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Professional paper

The Role of Optical Coherence Tomography (OCT) in Optic Neuritis (ON)

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A B S T R A C T

Axonal and neuronal degeneration are important features of multiple sclerosis (MS) and other neurologic disorders that affect the anterior visual pathway. Optical coherence tomography (OCT) is a non-invasive technique that allows imaging of the retinal layers. Our aim was to examine retinal nerve fiber layer (RNFL) thickness and macular volume (MV), measred by OCT, in patients with history of optic neuritis (ON). Patients with chronic ON had significantly decreased mean RNFL thickness and total MV when compared to acute ON eyes, controls and unaffected fellow eyes. There was also statistically significant difference between two chronic groups, with lower values in group with history of acute ON. OCT provides us unique insight in structural changes in the anterior visual pathway, therefore it may complement our existing diagnostic tests and, as a potential outcome measure, help develop more effective therapeutic strategies for ON and MS patients.

***Key words**: Optical coherence tomography, Optic neuritis, RNFL, macular volume, axonal loss*

Introduction

Optic neuritis (ON), one of the most common and characteristic manifestations during the course of the multiple sclerosis (MS), results from the development of an inflammatory demyelinating lesion in the optic nerve[1–4]. Consequently, optic nerve and retinal nerve fibre layer (RNFL) manifest axonal and neuronal degeneration[1,5].

The development of axonal loss and secondary retinal ganglion cell (neuronal) loss in the macula can be quantified with optical coherence tomography (OCT), by imaging and measuring the RNFL thickness and MV[1,6–8].

OCT is a simple, noninvasive, highly sensitive, precise, quantitative and reproducible technique that provides us *in vivo* high-resolution reconstruction and objective measurements of the thickness of the peripapillary mean RNFL (mRNFL), foveal, and macular thickness, macular volumes and segmentation of retinal layers[2,5,8–11]. Validation of OCT as an imaging biomarker in MS is important, because several aspects of the information it generates are unique. Imaging RNFL with ocular imaging techniques allows direct measurement of the most proximal region of the anterior visual pathway and this unique central nervous system (CNS) structure, because it is composed of unmyelinated axons of retinal ganglion cells, all the way to lamina cribrosa[2,8,9,12].

RNFL thinning, which represents axonal damage, in the eye of a patient with ON or MS, may function as a biomarker of global disease severity[13,14]. Therefore, RNFL is an ideal model for investigating the effects of standard and novel therapies on processes of axonal and neuronal degeneration, neuroprotection and, potentially, even neurorepair. Therefore, OCT can be an useful outcome measure in clinical trials investigating these therapies[2,5,8,9,15].

Based on OCT studies, it is confirmed that RNFL thickness and MV is significantly reduced in patients with a history of optic neuritis. Several studies showed that even eyes without acute demyelinating optic neuritis among MS patients or unilateral ON patients have decreased RNFL thickness over time, compared with the eyes of control subjects[5,7–9,16–18].

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OCT and its measurements of retinal layers thinning following ON or MS relapse could be considered as a potential outcome measure in MS clinical trials, but there is not enough dana on the reproducibility of this technique in MS centers[8]. Therefore, the objective of this study was to determine the current capabilities of OCT to detect changes in RNFL and MV integrity following ON, by measuring mRNFL and total MV.

Materials and Methods

We performed retrospective study of 33 patients (66 eyes), administered in our Clinic from July 2010 to the end of 2011, with the history of acute or chronic ON in at least one eye. Patients with some other acompanying ocular pathologies were excluded.

Patients' eyes were divided in several groups: 20 eyes with acute ON, 19 unaffected fellow eyes (non-ON eyes), eyes with chronic ON with (13 eyes) or withouth previous history of acute attack (14 eyes) and finally, 23 healthy control eyes.

SD-OCT (Spectral domain OCT, Copernicus HR (Optopol Technology S.A.)) measurement of mean peripapillary RNFL thickness as well as total macular volume in 6 mm diameter were performed.

