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ORIGINAL ARTICLE

Diagnostic utility of optical coherence tomography in patients with demyelinating optic neuritis

Utilidad diagnóstica de la tomografía de coherencia óptica en pacientes con neuritis óptica desmielinizante

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Abstract

Objective: *To determine differences in nerve fiber layer (NFL) thickness by Optical Coherence Tomography (OCT) in patients with neuromyelitis optica (NMO) and Multiple Sclerosis (MS).* **Methods:** *Case series study in adult patients diagnosed with MS and NMO.* **Results:** *The estimated median and interquartile range (IQR) for nerve fiber layer thickness in healthy subjects was 110 IQR (16) µm, in patients with MS was 94 (21) µm and in patients with NMO was 76.5 (61) µm. The differences between healthy and sick subjects were estimated, finding that the NFL thickness was significantly lower in absolute data: Δ = 16 µm for healthy-MS and Δ = 33.5 µm for healthy-NMO. Regarding the quadrants of retinal nerve fiber layer, it was found that the lower and upper quadrants have a greater loss of nerve fibers in both diseases.* **Conclusions:** *Our study supports evidence related to the involvement of ganglion cell layer and NFL observed in patients with MS and NMO. This study confirms what has been reported in other studies, that NFL thickness is a measure that can help diagnose the compromise and severity of optic nerve involvement in these two demyelinating diseases, with patterns that help to differentiate between NMO and EM.*

Key words: *Neuromyelitis optica. Multiple sclerosis. Optic neuritis. Tomography. Optical coherence. Nerve fibers.*

Resumen

Objetivo: *Determinar las diferencias en el grosor de la capa de las fibras nerviosas (CFN) por medio de la tomografía de coherencia óptica (OCT) en pacientes con neuromielitis óptica (NMO) y esclerosis múltiple (EM).* **Métodos:** *Estudio de serie de casos en pacientes adultos con diagnóstico de EM y NMO.* **Resultados:** *La mediana estimada y el rango intercuartílico (RIQ) para el grosor de la CFN en personas sanas fue de 110 RIQ (16) µm, en los pacientes con EM fue de 94 (21) µm y en los pacientes con NMO fue de 76.5 (61) µm. Se estimaron las diferencias entre pacientes sanos y enfermos, y se encontró que el grosor de la CFN era significativamente inferior en datos absolutos: Δ = 16 µm para sanos-EM y Δ = 33.5 µm para sanos-NMO. Respecto a los cuadrantes de CFN, se encontró que los cuadrantes inferiores y superiores tienen mayor pérdida de fibras nerviosas en ambas enfermedades.* **Conclusiones:** *Nuestro estudio soporta evidencia relacionada con el*

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compromiso de la capa de células ganglionares y CFN observado en pacientes con EM y NMO. Este estudio nos confirma lo reportado en otros estudios, que el grosor de la CFN es una medida que puede ayudar a diagnosticar el compromiso y la gravedad del nervio óptico que puede estar afectado en estas dos enfermedades desmielinizantes, con patrones en los que se puede diferenciar entre NMO y EM.

Palabras claves: *Neuromielitis óptica. Esclerosis múltiple. Neuritis óptica.Tomografía. Coherencia óptica. Fibras nerviosas.*

Introduction

Multiple sclerosis (MS) and neuromyelitis optica (NMO) are a spectrum of inflammatory, autoimmune, demyelinating diseases of the central nervous system[1,2]. These two conditions have a low prevalence in our population, but a high incidence of ophthalmological disorders, among which are the loss of monocular vision and neuronal degeneration at the level of the retina and optic nerve[3,4].

The use of optical coherence tomography (OCT) in patients with demyelinating diseases such as MS and NMO is of great importance in the diagnostic and progression evaluation of these diseases. In addition, it allows to establish the thickness of the nerve fiber layer (NFL), which will determine the patient's visual prognosis, quality of life and progression of the disease[4]. OCT is an innovative non-invasive high-resolution method that measures the thickness of the retinal NFL[5], gives information about the optic nerve head topography, the thickness of the peripapillary NFL and the macular volume.

