSLT thickness in the eyes that had an ON attack was significantly lower than that of the other eye or the control group. The examination of differences between quadrants demonstrated that RNFL thinning was more distinct in the temporal quadrant. The mean RNFL thickness in the unaffected eyes were thinner than that seen in the control group, but did not reach a level of significance. In the same study, the measurements of RNFL thickness were compared with visual acuity and it was observed that RNFL thinning remained despite the fact that visual function fully recovered following the ON attack. They reported 46% thinning in the affected eyes and 28% in the unaffected eyes.

Fisher et al. (17) also found that RNFL thickness was distinctly lower in the ON eyes of 90 MS patients compared with 36 healthy controls. The authors demonstrated that there was significant RNFL thinning in the ON eyes of asymptomatic MS patients. Costello et al. (6) conducted the first prospective study. For a period of 1 year, every 3 months they observed 54 patients who had an ON attack. RNFL thickness was lower in the ON eyes, as seen in the other studies, and no difference was observed between quadrants. A decrease in RNFL thickness was found in 11% of the patients at 3rd month following the attack, 85% of the patients in the 6th month, and 4% of the patients at the 12th month. The temporal area was the quadrant where thinning was most frequently observed to occur (16, 18, 22). The loss of NFL thickness may be stabilized 7 to 12 months following the attack (19).

In our study, as in the literature, the examinations of variations between quadrants demonstrated that the most frequently and most markedly affected quadrant was the temporal area.

Although OCT is a strong imaging device in the examination of optic nerve and peripapillary RNFL, it has also been demonstrated that there are significant differences between

devices in the RSLT thickness results obtained as a consequence of different methods of data analysis employed (20). Due to such issues, the RNFL thickness of all patients in this study was always measured using the same device.

In various studies, the authors demonstrated that RNFL thinning existed in the temporal quadrant following an attack of ON (6, 20, 21). Trip et al. (22) studied 11 patients with MS who had a single attack of ON and 14 patients who had a clinically isolated syndrome, and they found that RNFL thickness decreased despite an increase in visual acuity following ON. Yahu et al. (12) also demonstrated that the loss of RNFL thickness was similar in patients both with and without IV methylprednisolone treatment, and that there was thinning in all quadrants, especially the temporal quadrant, at the third month in all patients. In our study, thinning in RNFL thickness was found at the third month following the attack in both the treated and the untreated group, and was greater in the temporal quadrant compared with the other quadrants. The degree of thinning in the treated patients was similar to that of the untreated patients; our results were consistent with those of Yahu et al.

The results provided here suggest that thinning in the temporal quadrant may be the initial result of axonal loss further to optic neuritis, variations in RNFL are not correlated with visual acuity, and that IV methylprednisolone treatment had no impact on variations in RNFL.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Involved in design and conduct of the study (HHT, AK); preparation and review of the study (OB, GS); data collection (HHT, OB); and statistical analysis (AK).

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