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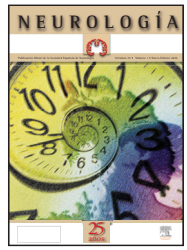

ORIGINAL ARTICLE

Optic neuritis, multiple sclerosis-related or not: structural and functional study

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KEYWORDS
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Abstract
Introduction: Multiple sclerosis (MS) is an inflammatory demyelinating disease with axonal degeneration. Optical coherence tomography (OCT) is a noninvasive technique that quantifies the thickness of the retinal nerve fiber layer (RNFL).
Objectives: To determine the thickness of the RNFL in MS patients with or without previous optic neuritis (ON) and in patients with ON and to determine the relationship between the structural damage and functional alterations in visual acuity (VA) and visual field (VF).
Methods: Three groups were studied: G1 – patients with ON, G2 – patients with MS and ON, and G3 - patients with MS and without previous ON. Ophthalmological (VA, VF, OCT) and neurological examinations were performed.
Results: OCT thickness in the unaffected eye was significantly thicker in ON patients (103.99) than in the other groups, however there was no differences among the affected eyes. There were significant differences in VA and VF among the non-affected eyes ($p = 0.007$), but not among the affected eyes ($p = 0.878$).
Conclusions: All MS patients showed axonal damage in both optic nerves, more in patients with previous ON. Axonal damage was detected early, so OCT could be used as a structural biomarker. Structural damage was related with the functional alterations.

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PALABRAS CLAVE
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TCO;
Daño axonal

Neuritis óptica asociada o no a esclerosis múltiple: estudio estructural y funcional

Resumen
Introducción: La esclerosis múltiple (EM) es una enfermedad inflamatoria cuyo sustrato patológico es tanto desmielinizante como axonal. La tomografía de coherencia óptica (TCO) es una técnica cuantitativa que evalúa *in vivo* el adelgazamiento de la capa de fibras nerviosas de la retina (CFN).
Objetivos: Valorar mediante TCO el estado de la CFN de pacientes con EM con y sin antecedentes de neuritis óptica (NO) y pacientes con sólo NO, así como valorar la repercusión de ésta en la agudeza y los campos visuales.
Métodos: Los pacientes fueron clasificados en tres grupos: *a*) G1: pacientes con NO; *b*) G2: pacientes con EM y NO, y *c*) G3: pacientes con EM sin brotes de NO documentados. A todos se les realizó una exploración oftalmológica que incluía agudeza visual (AV), campimetría (DM) y determinación del grosor de la CFN mediante TCO y una exploración neurológica.
Resultados: El grosor de la CFN en el ojo contralateral es significativamente superior en los pacientes con NO (103,99) que en los otros dos grupos (G2, 85,52; G3, 90,85); sin embargo, no hay diferencias significativas entre ojos afectos. No se encuentran diferencias significativas en AV y DM entre los grupos para el ojo afecto (p = 0,878), pero sí para el ojo contralateral (p = 0,007).
Conclusiones: En todos los pacientes con EM se evidencia una pérdida axonal en ambos nervios ópticos, que se acentúa en los casos que han sufrido brotes de NO. El daño axonal se detecta tempranamente, con lo que la TCO se podría usar como marcador de integridad axonal. Además, las alteraciones estructurales detectadas por la TCO están en concordancia con las alteraciones en las pruebas funcionales de AV y DM en los ojos afectos.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease which affects the central nervous system and whose aetiology is still unknown. For a long time, it was felt that demyelination was the fundamental substrate of this disease; however, axonal damage has now become critical in its pathogenesis and evolution[1]. The progressive accumulation of axonal damage appears to be the leading cause of disabling neurological alterations that can lead to permanent disability. This axonal damage occurs from the early stages of the disease. In 85%of patients who were subsequently diagnosed with clinically defined multiple sclerosis, the symptoms began with an acute or subacute episode of neurological dysfunction. This initial presentation is called isolated clinical syndrome (ICS)[2]. The most common forms of ICS are optic neuritis, myelitis and isolated brainstem syndrome.

