ORIGINAL COMMUNICATION

Retinal nerve fiber layer thickness in subgroups of multiple sclerosis, measured by optical coherence tomography and scanning laser polarimetry

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Abstract Optical coherence tomography (OCT) and scanning laser polarimetry (GDx ECC) are non-invasive methods used to assess retinal nerve fiber layer (RNFL) thickness, which may be a reliable tool used to monitor axonal loss in multiple sclerosis (MS). The objectives of this study are (1) to compare OCT with the GDx ECC; (2) to assess and compare the RNFL thickness in subgroups of MS. Ophthalmologic examination and RNFL assessment by OCT and GDx were performed in 65 MS patients (26 relapsing-remitting (RRMS), ten secondary-progressive (SPMS), 29 primary-progressive (PPMS)). Twenty-eight patients (43%) had a history of optic neuritis (ON). Adjustments were made for age and disease duration. RNFL thickness was reduced in eyes with previous ON ($p < 0.01$). No differences were found between PPMS and relapse-onset MS. OCT and GDx ECC measurements were moderately correlated (rho $= 0.73$, $p < 0.01$). Visual field-mean deviation (MD) values correlated with OCT means ($r = 0.44$, $p < 0.01$) and GDx ECC TSNIT average ($r = 0.41$, $p < 0.01$). In patients without previous ON, EDSS correlated with MD ($r = -0.36$, $p < 0.01$), visual field-pattern standard deviation (PSD) ($r = 0.30$, $p < 0.05$), OCT means ($r = -0.31$–0.30, $p < 0.05$) and macular volume ($r = -0.37$, $p < 0.01$). For MSIS-29 physical impact score, significant correlations were found with MD ($r = -0.48$, $p < 0.01$) and PSD ($r = 0.48$, $p < 0.01$). Conclusions: No differences between PPMS and relapse-onset MS subgroups were found. RNFL thickness was reduced in eyes with previous ON. Although OCT and GDx ECC findings were moderately correlated and showed significant correlations with measures of visual function in patients without previous ON, EDSS correlated significantly with visual and OCT measures, but not with GDx ECC.

Keywords Multiple sclerosis · Retinal nerve fiber layer · Optical coherence tomography · Scanning laser polarimetry

Introduction

The central origin of irreversible disability in patients with multiple sclerosis (MS) lies in axonal loss [1]. Brain atrophy on magnetic resonance imaging (MRI) is the most used marker to monitor disease progression. However, correlations between MRI measurements and clinical disability are limited [2, 3]. More specific measures of axonal damage and neuronal loss in MS are needed.

The retina is part of the central nervous system and easily accessible for clinical examination. The retinal nerve fiber layer (RNFL) is composed predominantly of unmyelinated axons of retinal ganglion cells. Measurements of the RNFL give relatively direct measures of axons and thus of axonal damage. Optical coherence tomography (OCT) and scanning laser polarimetry (GDx) are non-invasive methods used to measure peripapillary retinal nerve fiber layer (RNFL) thickness. Both are established techniques used in glaucoma, to detect early glaucomatous damage [4]. OCT measures RNFL thickness by using interference patterns of backscattered near-infrared light, analogous to B-scan ultrasound and with an axial resolution of less than

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10 μm [5]. In contrast, GDx indirectly quantifies the RNFL thickness by using polarized light that undergoes a phase shift after passing through the RNFL [6]. GDx ECC is a new device with enhanced corneal compensation (GDx ECC). It has been introduced to optimize images of RNFL morphology by improving the signal-to-noise ratio, and to obtain a better structure–function relationship than with earlier versions of GDx, the GDx FCC and GDx VCC [7–9]. Both OCT and GDx analyse and express the average RNFL thickness in micrometers. However, because of the difference in technique of both methods, the RNFL measurements of OCT and GDx in microns are not comparable [5].

Several studies with OCT have demonstrated RNFL thinning in optic neuritis (ON) [10–12], and MS [13–22]. In patients with optic neuritis or MS, fewer studies have used GDx [23–25]. Comparative studies on differences between OCT and GDx RNFL measurements mostly have been performed in controls, glaucoma [26], and only three groups published comparisons of the two techniques in MS patients [27–31]. However, the only studies available on GDx in MS until now, made use of GDx VCC instead of the newer software version GDx ECC. From these groups only one investigated correlations with disability (EDSS), but not with MS subtype [27, 29, 30]. These studies comparing OCT with GDx have produced conflicting results concerning the discriminating value of both techniques.