The main outcome measures included comparing differences in RNFL thickness and MV between groups, using Student's t-test.

Mean time from acute ON attack was 4.3 years.

RNFL thinning with age had been estimated at 0.3 μm/year or a decrease of approximately 0.27%/year[6]. This emphasized the need for age-matched healthy controls. We consider our patients speciment correspondent, because mean patients age was 37.7 years and controls 36 years.

Results

Eyes with acute ON had elevated mRNFL (124 μm) values by 12.9% compared to control eyes (108 μm), although statistical significance was not achieved. Total MV did not show such increase of values (Table 1).

Both the mRNFL and total MV in the eyes not previously affected by ON (non-ON eyes), were not significantly decreased, when compared to healthy control eyes.

Eyes of the patients with chronic ON and a history of acute ON had significantly decreased mean RNFL thickness (80.3 μm) compared to controls (108 μm) ($p< 0.0001$) and to non-ON eyes (112 μm) ($p<.0001$). Also, the patients with chronic ON and a history of acute ON demonstrated significantly decreased total MV (6.42 mm^3) compared to the control group (7.24 mm^3) ($p<0.0001$) and group with non-ON eyes (7.19 mm^3) ($p<0.0001$, Table 1, Figures 1 and 2).

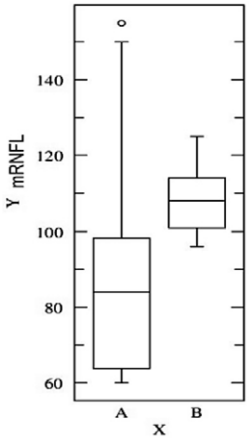

Fig. 1. Comparison of mRNFL in chronic ON eyes with history of acute ON (A) and control eyes (B), p<0.0001.

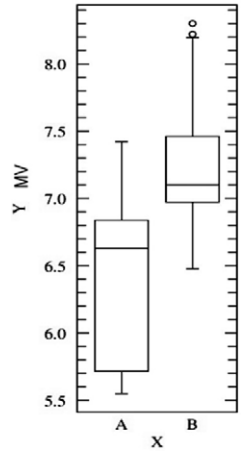

Fig. 2. Comparison of MV in chronic ON eyes with history of acute ON (A) and control eyes (B), p<0.0001.

TABLE 1
RNFL AND MV COMPARISON AMONG GROUPS

Groups	mRNFL (μm)	*p* value compared to controls	Total MV (mm^3)	*p* value compared to controls
Acute ON eyes	124	<0.23	6,76	<0.18
Chronic with history of acute ON	80.3	<0.0001	6.42	<0.0001
Chronic without history of acute ON	94.3	<0.0005	6,89	<0.036
Non-ON eyes	112	<0.39	7.19	<0.73
Control eyes	108		7.24	

When comparing mRNFL of eyes with chronic ON, but without history of acute ON (93.8 μm), we noticed statistically significant difference to controls (108 μm) ($p<0.0005$) and non-ON eyes (112 μm) ($p<0.0018$). Total MV in the same group (6.89 mm^3) also showed statistically significant difference when compared to control eyes (7.24 mm^3) ($p<0.036$) and non-ON eyes (7.19 mm^3) ($p<0.043$, Table 1).

A statisticaly significant difference in mRNFL ($p<0.03$) and MV ($p<0.028$) was also found between eyes with chronic ON and history of acute attack when compared to eyes with chronic ON withouth previous history of acute attack (Figures 3 and 4).

The mean RNFL thickness in chronic ON eyes with history of acute ON (80.3 μm) ($p<0.022$), was reduced by 35.2% compared to eyes with acute ON (124 μm). The total MV in eyes with chronic ON and history of acute attack (6.42 mm^3) was decreased by 9.4% when compared to eyes with acute ON (7.09 mm^3).