Optic neuritis is an inflammatory optic neuropathy and is the first symptom of multiple sclerosis in 20% of patients affected by this disease[3]. The ganglion cells of the retina are the first neurons in the visual pathway; their axons constitute approximately 82% of the width of the retinal nerve fibre layer (RNFL), while at least 18% of the rest is formed by glia[4]. It has been shown that an outbreak of optic neuritis causes damage to these axons and is manifested by the pallor of the optic disc and loss of RNFL thickness. In addition, the axons of the ganglion cells are not myelinated until they cross the cribriform plate, thus making the optic nerve accessible for studying axonal damage in the central nervous system, regardless of the state of the myelin. Therefore, measuring RNFL thickness is a viable method of monitoring axonal damage in patients with multiple sclerosis and optic neuritis could become a model for studying axonal damage[5].

Optical coherence tomography (OCT) is an exploratory technique designed to evaluate the thinning of the retinal nerve fibre layer, optic nerve head (ONH) and the macula, *in vivo*, qualitatively and quantitatively[5]. It is a non-invasive, accurate, quantitative, easy to use and reproducible technique used to obtain images of the width of the retina and to measure its thickness and that of its innermost layer, the RNFL[6,7]. Some studies have shown that OCT is capable of detecting a sudden RNFL thinning after an ON outbreak and that patients with MS may also present axonal loss measurable by OCT[8-14]. Therefore, if all patients with MS, regardless of whether or not they suffered from optic neuritis, presented axonal damage in their optic nerves, this technique could be used as a marker of axonal integrity. In addition, in the future, the technique could be used as a prognostic and evolution marker and the structural damage measured by OCT should also have a functional impact on vision.

The aim of this study was to assess through OCT the state of the RNFL in patients with MS, with and without ON history, and in those who have suffered a single episode of ON, and to evaluate the impact of structural alterations on the sharpness and visual field in each of the patient groups.

Patients and methods

For this study, we recruited patients who met the following criteria: having suffered an episode of isolated optic neuritis

or suffering a relapsing-remitting multiple sclerosis with or without documented signs of optic neuritis. Patients should have been without corticosteroid treatment for at least 30 days before inclusion in the study. Some of the patients were receiving immunomodulatory therapies. Other neurological diseases were ruled out. A neurological examination was performed on all patients and their neurological status was determined by means of the EDSS scale[15].

We performed a full ophthalmologic examination that included: visual acuity (VA), intrinsic and extrinsic ocular motility, applanation tonometry, biomicroscopy (BMC) of the anterior pole, visual field, fundus and OCT (Stratus, Carl Zeiss Meditec). For the OCT examination we used the acquisition protocol Fast RNFL Thickness (3.46) and the analysis protocol RNFL Thickness Average, which provides RNFL thickness in absolute terms expressed in µm, and qualitatively through a colour code indicating the position with respect to the normal curve according to age[16].

The variables analysed were: *a*) VA, as measured by Snellen lines and expressed in the decimal scale, although transformed to a LogMAR logarithmic scale for statistical analysis; *b*) average deviation (AD) of the visual field expressed in decibels (dB): this is a measure of the light sensitivity at each point of the field explored in relation to the age of the patient; and *c*) RNFL thickness in absolute terms measured in µm and qualitatively as normal or atrophied, which is defined by an average thickness below the 5th percentile compared with the standard database for the age group provided by the Stratus OCT software.

The patients were grouped for analysis into: Group 1 (G1), patients with isolated clinical syndrome of the optic neuritis type of more than 3 months duration; Group 2 (G2), patients with MS and history of unilateral ON, and Group 3 (G3), patients with MS without documented ON outbreaks.

The affected eye was compared in G1 and G2 with the right eye of G3 and the contralateral eyes of the first two with the left eye of G3. The three variables, VA, AD and RNFL thickness, were compared using the Student's t-test for paired samples and the established level of statistical significance was $p < 0.05$. We measured the correlation between the disability and the decrease in RNFL thickness using the Pearson coefficient.