The aim of the present study was (1) to compare the OCT with GDx ECC; (2) to assess the value of these techniques in subgroups of MS.

Methods

Participants

Consecutive patients with a diagnosis of MS were recruited through the Department of Neurology of the Erasmus Medical Centre (Rotterdam), from December 2004 to March 2008. Patients were included if the diagnosis was verified by one of the senior neurologists based on the McDonald criteria [32]. For specific sub-comparison of MS types, we purposely included a relatively high number of patients with primary progressive MS (PPMS). Excluded were patients with ophthalmologic diseases that might impair or bias OCT and GDx ECC measurements (e.g. diabetes, primary open angle glaucoma, abnormal discs with suspicion of normal tension glaucoma, anomaly of the disc, opacity of cornea or lens, severe nystagmus). The medical ethical committees of the participating hospitals approved this study, and all patients gave written informed consent.

Measurements

All patients underwent a neurological and ophthalmologic examination. Type of MS (relapse-onset (RRMS/SPMS) or PPMS), time since first symptoms, time since diagnosis, Expanded Disability Status Scale (EDSS), Multiple Sclerosis Impact Scale (MSIS-29) and Multiple Sclerosis Severity Scale (MSSS) were assessed.

MSIS-29 measures the physical and psychological impact of MS from the patient's perspective. The physical subscale includes 20 items and the psychological subscale nine items. Total scores for both subscales are generated by summing individual items (scored 1–5), with high scores indicating greater impact [33]. MSSS corrects EDSS for disease duration (time since first symptoms) by comparing an individual's disability with the distribution of scores in cases having equivalent disease duration [34]. To be able to compare outcome parameters in different groups, we aimed to match for disease duration (time since first symptoms and time since diagnosis).

A history of acute ON was determined by self-report and physician report and confirmed by medical record review. Eyes with ON in the last 3 months were not included.

Visual testing

All participants underwent a complete ophthalmologic examination including measurement of visual acuity (logMAR acuity); intraocular pressure (IOP) measurement by Goldmann applanation tonometry and fundoscopy, standard automated perimetry (SAP; Humphrey Field Analyzer (30-2 SITA standard), Carl Zeiss Meditec Inc, Dublin, CA), evaluating visual field mean deviation (MD) and visual field pattern standard deviation (PSD).

Retinal imaging: GDx

Both eyes of all participants were imaged with GDx ECC (released for research purposes in the commercially available GDx VCC, Carl Zeiss Meditec, Inc., Dublin, CA), to measure RNFL thickness. Details of the working principle of the GDx device and GDx ECC have been described elsewhere [8, 35].

Images were taken through undilated pupils while the ambient light was left on. Only typical images of high quality, that is those with a centred optic disc, well-focused, evenly and justly illuminated throughout the image, without any motion artefacts, were selected. The TSNIT RNFL thickness was used as summary parameter for GDx, furthermore a superior average, inferior average and nerve fiber indicator (NFI) were calculated.

Retinal imaging: OCT

Participants underwent measurement of RNFL thickness for both eyes using OCT (Stratus OCT 4.01 software, Carl Zeiss Meditec, Dublin, CA). The macula volume (macula thickness) and RNFL thickness 3.4 scan protocol were used for OCT (we calculated the average of three circumferential scans for 360° around the optic disc; 256 axial scans; diameter 3.4 mm). Scanning was performed after pharmacological dilation. Average RNFL thickness for 360° around the optic disc was recorded as the OCT 3.4 average. Also, temporal quadrant thickness (316° to 45°), superior quadrant thickness (46° to 135°), nasal quadrant thickness (136° to 225°) and inferior quadrant thickness (226° to 315°) were measured.

Statistical analyses

Differences between groups on clinical and demographic characteristics were analysed by independent-samples t tests (two-tailed), independent-samples Mann–Whitney test for ordinal data (two-tailed), and the Chi-squared test for categorical data. The associations between patient characteristics and ophthalmological test results were explored using Spearman correlations (rho) and partial correlations (r). Linear regression analysis was used to compare scores on the ophthalmological tests between eyes with and without previous optic neuritis (adjusted for age and time since diagnosis), and between eyes of patients with primary progressive MS (PPMS) and relapse-onset MS (adjusted for age and time since diagnosis). All analyses were performed using SPSS 12.0, and a p value lower than 0.05 was considered statistically significant.

