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Retinal nerve fiber layer sector-specific compromise in relapsing and remitting multiple sclerosis

Anette S. Loughran-Fjeldstad [a,*], Noel G. Carlson [b,c], Cassandra D. Husebye [a], Lawrence J. Cook [d], John W. Rose [a,b]

[a] Department of Neurology, University of Utah, 729 Arapeen Drive, Salt Lake City, UT 84108, USA
[b] Neurovirology Research, VA SLC HCS, GRECC, 500 Foothill Drive, Salt Lake City, UT 84148, USA
[c] Department of Neurobiology & Anatomy, University of Utah, 20 North 1900 East, Salt Lake City, UT 84132 USA
[d] Department of Pediatrics, University of Utah, 295 Chipeta Way, Salt Lake City, UT 84108, USA

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ABSTRACT

Objective: To evaluate quadrant and sector retinal nerve fiber layer (RNFL) thickness and total macular volume (TMV) in relapsing–remitting multiple sclerosis (RR-MS) patients.
Methods: Optical coherence tomography measures of RNFL and TMV were studied in 321 eyes without prior optic neuritis (ON) (MS unaffected), 151 eyes with prior ON (MS affected), and 148 healthy control eyes.
Results: Mean RNFL thickness was significantly lower in the MS affected and MS unaffected groups relative to the control group ($p < 0.0001$). RNFL thicknesses in the superior, inferior, and temporal quadrants were significantly reduced in MS unaffected (113 ± 15 μm, 119 ± 17 μm, 63 ± 13 μm) ($p < 0.001$) and MS affected groups (99 ± 19 μm, 103 ± 21 μm, 51 ± 13 μm) ($p < 0.0001$) compared with that in controls (120 ± 14 μm, 128 ± 15 μm, 69 ± 8 μm, respectively). TMV was significantly reduced in both the MS affected and MS unaffected groups compared with that in the controls ($p < 0.0001$).
Conclusion: Quadrant, sector, and PMB RNFL thicknesses are significant individual measures in RR-MS for both affected and unaffected eyes and may prove valuable in future investigations including biomarker and outcomes research.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease that affects the central nervous system (CNS) [1] and is a leading cause of neurological disability affecting young adults [2]. MS leads to progressive axonal loss and degeneration of neurons [3], and often result in permanent disability [4]. Optic neuritis (ON) [5] is the first demyelinating event in approximately 20% of MS patients, and 30–70% of MS patients experience ON during the course of the disease [6]. ON results in thinning of the retinal nerve fiber layer (RNFL) and compromise of the total macular volume (TMV) [7,8]. These detrimental retinal changes result from both axonal thinning with associated loss of neurofilament phosphorylation and subsequent axonal transection with retrograde degeneration [9,10]. Visual problems in MS can result from a range of pathologies, including inflammation, degeneration, demyelination, and axonal loss in the anterior visual pathway (retina, optic nerves, chiasm and tracts) [11]. Alterations in the visual system can be important indicators of CNS neurodegeneration and potential impact of neuroprotective therapy [12]. Optic atrophy and compromise of the RNFL are common findings on ophthalmologic examinations of patients with MS [13], and RNFL thinning in MS patients has been linked to brain atrophy [14] and volumetric changes in the white matter as assessed by magnetic resonance imaging [15]. Other studies found that RNFL and ganglion cell layer (GCL) associated with normalized brain volume, white matter volume and gray matter volume in relapsing and remitting (RR)-MS patients with previous ON [16], whereas Saidha et al. found the strongest relationship between GCL and whole-brain atrophy in progressive MS [17]. RNFL decrease and optic nerve atrophy are more prevalent in those with a prior history of ON [18,19], but can also occur throughout the natural progression of MS in the absence of ON [20].

Optical coherence tomography (OCT) is a non-invasive imaging technique that can quantify RNFL thickness in vivo [20]. Initially, OCT was used to not only examine retinal axonal loss in glaucoma [19,21], but also to demonstrate RNFL loss in the eyes of MS patients with [19,22] and without previous ON [18,19].

Our objective was to use spectral-domain (SD) OCT to examine the RNFL thickness with special attention to analyses of RNFL quadrants and sectors as well as TMV. These measurements were completed in patients diagnosed with RR-MS (with or without a prior history of ON) and compared to results obtained with healthy controls to determine

* Corresponding author at: Department of Neurology, University of Utah, Imaging & Neuroscience Center, 729 Arapeen Drive, Salt Lake City, UT 84108, USA.
E-mail addresses: a.fjeldstad@utah.edu (A.S. Loughran-Fjeldstad), noel.carlson@neuro.utah.edu (N.G. Carlson), dee.husebye@genetics.utah.edu (C.D. Husebye), Larry.cook@hsc.utah.edu (L.J. Cook), jrose@genetics.utah.edu (J.W. Rose).

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the significance of the measurements, their distribution and their suitability as biomarkers for disease state. We hypothesized that when compared to controls, the thickness of the RNFL quadrants and the RNFL sectors may be selectively compromised in MS patients both with and without ON. Here we describe the injury to the RNFL in more detail through quadrant and sector analysis.