Results

A total of 49 patients were included in the study: 19 (38.8%) in G1, 12 (24.5%) in G2 and 18 (36.7%) in G3. Of this total, 31 were female (63.3%) and 18 were male (36.7%). The average ± standard deviation (SD) age of patients was 31.20 ± 10.25 years, with no significant differences between groups (ANOVA, $p = 0.086$). Table 1 shows the age, VA and AD for each group. We found no significant differences between groups for the affected eye ($p = 0.878$), although we did find them for the contralateral eye ($p = 0.007$). Both VA and AD were significantly better in the contralateral eyes of the groups that had suffered ON (G1 and G2) than in G3, patients with MS.

Table 2 shows that there was no significant difference for the average RNFL thickness between affected eyes (G1, 88.07; G2, 76.42; G3, 89.45; $p = 0.132$). However, RNFL thickness was significantly higher in patients with optic neuritis (G1, 103.99) than in the other two groups (G2, 85.52 and G3 90.85) in the contralateral eye ($p = 0.005$).

Table 1 Functional variables: visual acuity and average deviation in visual field

	G1	G2	G3	p[a]
Age (years)	32.74 ± 9.18	32.75 ± 10.99	39.44 ± 9.97	0.086
Visual acuity (dB)[b]				
Affected	0.85 ± 0.38	0.85 ± 0.28	0.88 ± 0.28	0.878
Contralateral	1.05 ± 0.11	0.97 ± 0.16	0.82 ± 0.23	0.002
Visual field average deviation (dB)[c]				
Affected	−3.67 ± 5.5	−5.95 ± 6.47	−4.07 ± 6.35	0.584
Contralateral	−0.1 ± 1.28	−2.49 ± 2.45	−4.13 ± 4.90	0.006

[a] ANOVA test.
[b] Student's t-test, G1 versus G2, $p = 0.502$; G2 versus G3, $p = 0.007$; G1 versus G3, $p < 0.001$.
[c] Student's t-test, G1 versus G2, $p = 0.05$; G2 versus G3, $p = 0.02$; G1 versus G3, $p < 0.001$.

Table 2 Average thickness of the nerve fibre layer in the three groups

	G1	G2	G3	p*
Affected	88.07 ± 19.24	76.42 ± 16.87	89.45 ± 17.68	0.132
Contralateral	103.99 ± 9.64	85.52 ± 18.62	90.85 ± 16.35	0.005

*ANOVA test.
Student's t-test, G1 versus G2, $p = 0.002$; G2 versus G3, $p = 0.432$; G1 versus G3, $p = 0.007$.

Table 3 Patients with atrophy of the nerve fibre layer

	G1	G2	G3	Total
Affected eye (χ^2, p = 0.07)				
Without atrophy	8 (42.1%)	3 (25%)	12 (66.7%)	23 (46.9%)
With atrophy	11 (57.9%)	9 (75%)	6 (33.3%)	26 (53.1%)
Contralateral eye (χ^2, p = 0.007)				
Without atrophy	17 (100%)	6 (54.5%)	10 (58.8%)	33 (73.3%)
With atrophy	0	5 (45.5%)	7 (41.2%)	12 (26.7%)

Atrophy is considered when the average thickness is below the 5th percentile compared with the standard database.

In considering the state of the RNFL (taking as reference the normative base of age), we found that the average thickness was classified as atrophic in the affected eyes in 75% of cases in G2, in 57.9% of those in G1 and in 33.3% of those in G3. In the contralateral eyes, atrophy was detected only in the groups with MS: 45.5% in G2 and 41.2% in G3 (table 3).

The average score obtained in the EDSS for G2 was 1.12, with an interval of 0-3 points, and of 2.47 (0-4.5) for G3 (p = 0.035, Student's t-test).

The correlation between the EDSS of groups G2 and G3 and RNFL thinning was very slight and not significant (r = −0.23 for the affected eye and r = −0.11 for the contralateral eye).

Discussion

Optic neuritis is an inflammation of the optic nerve that was previously associated only with a demyelination process, but it has currently been proven to be associated with an axonal alteration as well. It can be suffered in isolation (ICS) or as a manifestation of MS. Optic neuritis typically presents as sudden monocular visual loss accompanied by mild periorbital pain that increases with eye movements. Visual loss may progress over one or two weeks and then begins to recover during the first month of evolution. The diagnosis of ON is clinical, but it should be confirmed through visual evoked potentials, OCT and MRI. It is important to identify and quantify the axonal damage in the different MS stages to determine disease severity and progression and the relationship between the axonal damage and the degree of patient disability. Until now, *in vivo* detection of axonal damage had been achieved using non-conventional, magnetic resonance techniques. It has currently been found that OCT can also measure axonal damage[17].