Results

Study population

The study enrolled 65 patients; 28 of these patients (43%) had a history of optic neuritis, 20 unilateral and eight bilateral. For analyses, we included randomly one eye for patients without ON (37 eyes) and randomly one eye for patients with a history of bilateral ON (eight eyes). For patients with a previous unilateral ON (19 eyes) the measurements of the other eye (=fellow eye; 20 eyes) were included in a sub-analysis. In one patient with a previous unilateral ON, this eye could not be measured because of an artefact, and only the fellow eye was included. Three patients could not be included in the study because of nystagmus, which interfered with the measurements.

For patient characteristics see Table 1. Fifty-seven percent of the patients had EDSS scores higher than 4.0. Disease duration (time since first symptoms and time since diagnosis) of patients with relapse-onset MS and PPMS were not statistically different ($p > 0.5$). Figure 1 shows average RNFL thickness, TSNIT average measured with GDx ECC and OCT means, in patients with and without a previous ON. We included the unaffected fellow eyes in the group of eyes "without ON" because a sub-analysis did not show any significant differences between measurements of the fellow eyes in comparison with eyes without a

Table 1 Characteristics of the study population

	MS type		
	Total	Relapse-onset	PP
n	65 (100%)	36 (55%)	29 (45%)
Age (years)	48.5 (11.5)	44.7 (10.2)	53.2 (11.5)
Sex (women)	69% (45)	81% (29)	55% (16)
Time since first symptoms (years)	12.5 (7.8) (median 11.5)	12.0 (7.4) (median 10.5)	13.1 (8.3) (median 12.7)
Time since diagnosis (years)	8.6 (7.1) (median 7.4)	9.1 (7.1) (median 8.0)	8.0 (7.2) (median 6.9)
EDSS median (IQR)	6.0 (3.5–6.5)	4.0 (2.0–6.5)	6.0 (4.0–6.5)
MSSS	6.2 (2.5) (median 6.4)	5.4 (2.7) (median 5.9)	7.0 (2.0) (median 7.4)
MSIS-29 physical score	40.6 (26.1)	31.1 (25.0)	52.3 (22.8)
MSIS-29 psychological score	29.2 (21.3)	23.7 (20.4)	36.0 (20.6)
Number of eyes analysed	84	50	34
Eyes with history of optic neuritis/insidious progressive optic neuropathy	32% (27)	42% (21)	18% (6)

Categorical variables are shown in % (n) and continuous variables in mean (SD), unless otherwise indicated
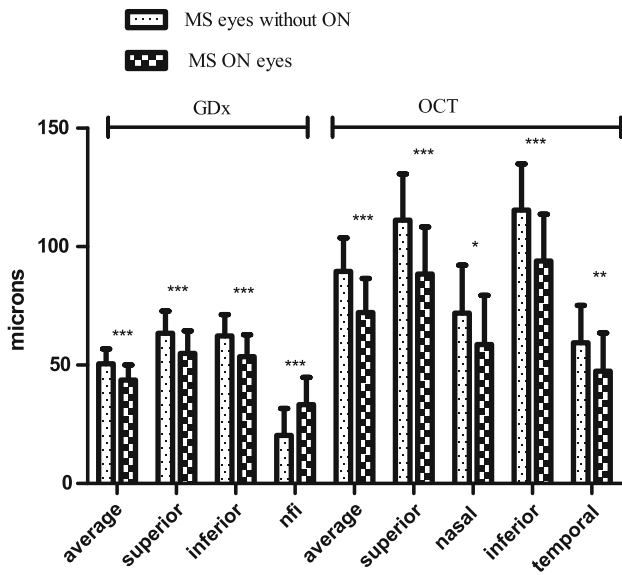
IQR interquartile range