The currently used OCT is time-domain, which provides real-time cross-sectional images of the retinal layers with a resolution of 10 µm (OCT Stratus® Zeiss). The limitation of this equipment is the low resolution and the slow speed (400 A-scans/sec), which results in a less accurate measurement of the retinal layers compared to other OCT devices[6]. The RS3000® (NIDEK®) is the latest OCT model that uses spectral-domain (SD) detection, which is available and commercially approved by the Food and Drug Administration. It also acquires real-time images with a resolution of 4 µm and a scanning speed of 53,000 A-scans/sec, improving the resolution and identification of the retinal layers[7].

The objective of our project is to characterize the NFL thickness in patients with a history of MS and NMO, using the new OCT RS-3000® (NIDEK®) and to establish the thickness differences when comparing the results with healthy patients.

Methods

This study was conducted following the ethical guidelines contained in the Helsinki declaration. The informed consent was conducted after approval from the Ethics in Research Committee of the Hospital Universitario de la Samaritana (05IC10-V1), Bogotá, Colombia.

Subjects older than 18 were enrolled consecutively in three groups: patients clinically diagnosed with MS or NMO, regardless of the time since diagnosis; patients without active optic neuritis and with the last event of optic neuritis reported more than a year ago, and healthy subjects. For patients with MS and NMO, a search was made in the medical records of the Neurology and Ophthalmology department of the Hospital Universitario de La Samaritana, collecting 35 possible candidates for the study. Based on medical records, compliance with the McDonald 2010 classification criteria and oligoclonal bands for MS were verified[8,9]; as well as the Mayo Clinic criteria updated in 2006 for NMO[10]. After this evaluation, 8 patients with MS and 2 with NMO were selected. The patients diagnosed with NMO were monitored in the neurology department, receiving maintenance treatment with prednisolone and azathioprine, an immunosuppressant. However, most of the patients were treated with rituximab, a monoclonal antibody that is used by intravenous infusion every 6 months. Patients diagnosed with MS were on first-line medications such as interferon B1a, interferon B1b, and second-line drugs such as fingolimod and natalizumab.

In order to make comparisons between groups, patients who did not refer a history of NMO or MS were selected. We excluded patients who did not agree to participate in the study and with comorbidities that could affect the NFL thickness (diabetes mellitus, vascular occlusions, HIV retinitis, chorioretinitis, glaucoma), or with active optic neuritis, relapsing disease or presence of new lesions in nuclear magnetic resonance imaging, and patients with incomplete data in the medical or database records. The collection of the information consisted in the selection of patients who have attended the Hospital Universitario de la Samaritana from January 1, 2012 to July 31, 2016. Once the compliance with the classification criteria was established, the patients were contacted to explain the protocol and

Table 1. Description of the main demographic characteristics

Item	Healthy patients	Multiple sclerosis	Neuromyelitis optica
Number of eyes	20	16	4
Age median (IQR/min/max.)	35.5 (15/18/52)	35 (11/24/51)	35 (34/18/52)
Women (n)	12	8	4
Time since diagnosis (years)	N/A	5 (9/1/17)	2 (2/1/3)
Number of relapses (years)	N/A	1 (1.5/0/2)	1 (0/1/1)

IQR: interquartile range.