In our study, we measured RNFL thickness in different groups of patients with MS and ON. The average values of the final RNFL thickness range between 75 and 89 µm in the G1 and G2 study groups, which include patients who have suffered optic neuritis, with values that are similar to those described in the literature[10,16-18]. The patients in groups G2 and G3 with multiple sclerosis show a reduction in RNFL thickness in both optic nerves, regardless of whether they have suffered optic neuritis or not. This is confirmed by the histological[19] and MRI[20-22] studies, where axonal damage is detected in patients with MS from disease onset. It is significant that in the G3 group, with patients who have never suffered optic neuritis, there is a bilateral RNFL thinning, which supports the idea that OCT can serve to measure axonal damage occurring in MS, regardless of whether optic neuritis has been suffered, and that this technique could be used as a marker of axonal integrity[23].

In the group with optic neuritis, there is a significant difference in the decrease of RNFL thickness between both eyes, thus confirming axonal damage in the initial disease stages. In our study, the contralateral eye showed no alteration, as was the case in some previous studies[10,24]. There is controversy about this fact because in some studies the contralateral eye was also subclinically affected in the acute phase, as demonstrated in the ONTT (Optic Neuritis Treatment Trial) multicentre study; in that study, only one out of every 3 patients showed normal results in all tests, although most registered changes were small[25,26], and only in some cases were these differences significant compared with healthy controls[7,27]. In our study, unlike in others, the cases of ON had a short evolution, and this could explain why the contralateral eye was not yet affected.

In the groups of patients with multiple sclerosis (G2, G3), axonal damage is observed in both optic nerves; however, there is a significant difference in terms of atrophy, since 75% of affected eyes and 45% of contralateral eyes in G2 show atrophy. In group 3, the percentage of patients with atrophy is less. This occurs because, after an ON outbreak, it is estimated that there is a sudden reduction in RNFL thickness of approximately 27%[7,17] and, on the other hand, it is expected that the characteristic axonal loss of patients suffering from MS is slowly progressive, so both factors are coupled in G2.

Through the VA and AD of the visual field, we evaluated the functional impact of the condition of the RNFL. In general, the visual prognosis of patients who have suffered ON is not good, as was demonstrated in the ONTT[25], in which up to 95% of patients achieved vision = 20/40 and in which at 6 months, 51% of visual fields were classified as normal with a final AD of -1.94 dB[28,29]. As with RNFL thickness, our study did not detect significant differences between affected eyes among the groups, in which the VA of the affected eye was similar, approximately 0.85 in the Snellen scale, and VF sensitivity showed a slight average AD decrease (table 1). Consistent with the OCT results, significant differences were observed in the contralateral eye of the group with optic

neuritis compared to the other two groups, given that the functional variables (VA and AD) remained within the normal range in Group 1, whereas slight affectation could be observed in the other two groups. However, it is noteworthy that in G3, both VA and AD were worse than in G2 for the contralateral eye (table 1), despite the fact that the RNFL thickness trend was better for G3 (table 2). This could be explained by the fact that functional tests require the active patient cooperation and, therefore, depend on their cognitive ability and, in addition, the patients in group G3 were more disabled than those in group G2.

In agreement with the work done by Pueyo et al.[14], our study found no significant correlation between RNFL thickness and the neurological disability measured by the EDSS scale in Groups G2 and G3.

In conclusion, this study shows that in patients with multiple sclerosis, it is possible to identify the axonal damage occurred in both optic nerves regardless of whether they have suffered optic neuritis or not. This means that OCT could be used as a marker of axonal integrity, which could be very important in determining the evolution and prognosis of the disease.

Furthermore, we confirm that the contralateral eye in patients suffering optic neuritis of short evolution presents normal OCT; however, the affected eye shows axonal damage, confirming that neurodegeneration begins in the early stages of the disease. The anatomical changes detected by OCT are consistent with the alterations found in the functional tests of VA and AD in affected eyes.

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