Fig. 1 GDx and OCT measurements for MS eyes without ON and MS ON eyes. GDx and OCT adjusted for age and time since diagnosis. *nfi* nerve fiber indicator. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$
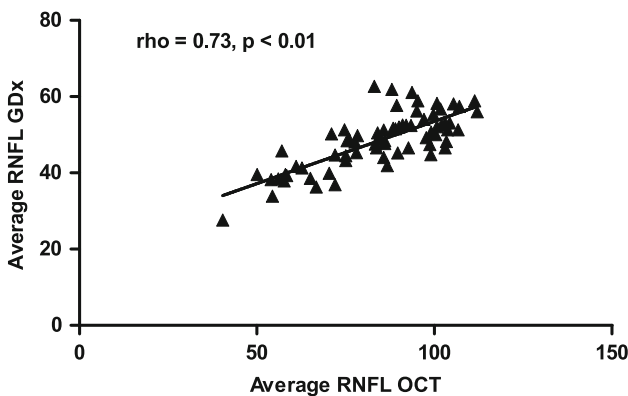

Fig. 2 Correlations between OCT and GDx measurements (MS eyes total). For eyes without ON: rho = 0.57, $p < 0.01$; eyes with ON: rho = 0.79, $p < 0.01$

Table 2 Correlations between visual function measures and GDx TSNIT average/OCT average

	GDx	OCT
LogMAR acuity	−0.61	−0.56
Mean deviation (dB)	0.41	0.44
Pattern standard deviation (dB)	−0.31	−0.34

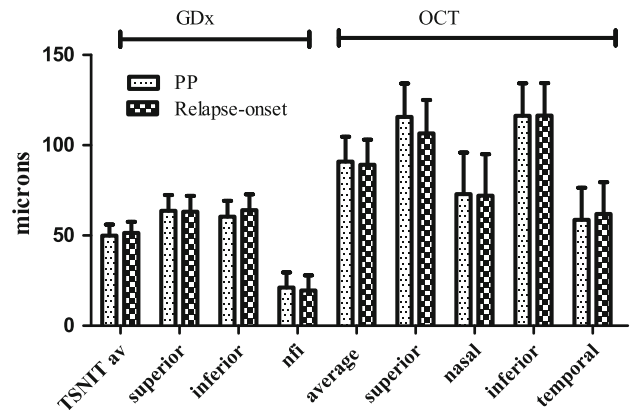Correlations for MS eyes total; all correlations $p < 0.01$

Fig. 3 OCT and GDx in PP and relapse-onset MS. Eyes without previous ON, adjusted for age and time since diagnosis

(Table 2). Macular volume measured with OCT was significantly reduced in MS eyes with previous ON (6.3 ± 0.5) in comparison with MS eyes without previous ON (6.7 ± 0.5; $p = 0.001$), adjusted for age and time since diagnosis.

OCT and GDx ECC in different subgroups of MS

Specifically for this sub-comparison we included a relatively high number of PPMS patients in this study. However, no significant differences were found in RNFL thickness when comparing eyes of patients with PPMS and relapse-onset MS. Figure 3 shows results for eyes without previous ON, adjusted for age and time since diagnosis.

In both subgroups, OCT and GDx measurements were highly correlated (PPMS rho = 0.73; relapse-onset MS rho = 0.77, $p < 0.01$).

Relationship between visual measures and disability

EDSS was negatively correlated with measures of visual field and OCT RNFL thickness, for eyes without previous ON, after adjustment for age. For GDx ECC correlation with EDSS was not statistically significant (Table 3). For MSIS-29 physical scores, significant correlations were found with visual field MD and PSD, after adjustment for

history of ON (results not shown). MS eyes with previous ON had reduced RNFL thickness compared to patients without ON measured with GDx ECC (TSNIT average 43.7 ± 6.4 versus 50.5 ± 6.3; $p < 0.001$) as well as with OCT (mean 72.2 ± 14.4 versus 89.5 ± 14.2; $p < 0.001$), adjusted for age and time since diagnosis. Measurements with OCT and GDx ECC were moderately correlated (MS eyes total rho = 0.73, $p < 0.01$; MS eyes without previous ON rho = 0.57, $p < 0.01$; MS eyes with previous ON rho = 0.79, $p < 0.01$). Figure 2 shows correlations for MS eyes total. Average RNFL thickness measured with OCT and GDx ECC showed significant correlations with measures of visual function (visual acuity and visual field)

Table 3 Age-adjusted correlations (r) between EDSS and visual/retinal measures

	EDSS	p
LogMAR acuity	−0.02	NS
Mean deviation (dB)	−0.36	<0.01
Pattern standard deviation (dB)	0.30	<0.05
GDx TSNIT average	−0.20	NS
OCT 3.4 average	−0.30	<0.05
Macular volume (OCT)	−0.37	<0.01

Correlations for eyes without previous ON

age ($r = 0.48$, $p < 0.01$), but MSIS-29 physical scores showed no correlations with GDx ECC and OCT measurements. After excluding the fellow eyes from the eyes without previous ON, the same correlations were found.