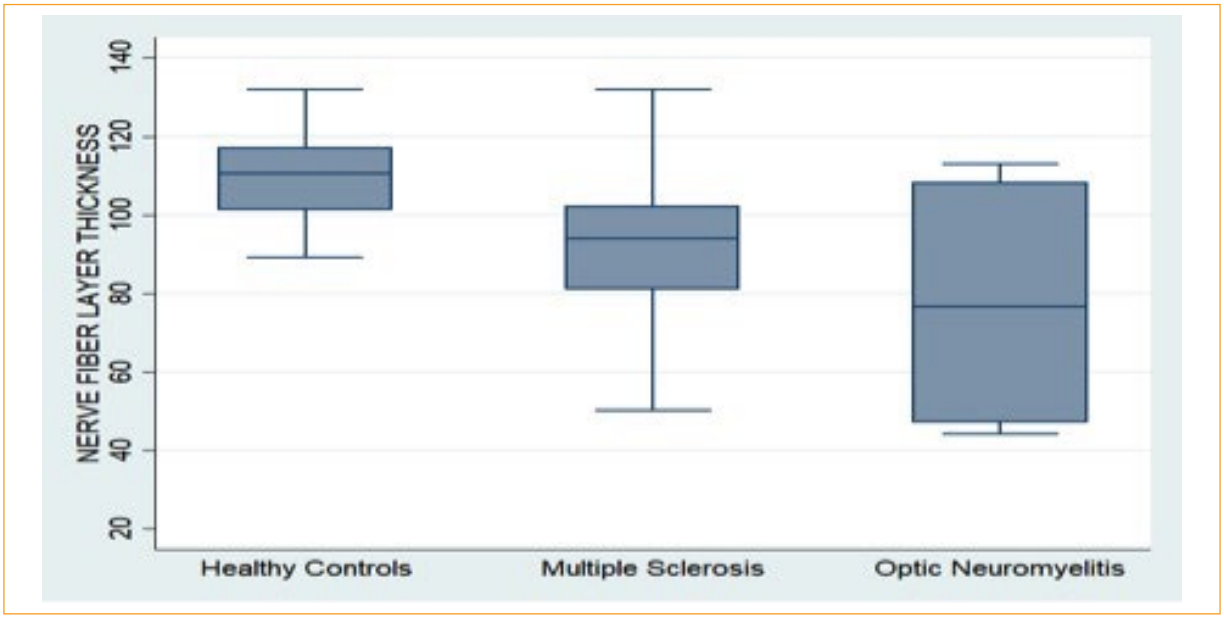

Figure 1. Nerve fiber layer thickness in µm by diagnosis (0 = healthy, 1 = MS, 2 = NMO).
MS: multiple sclerosis; NMO: neuromyelitis optica.

if they agreed to participate, they signed the informed consent and were scheduled for examination.

The selected patients underwent a complete ophthalmological examination, including OCT to measure the retinal layers thickness. A descriptive statistical analysis was performed, reporting frequencies and proportions for qualitative variables and medians and interquartile ranges for continuous variables. Differences were assessed by the hypothesis test between the measurements corresponding to the NFL and the thickness of the ganglion cell layer between patients with and without the disease. When the criterion of non-normality was met, a mean comparison was performed with the Wilcoxon rank test, considering the level of significance <0.005. The analysis was carried out using STATA software version 12.

Results

The study included 10 patients for a total of 20 eyes, 16 eyes with MS and 4 eyes with NMO (Table 1). No differences were found between the three groups in terms of age, gender, time since diagnosis and number of previous episodes of optic neuritis.

Absolute differences between medians corresponding to the NFL and the ganglion cell layer in patients with and without the disease were assessed. The median (interquartile range) estimated for the NFL thickness in healthy subjects was 110 (16) µm, for patients with NMO was 76.5 (61) µm, and for patients with MS was 94 (21) µm. Patients with NMO had significantly lower absolute values compared to subjects with MS (Fig. 1).

