

Effectiveness of Time Domain and Spectral Domain Optical Coherence Tomography to Evaluate Eyes with And Without Optic Neuritis in Multiple Sclerosis Patients

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Abstract

Purpose: To compare the macular assessment and retinal nerve fiber layer (RNFL) thickness by using two different optical coherence tomographies (OCTs): a time domain (TD) and a spectral domain (SD) OCT, in multiple sclerosis (MS) patients with and without unilateral optic neuritis (ON).

Methods: We enrolled 34 patients (13 males and 21 females): 18 without previous episodes of ON and 16 with a previous monolateral episode of ON occurred at least 3 months prior to examination. Patients underwent ophthalmological examination, TD OCT and SD OCT scans. We compared the outcomes of eyes with and without ON by using Student's t test.

Results: In the affected eye group a reduction of the average RNFL was found using TD OCT (reduction of 22.8%) with the difference between the two groups being statistically significant ($p < 0.05$) in almost all the investigated retina areas. Similar results were found when eyes were analysed with SD OCT, also when the ganglion cell layer (GCC) was considered: a reduction of 18.1% of GCC average thickness was found. No significant difference was found when the outer retina was considered.

Conclusions: In MS patients both OCT systems were able to detect a difference between eyes with an outcome of optic neuritis and those without optic neuritis.

Keywords: Multiple sclerosis; Optic neuritis; Optical coherence Tomography; Ganglion cell complex; Retinal nerve fibre layer

Introduction

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease of the central nervous system that often leads to inexorable neurological disability. The anterior visual pathway is frequently affected by MS resulting in inflammation, demyelination, and axonal degeneration [1-4]. Axonal loss is responsible for disease progression and the development of disability and new strategies are warranted for monitoring MS and preventing neuronal degeneration and disability.

Acute idiopathic demyelinating optic neuritis (ON) is the initial clinical manifestation in 20% of patients with MS and it occurs during the course of the disease in 50% of patients [5]. Axonal loss occurs both in the retina and in the optic nerve and is widespread and diffuse. This neuronal thinning has also been documented to be more consistent in ON patients between 3 and 6 months after onset. The atrophy of the optic nerve, which is part of the central nervous system, is in agreement with other findings of generalized cerebral atrophy in patients with multiple sclerosis [6].

Since the retina is the only area where the retinal nerve fiber layer (RNFL) is directly visible, it could theoretically be possible to monitor the neurodegeneration through the quantification of the same, using an innovative instrument such as optical coherence tomography (OCT) [7-17].

The purpose of this study was to compare the macular assessment and peripapillary RNFL thickness by using two different OCTs: a time domain (TD) and a spectral domain (SD) OCT, in MS patients with and without unilateral optic neuritis.

Patients and Methods

This is a retrospective, cross-sectional study. The study was

approved by the local ethical committee and written informed consent was received from all patients. The study was performed according to the tenets of the Declaration of Helsinki for research involving human subjects. This study was carried out in the MS clinic of the University of Genoa.

All the included patients were classified as MS patients if the revised McDonald Criteria were met [18]. Patients were recruited between January 2010 and June 2011. We enrolled 34 patients (13 males and 21 females), 18 without previous episodes of ON, 16 with a previous monolateral episode of ON. Patients with more than one ON attack in the same eye were excluded. The episode of ON must have occurred at least three months before examination, if not, they were excluded.

Patients with ocular comorbidity conditions unrelated to MS were excluded as this could weaken or impair the examination with OCT. More specifically, patients with diabetes, open-angle glaucoma, abnormal optic nerve head (ONH), normal-tension glaucoma, opacity of the cornea or lens or nystagmus were excluded.

All patients underwent ophthalmic examination including best-corrected Snellen visual acuity, assessment of intraocular pressure, slit lamp biomicroscopy and binocular ophthalmoscopy with pupil

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dilation. The same day, OCT examination was performed on each eye using a Time Domain OCT (Stratus; Carl Zeiss Meditec, Dublin, CA, USA) and a Spectral Domain OCT (RTVue-100, Optovue Inc., Fremont, CA, USA). Patients were also selected on the basis of their ability to maintain steady fixation throughout scanning with each scan being accurately checked to avoid misalignment of foveal imaging.

Time Domain OCT

Stratus OCT has been used until recently in the majority of clinical trials. The details of this technique have already been published elsewhere [7-17]. In this study the OCT protocol for the measurement of the RNFL around the optic nerve was the “fast RNFL thickness” while for assessment of the macular thickness the “fast macular thickness map” was used. The “fast RNFL map protocol” consists of three circular scans, with diameters of 3.4 mm centred on the optic disc. The mean overall and sectoral (superior, nasal, inferior and temporal) RNFL thickness values were recorded for each eye. The “fast macular thickness map” protocol consists of six evenly spaced radial lines centred on the fovea, each having a 6 mm transverse length. In this study the following parameters have been used: Superior max, Inferior max, Inferior average thickness, Superior average thickness, Average thickness and Foveal thickness. To be accepted, each scan had to have a signal strength of at least 7.