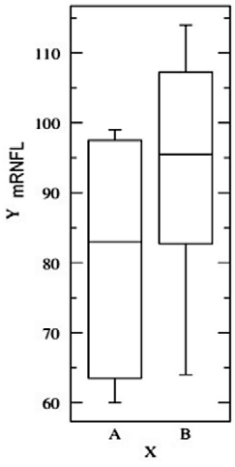

Fig. 3. Comparison of mRNFL in chronic ON eyes with history of acute ON (A) and chronic ON eyes without history of acute attack (B), p<0.03.

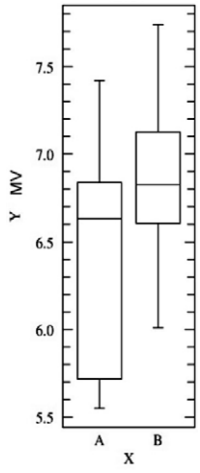

Fig. 4. Comparison of MV in chronic ON eyes with history of acute ON (A) and chronic ON eyes without history of acute attack (B), p<0.028.

There were no statistically significant results when comparing mRNFL and MV in acute ON with control and non-ON eyes.

Discussion and Conclusion

Whereas the reductions in RNFL thickness implicate the loss of ganglion cell axons, macular changes indirectly implicate loss of the ganglion cell neurons themselves[1,5–8,12].

There is a quantifiable, highly significant loss of mRNFL axons and total MV in patients eyes after acute optic neuritis (ON). Reduced macular volumes accompanyed peripapillary RNFL thinning. This study confirmed an average 25.6% reduction in mRNFL thickness in the chronicaly affected eyes of patients with previous optic neuritis compared with the healthy control eyes ($p<0.0001$), and an average 28.3% reduction when the affected and unaffected eyes were compared ($p<0.0001$). Thinning of the RNFL after optic neuritis has been confirmed in all subsequent studies[6,7,19,20].

Total MV values decrease by approximately 11.3% in the affected eyes compared to control eyes ($p<0.001$) and by 10.7% when compared to non-ON eyes ($p<0.001$). These findings are important because the inner retinal complex (ganglion cell layer, inner plexiform and nuclear layers) comprises 34% of the total average macular thickness[14]. Thus, MV can indirectly give us informaton about neuronal cell loss. Tracking macular volumes in ON patients may help determine the temporal relation between primary neuronal cell death and axonal loss after a CNS inflammatory event[9]. These observations are analogous to studies of gray matter in MS[14].

The mean RNFL of eyes with chronic ON, but without history of acute ON was reduced by 15.1% when compared to control eyes and by 19.4% when compared to non-ON eyes. In the same group, total MV was 4.8% lower than in control eyes, and 4.17% lower than in non-ON eyes.

The mean RNFL thickness was reduced in both chronic ON groups (80.3/93.8 μm) relative to controls (108 μm) ($p<0.0001$ and $p<0.001$), with lower values noted in the ON eyes with history of acute ON. Similarly, MV decreased in both chronic groups (6.42/6.89 mm^3) relative to controls (7.24 mm^3) ($p < 0.0001$ /$p< 0.001$), with more severe reduction in a group with history of ON.

Peripapillary RNFL thinning and MV loss are less strongly linked in eyes with chronic ON without history of acute ON, than in eyes of patients with a history of ON.

Eyes of patients with acute ON had mRNFL 124 μm, higher than control eyes (mRNFL 108 μm. Although the difference was not statistically significant, we can see that there is increase in mRFNL due to the disc edema. This could also explain the more pronounced difference in mRNFL reduction comparing the chronic ON with acute ON group (35.2%) than with control group (25.6%).