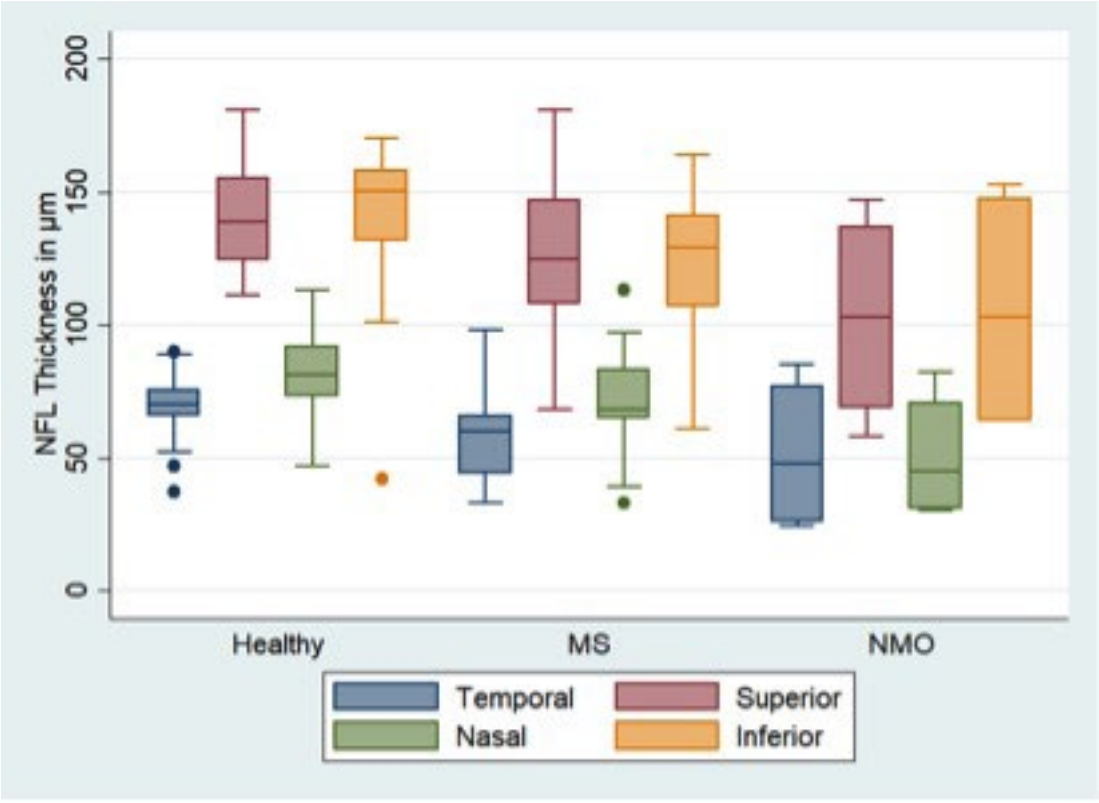

Figure 2. Thickness in µm of the NFL by quadrants by diagnosis (0 = healthy, 1 = MS, 2 = NMO).
MS: multiple sclerosis; NMO: neuromyelitis optica.

When examining the NFL quadrants (Fig. 2), it was observed that the inferior and superior quadrants showed a greater loss of nerve fibers in both diseases. Regarding the ganglion cell layer, it was observed that there is greater loss of ganglion cells in all quadrants in patients with NMO compared to patients with MS. In addition, there is a greater loss of these in the inferonasal quadrant in patients with MS and in the superonasal quadrant in patients with NMO (Fig. 3).

Discussion

Histopathological studies on NMO have revealed that this disease has an inflammatory and ischemic component that leads to a greater inflammatory response and axonal destruction[11]. Charcot, et al. demonstrated that in MS there is demyelination with a relative axonal preservation[12]. Based on this and in our findings, we infer that when measuring the NFL thickness in a patient with a suspected demyelinating disease, the NFL would be thinner in patients with NMO compared to MS, as previously reported[13-15].

Our study suggests a NFL and ganglion cell layer thickness decrease in patients with demyelinating diseases, specifically in patients with MS and NMO. In addition, we found that the superior and inferior quadrants of the NFL were more affected in patients with NMO compared to MS[13,16]. However, it is important to increase the number of patients in the long-term to improve the power of our results.

Previous studies reported that the average thickness of the NFL in MS is of 92 µm and in eyes of healthy subjects is of 105 µm[17]. Our results report a thickness of 94 µm in patients with MS and of 110 µm in healthy subjects, which agrees with the previously mentioned studies. The thickness is much lower in patients with NMO (76.5 µm), both in our study and in previously reported studies[2,13].

The possible usefulness of OCT in the diagnosis of NMO has been described. It depends on the thickness of the superotemporal ganglion cell layer being less than 62 µm[2,16]; however, this cut-off value was not identified in our population, which had a value of 82.5 (IQR: 49) µm.