Spectral domain OCT

Compared to time-domain OCT, Optovue RTVue Fourier/Spectral domain OCT is faster and presents a higher resolution. The details of this technique have been already published elsewhere [7-17]. The increased speed of acquisition of A-scans is the basis of improved definition of tomographic images of this new generation of OCT. Moreover, artefacts due to patient movements present in the time domain OCT are almost entirely eliminated thanks to the speed of execution reached by the new technology.

Each eye underwent the Nerve Head Map (NHM4), Macular Map (MM5), and Ganglion Cell Complex (GCC) scan protocols. All scans had signal strength of at least 50 (range, 30-79.4) and no artefacts. MM5 scan protocol measures the macular retinal thickness map with 5x5 mm square grid centred on the fixation point. Macular volume within 5 mm was measured. NHM4 scan measures the average parapapillary RNFL thickness. GCC scan protocol measures the GCC layer which encompasses RNFL, ganglion cell bodies and inner plexiform layer. The scan is centred 1 mm temporally to the fovea and consists of a 7 mm horizontal line and 15 vertical lines with 6 mm scan length and 0.5 mm interval. In this study the following parameters have been used: Average ganglion cell complex, superior ganglion cell complex, inferior ganglion cell complex, focal loss ganglion cell complex, global loss ganglion cell complex, average full retina, superior full retina, inferior full retina, focal loss full retina, global loss full retina, average outer retina, superior outer retina, inferior outer retina, focal loss outer retina, global loss outer retina.

Statistical Analysis

Both eyes of each patient were included in the study. The ON eyes were compared to the normal database of the instruments and to the unaffected fellow eye. All the data were analysed by a descriptive analysis. Student’s t-test was used to compare the two sets of data when the distribution of the data was normal. Mann-Whitney test coefficient was utilized to compare the two sets of data when they did not follow a normal distribution. The statistical power of the study ranged between

76.2 and 94.2% with an alpha of 0.05 and a beta of 0.5. Bonferroni correction was applied to Student’s t-test because otherwise we would have a significant chance of 40.1% of our finding.

Results

Thirty-four MS patients with average age of 39 years were recruited in our study. The group of patients with a history of ON (18 patients) had a mean age of 41.2 years (SD 9), while the group without ON (16 patients) had an average age of 37.9 (SD 9.1).

Examination with TD-OCT demonstrated a statistically significant difference between eyes with previous ON and those without. In particular, in the subgroup of ON eyes, the parameters concerning the measurement of retinal thickness showed a statistically significant decrease in all evaluated sectors except for foveal thickness (Table 1). The reduction of the average RNFL thickness was 22.8%.

When the patients were analysed by SD-OCT, statistically significant differences were found between the two subgroups considered, both in the case where it was investigated throughout the retina in its overall thickness (Table 2). Full retina reduction was 18.1%, and a significant difference was found between the two groups. Also Focalized and global loss full retina were found statistically different between groups (Table 3). However when the outer retina was assessed, no significant difference was found except for the global and focal loss of volume suggesting that the damage occurred in the inner layers (Table 4).

Discussion

	Eye without optic neuritis	Eye with optic neuritis	
	Mean (SD)	Mean (SD)	P value
Superior max	151.7 µm (35.6)	126.44 µm (42.8)	0.012
Inferior max	146.5 µm (26.3)	117.16 µm (32.8)	0.0001
Superior Average Thickness	115.8 µm (23.8)	92.64 µm (28)	0.001
Inferior Average Thickness	114.2 µm (22.6)	87.12 µm (23.7)	0.0001
Average Thickness	92.3 µm (15.5)	71.30 µm (21.1)	0.0001
Foveal Thickness	174.1 µm (27)	175.80 µm (33.3)	0.821

Table 1: OCT-TD Time Domain.

	Eye without optic neuritis	Eye with optic neuritis	
	Mean (SD)	Mean (SD)	P value
Average Ganglion Cell Complex	91.4 µm (8.1)	74.9 µm (10.3)	0.0001
Superior Ganglion Cell Complex	91.7 µm (7.4)	74.8 µm (10.2)	0.0001
Inferior Ganglion Cell Complex	90.1 µm (10.2)	76.5 µm (10.1)	0.0001
Focal loss Ganglion Cell Complex	1.8 µm (2.6)	7 µm (4.1)	0.0001
Global loss Ganglion Cell Complex	8.5 µm (6)	27.3 µm (18.5)	0.0001

Table 2: OCT- SD Spectral Domain.

Eye without optic neuritis	Eye with optic neuritis		
	Mean (SD)	Mean (SD)	P value
Average full retina	263,4 µm (12,7)	245,8 µm (14,2)	0.0001
Superior full retina	266,1 µm (12)	247,3 µm (13,3)	0.0001
Inferior full retina	257,8 µm (25,8)	241,7 µm (27,7)	0.037
Focal loss volume full retina	2,1 µm (3,1)	6,7 µm (5,1)	0.0001
Global loss volume full retina	10 µm (8,2)	20,7 µm (9,3)	0.0001

Table 3: OCT- SD Spectral Domain.