It is important to be aware of such effects, because potential swelling during the acute stages of ON may confound baseline measurements[10]. Total MV, which indirectly represents ganglion cell layer, did not demonstrate swelling in acute phase, when compared with controles and contralateral unaffected eyes, whereas mild peripapillary retinal nerve fibre layer oedema was observed in affected eyes. Total MV was lower in participants with acute ON than in controls, although statistical significance was not achieved. Total MV in chronic ON and history of acute attack showed significant reduction compared to acute ON eyes (9.4%), which is similar to comparison with control eyes (reduction of 11.3%), due to the absence of MV values increase in acute phase.

In unaffected fellow eyes, both the mean RNFL thickness and MV were not reduced when compared with control values, which is not in concordance with other studies[12,14,17].

The most reproducible RNFL measurement in our study was mean RNFL, showing the greatest dfferences, which correlates with previously published results[6,7,19,20].

In our study, mean time from acute ON in chronic ON group was 4.3 years. As was noted in previous studies, RNFL thinning is usually evident within 3 months of an acute ON event and achieves stabilization in an overall 12 months period. This period is a potential therapeutic »window« and it is important for the design of future trials employing OCT as an outcome measure in ON patients[9,12,21]. Our speciment, with mean time over 14 months in chronic phase, is representative for clinical trials design.

In conclusion, this study has demonstrated structurally relevant changes indicative of axonal loss and retinal neuronal cell loss in the RNFL and macula, respectively, after optic neuritis, measured by OCT.

There is increasing evidence suggesting a role of OCT in the evaluation of ON and MS patients. It is an established technique used to measure RNFL thickness and macular volume (MV), a measurement that may provide information relating to visual pathway axonal loss and neuronal cell thinning following ON[10,14].

Results from our study demonstrate retinal neuronal layer thinning following acute optic neuritis, corroborating the hypothesis that axonal injury may cause neuronal pathology in ON or MS. The data from this study may be used to provide reference values for the development of clinical trial protocols.

Our results support validity of RNFL thickness as a structural marker for axonal degeneration and support other recent findings about the use of OCT, quantitative and noninvasive imaging technique, and its retinal layer segmentation as an outcome measure in clinical trials that examine neuroprotective and other disease-modifying experimental therapies[7,8,10,20,22].

Limitations

We performed retrograde study, in which we only had one OCT scan, however, results from other studies on the same subject indicate that a single scan can provide reliable results[8].

The major limitation of our study was the small sample size studied. When a patient population size is limited, interpretation of results might not be as objective, even in the context of an elegantly designed study[9]. Therefore, further controlled, prospective clinical trials involving a larger numbers of patients will be needed to firmly establish the role of OCT in ON and MS and how this technology can be optimally implemented in developing new therapeutic strategies in ON patients.

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VAŽNOST OPTIČKE KOHERENTNE TOMOGRAFIJE (OCT) KOD OPTIČKOG NEURITISA (ON)

S A Ž E T A K

Degeneracija aksona i neurona je važna u patogenezi multiple skleroze (MS) i kod drugih neuroloških bolesti koje zahvaćaju prednji dio vidnog puta. Optička koherentna tomografija (OCT) je neinvazivna tehnika koja omogućava snimanje sloja retinalnih živčanih vlakana (RNFL). Cilj našeg ispitivanja bio je ispitati debljinu RNFL i volumen makule (VM) kod pacijenata s optičkim neuritisom (ON), mjerene OCT-om. Kada smo ih usporedili s očima s akutnim ON, sa nezahvaćenim drugim okom i kontrolnom skupinom, oči pacijenata s kroničnim ON su imale značajno snižene srednje vrijednosti debljine RNFL-a (mRNFL) i ukupnog VM. Također smo dobili statistički značajnu razliku između dvije kronične grupe, s nižim vrijednostima u grupi s prethodnim akutnim ON. OCT omogućuje jedinstven uvid u strukturalne promjene prednjeg dijala vidnog puta, te može dopuniti uobičajeni spektar pretraga i pomoći u razvijanju efikasnijih strategija liječenja pacijenata s ON i MS.