Discussion

Studies on retinal measures in distinct subgroups are scarce [18, 20]. The aim of this study was to compare OCT and GDx ECC in different subgroups of patients with MS, in assessing RNFL thinning as a measure of axonal loss.

Before interpreting the results in a group of patients in which a substantial proportion had a history of ON, it should be noted that we chose to use the ophthalmological parameters of the previously unaffected eye for comparison of subgroups of MS and disability. This appears the most reliable method, as previous inflammatory attacks may confound the natural cause of neurodegeneration in the eye. Unfortunately, whether only the unaffected eye has been studied has not always been clearly described in other publications.

Results of OCT and GDx ECC were correlated to a moderate extent (rho = 0.73). Both techniques did not differ in their capacity to distinguish eyes with and without previous ON, and they both showed good correlations with measures of visual function. Our a priori idea was to find differences in RNFL thickness between relapse-onset and PPMS. Regarding the eyes without a history of ON, there were no differences observed between relapse-onset MS and PPMS after adjustment for disease duration. Previous studies have mainly included patients with RRMS, therefore studies that included different subgroups of MS are scarce. One investigation that compared PPMS patients with SPMS patients showed relatively enhanced thinning of RNFL in secondary progressive patients [18]. The first group that combined the whole spectrum of disease courses, studying RRMS, SPMS and PPMS subgroups in comparison to controls, did not find any differences in average RNFL thickness between the different subgroups

[20]. The fact that in our comparable study we also observed no differences between relapse-onset and PPMS may relate to the lack of clear cut differences between these two disease subtypes [36, 37].

With respect to disability, we showed that EDSS scores correlated moderately with OCT-assessed RNFL thinning in MS patients. No correlation was found between EDSS and the GDx-assessed values. It cannot be excluded that this is due to the lack of statistical power. Still, the few other studies after GDx in MS patients also did not find correlations between EDSS and GDx RNFL thickness [27, 29, 30]. This could lead to a cautious conclusion that GDx is not the appropriate tool to investigate the correlation between retinal axonal damage and neurological disability. Also, others have suggested that GDx is less accurate than OCT for detecting the inflammatory and neurodegenerative components of the MS disease process [23, 31], perhaps because it was less sensitive in detecting temporal and nasal quadrant losses in the RNFL previously [38]. The relation observed here between EDSS and OCT parameters is in line with several other studies concerning the correlations with neurological disability [14, 16, 17, 21, 39]. It should be acknowledged that a couple of studies do not confirm these findings [18, 22]. Differences between these studies may well be caused by different compositions of the included study populations. Our study population had relatively progressed disease, with a median EDSS of 6.0. It is known that the EDSS in the higher ranges have poorer responsiveness because of a ceiling effect [40]. Despite the indications that RNFL measurements can be a used as a surrogate marker for neurodegeneration in MS, one should not forget that in our study conventional visual field parameters showed significant correlations with neurological function (EDSS and MSIS-29 physical subscore). In the future it would seem of interest to determine whether the levels of association between either visual field or retinal parameters and disability are in fact distinct for low and high disability subgroups of MS patients. Also more sensitive instruments to determine visual acuity could provide extra information. A promising measure for visual acuity in MS patients is the low-contrast Sloan letter acuity chart [41], which unfortunately has not been used in our study protocol.

As previous studies that noted clear correlations between RNFL thickness and EDSS were mostly performed in groups with relatively lower disability (median around 2.0) [14, 16, 17, 21, 39], one might expect the best associations between RNFL thickness and neurological disability in patients with an EDSS in the lower range. Therefore the use of this novel tool for measuring neurodegeneration in MS patients may be optimally used in little or modestly affected patients. This is especially the group of patients at whom most current trials are focusing.

A recent longitudinal study could not detect disease-related ongoing loss of retinal axons in 34 progressive MS patients [42]. Further investigations with longitudinal data are needed, so that the determinants of the association between RNFL thinning, visual function disability and axonal loss can be unravelled.

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