Eye without optic neuritis	Eye with optic neuritis		
	Mean (SD)	Mean (SD)	P value
Average outer retina	171,7 µm (8,2)	171,7 µm (7)	0.999
Superior outer retina	173,9 µm (8,0)	178,3 µm (23,9)	0.336
Inferior outer retina	169,6 µm (8,8)	170,2 µm (7,6)	0.795
Focal loss volume outer retina	2,2 µm (3,2)	6,7 µm (5,1)	0.0001
Global loss volume outer retina	9,9 µm (8,1)	20,7 µm (9,3)	0.0001

Table 4: OCT-SD Spectral Domain.

OCT is a non-invasive and reproducible tool and might present valuable data for axonal degeneration. It has been introduced to detect glaucomatous ganglion cell loss, and recently is a new method used to assess the impact of MS on RNFL thickness by measuring the echo time delay and intensity of back-reflection of light from different structures in the eye [7-16].

Currently, no sensitive nor specific OCT markers exist for predicting and preventing disability. As the optic nerve may be involved in the disease process, close correlation has been observed between OCT findings and the histological evaluation of RNFL [18]. Recent studies have suggested that reduced RNFL thickness may be a potential MS outcome measurement and serve as a surrogate marker for MS disability [19-22]. In a previous study we analysed RNFL by using a confocal scanning laser (HRT) and a polarimeter scanning laser (GDx), the results obtained were completely different: all the HRT parameters were not able to detect ONH changes due to MS, likely because MS patients can suffer from loss of ganglion cells but without creating a deep cup; astroglia cells can indeed occupy the damaged space. Also the HRT cup shape measure (CSM), which is the most sensitive parameter to distinguish normal from glaucomatous ONHs, did not show any difference between controls and both ON and unaffected eyes of MS patients [23]. CSM indicated that the measurement was normal in both groups. Even when the HRT classification was used, the system did not show good diagnostic capacity. The GDx VCC is a different technique, able to detect ganglion cell loss, because of change in retardation time. The polarized light needs time to cross the microtubule of the ganglion cell and, when these cells die, the retardation time changes. The nerve fibre indicator did not have good diagnostic capacity as in glaucoma clinics and we found a poor agreement between techniques. However, few GDx parameters showed a good capacity to distinguish ON eyes and those without a history of ON. Thus, GDx VCC could be able to detect small differences also between the two eyes, one with a large amount of ganglion cell loss post-ON and the other one with some subclinical involvement of the optic disc, but with a smaller loss of ganglion cells.

Our study, using both HRT and GDx VCC, indicated that these imaging technologies could detect a different degree of RNFL loss between the eyes with ON and the unaffected fellow eyes, although they did not distinguish ON eyes from healthy control eyes, probably because of the parameters considered.

Although the differences we found were statistically significant as individual groups, for some parameters listed in Tables 1-3, the distributions of both groups were so wide that about 50% of patients in the ON group and about 50% of those in the control group were distributed in the same range. Due to such wide overlapping areas, one can neither clinically evaluate the structural changes of the retina of MS patients, nor can discriminate healthy eyes from eyes of MS patients. On the other hand we found some parameters such as ganglion cell complex or the global and focal loss, that were promising in detecting changes. As a result of neuronal loss, other than a decrease in RNFL

thickness, we found a thinning of the macula as also seen in previous reports and a decrease in GCC. The outer layer of the retina was not analysed by OCT as histopathological studies have already shown the atrophy to not be present in this area in MS eyes [7-16]. However, no quantitative measurements were performed because of technical difficulties, e.g. the partial post-mortem retina detachment in many of the eyes [23-25].

Both OCT devices were able to detect ganglion cell loss, however the TD-OCT was not able to segment the retinal layers and distinguish which layer was involved. In ON eyes an 18.1% reduction of the average thickness of the ganglion cells was observed in contrast to eyes without ON. However, when analysing ganglion cell volume global loss this was 27.3 µm in eyes with previous ON, compared to a loss of about 8.5 µm in eyes without ON. This indicates that also MS patients without ON present a mild loss of ganglion cells. This cross-sectional study could be useful in distinguishing healthy patients from patients with a loss of GCC, however, no correlation or diagnostic capacity of GCC was studied.

A potential limitation of the study is the relatively low number of MS patients included. Although the size of our study is in accordance with previous similar reports, a larger set of patients may be desired to obtain information with even higher power.

In conclusion this study evaluated the usefulness of OCT imaging in patients with MS in order to determine the structural changes of the retina of MS patients. Furthermore, the parameters such as focal and local loss which could best discriminate eyes of healthy subjects from eyes of MS patients were determined, even in a further studies needed in the future. Thinning of the inner retinal layers is present in eyes of MS patients regardless of previous ON. Macular OCT image might provide a better insight into the pathology of neuronal loss and could therefore play an important role in the diagnosis and follow-up of patients with MS.

Running Head: OCT Imaging In MS

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