2. Materials and methods

2.1. Study design and patient population

A total of 236 patients from the University of Utah with clinically definite RR-MS (ages 49 ± 12 years) according to the revised 2005 McDonald criteria [23] and 74 healthy controls (ages 47 ± 12 years) participated in this cross-sectional study. MS sub-type classification was based on the clinical course and determined by the treating physician (JWR), and the ON attacks were documented in our medical records and determined by the treating physician (JWR). All MS patients underwent a fundoscopic eye exam and a visual acuity test at the time of the clinic visit. Patients with a history of eye disease that may affect OCT measures (e.g. glaucoma, retinal disease, age-related macular degeneration, diabetes, neuromyelitis optica (NMO), Alzheimer's disease or Parkinson's disease) were excluded. Patients had to be free of relapse and ON for at least six months prior to the OCT assessment. None of the patients were taking Gilenya® (fingolimod) at the time of the study.

One goal of this study was also to assess whether there were RNFL differences between the MS patients that had 2 affected eyes compared with 1 affected eye, and similarly, examine potential differences between MS patients with 2 affected eyes compared with 2 unaffected eyes. The rationale behind this partitioned approach is based on evidence from previous studies that suggest a more frequent thinning of the RNFL in eyes with a prior history of ON [18,19], but this can also occur through the natural progression of MS in the absence of ON [20]. Even if the clinical burden of MS is low, a subclinical loss of RNFL in MS patients without prior ON has been suggested [22].

2.2. Ethics

These investigations were approved by the Institutional Review Board of the University of Utah, and all participants provided written informed consent prior to their participation in accordance with the ethical standards of the 1964 Declaration of Helsinki.

2.3. Spectral-domain optical coherence tomography

The subjects in this study underwent SD-OCT examination using the Heidelberg Engineering Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany, Spectralis software version 5.6.3.0, Eye Explorer Software 1.7.1.0). This SD-OCT utilizes a scanning superluminescence diode to emit a scan beam with a wavelength of 870 nm to acquire 40,000 A scans/s with a depth resolution of 7 μm, from which various retinal layers can be identified, and objectively and precisely assessed [24] (Fig. 1). The OCT device also combines OCT and confocal infrared laser ophthalmoscope, which provides a reference infrared fundus image [24]. The combination of eye tracking (TruTrac) and high-speed scanning reduce noise caused by natural eye movement [25]. In addition, TMV scan (30° × 25°, 61 B-scans (121 μm distance between B-scans), ART 9; 768 A-scans each) was centered over the macula after the TruTrac was activated. The following OCT parameters were calculated: global mean RNFL thickness around the optic nerve head from nasal, inferior, temporal, superior to nasal (NITSN) quadrant, and further RNFL sector thicknesses (temporal–inferior; TI, temporal–superior; TS, nasal–inferior; NI, nasal–superior; NS and peripapillary macular bundle (PMB)). The mean retinal thickness was measured in μm per quadrant of the peripapillary area whereas the macular scan provided volume data (mm^3). All scans were performed by an experienced operator (ASL-F). The images were subsequently reviewed for acceptable signal strength (>25), correct placement of the scan ring and appropriate beam placement.

2.4. Expanded disability status scale (EDSS)

The EDSS scale ranges from 0 (no disability) to 10 (death from MS) [26]. EDSS scores for the MS patients participating in the study were determined by the treating neurologist (JWR) and ranged from 0–7 with a mean of 1.7 (Table 2).

2.5. Data analyses

For our studies we have examined the eyes of patients and healthy controls by status as unaffected or affected by ON. Group 1 and group 2 together are labeled the 'MS unaffected group'. Group 3 and group 4 together are labeled the 'MS Affected group'. In more detail: The MS unaffected group consists of patients with 2 eyes not affected by optic neuritis (*number of eyes* = 256) in addition to the patients that have unilateral optic neuritis (*number of eyes* = 65), where the non-optic neuritis eyes are included in the 'MS unaffected group' (*Total number of eyes* = 321) (Table 1). The same grouping procedures were applied when creating the 'MS Affected group' (*Total number of eyes* = 151). Here we included the eyes of patients with bilateral optic neuritis (*number of eyes* = 86) and the eyes that were affected in the unilateral optic neuritis group (*number of eyes* = 65). These five groups of eyes are summarized as;

Here we compare the eyes in the MS unaffected (no prior optic neuritis) and MS affected (prior optic neuritis) groups with the healthy control group. Further, the MS patients that had 2 affected eyes and the MS patients that had 2 unaffected eyes were also compared with the healthy control eyes. Similarly, the MS patients that had 1 affected eye and 1 unaffected eye were compared with the control eyes. In addition, the MS patients that had either 2 affected or 2 unaffected eyes were compared with those MS patients that had only 1 affected or 1 unaffected eye. Only MS patients and healthy controls with complete data for both eyes were included in the analyses.

2.6. Statistical analyses

This was a cross-sectional exploratory study design, where no adjustments for multiple comparisons were made. Kolmogorov and Smirnov test was performed on all dependent variables to test for assumption of normality. Mann–Whitney *U*-tests were performed to examine significant differences in age between the groups. Partial correlation analyses, adjusted for disease duration, were used to examine the relationships between EDSS and OCT parameters in the MS groups. Statistical differences of the various OCT variables between the groups were calculated with a linear model using generalized estimating equations (GEE) with compound symmetry correlation structure to account for gender and within-subject inter-eye differences. Statistical analyses were performed using commercially available software (SPSS 17.0, SPSS Inc., Chicago, IL and Graphpad Software InStat 3.0, La Jolla, CA). All of the data are expressed as mean ± SD. Statistical significance was set as $p \leq 0.05$.

3. Results

3.1. Patient population

We enrolled 310 subjects including 74 healthy controls and 236 patients with relapsing and remitting multiple sclerosis. The RR-MS group included patients without ON, with unilateral ON, and with bilateral ON. The subject demographics are presented in Table 2. There were no significant differences in age between individuals in the MS group as a