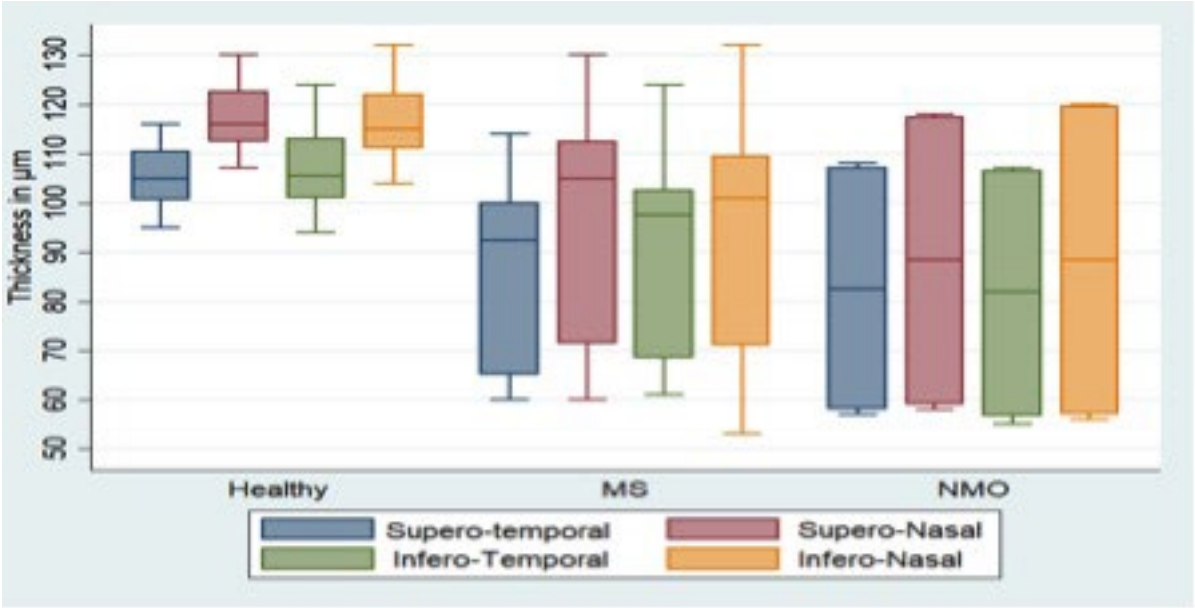

Figure 3. Thickness in µm of the ganglion cell layer per quadrant.
MS: multiple sclerosis; NMO: neuromyelitis optica.

Since the macula contains mainly ganglion cell bodies, the evaluation of macular volume allows to determine if the axonal loss (measured by the NFL thickness) is associated with neuronal degeneration[18-20]. In this study, we observed a greater ganglion cell loss at the macular level in the superotemporal and inferonasal quadrants in patients with MS, and in the superonasal and inferonasal quadrants in patients with NMO. This correlates with the loss of ganglion cells in the superior and inferior quadrants of the NFL at the level of the optic disc, which explains the neuronal degeneration observed in these two diseases.

It is necessary to clarify that the few available evidence of spectral-domain OCT is not comparable with our data, given that variability in the measurement has been described, even among different companies that use the same technology[16,18].

The measurement of the NFL and ganglion cell thickness deserves a greater research effort, particularly in longitudinal studies, due to their usefulness for evaluating prognosis and therapeutic assessment[19,21].

Conclusions

Patients with NMO and MS show a loss in the NFL and ganglion cell complex. Patients with NMO present a greater loss in the NFL compared to patients with MS. The pattern of loss (regarding the quadrants) tends to be more generalized in NMO (affecting the superior and inferior quadrants) and to affect mainly the temporal quadrant in MS. In patients with NMO, the difference in the NFL between both eyes (the one that had neuritis versus the healthy one) could help differentiate between NMO and MS. In MS, the NFL loss can be documented, even in eyes that have no history of clinical optic neuritis.

Since this is a case series study, no association or prediction can be established in terms of progression or severity.

The behavior of the involvement of the two layers measured by quadrants is similar to the data reported by other authors, where suspicion of NMO can be established if the ganglion cell layer thickness in the superotemporal quadrant is less than 62 µm. However, the thickness observed in our patients, although it is lower compared to healthy subjects, did not reach this threshold. This may be due to the sample size and the design of our study, which make difficult to evaluate the spectrum of the disease.

The low prevalence of patients with demyelinating diseases such as MS and NMO limited the sample size of this study. It should be noted that this study was only performed in patients without active optic neuritis. This prevented the evaluation of the role of SD-OCT in the acute phase of these two diseases.

In view of all available information on NFL and ganglion cell measurements with SD-OCT, our results

provide valuable information regarding the behavior of MS and NMO and their ocular involvement.

Conflicts of interest

The authors declare there is no conflict of interest in this research work and that they did not receive any funding.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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