Journal of the Neurological Sciences 302 (2011) 19–24

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Cup to disc ratio by optical coherence tomography is abnormal in multiple sclerosis

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ARTICLE INFO

Article history:
Received 29 September 2010
Received in revised form 13 December 2010
Accepted 15 December 2010
Available online 11 January 2011

Keywords:
Multiple sclerosis
Demyelinating disease
Neuro-ophthalmology
Optic nerve
Cup to disc ratio
Optic neuritis

ABSTRACT

Objective: To identify and characterize cup to disc ratio (CDR) and related optic nerve head abnormalities in multiple sclerosis (MS) using spectral domain optical coherence tomography (OCT).
Background: While CDR is routinely assessed by ophthalmologists in the evaluation of glaucoma, CDR and related optic nerve head metrics remain largely unexplored in MS.
Design/methods: Cirrus-HD (high density) OCT was used to evaluate average CDR, vertical CDR, optic disc area, optic cup volume, and neuro-retinal rim area in 105 MS patients and 88 age-matched healthy individuals. High-contrast (100%) visual acuity, 2.5% low-contrast letter acuity and 1.25% low-contrast letter acuity were assessed in 77 MS patients. Two-sample t-tests were used in the analysis of OCT-derived optic nerve head measures between healthy controls and MS patients. Multivariate regression (accounting for age and gender) was used to assess relationships between optic nerve head measures and visual function.
Results: Average CDR ($p = 0.007$) and vertical CDR ($p = 0.005$) were greater in MS patients compared to healthy controls, while neuro-retinal rim area was decreased in MS patients ($p = 0.001$). CDR increased with retinal nerve fiber layer (RNFL) thinning ($r = -0.29$, $p = 0.001$). 2.5% low-contrast ($p = 0.005$) and 1.25% low-contrast letter acuity ($p = 0.03$) were lower in MS patients with higher vertical CDR.
Conclusions/relevance: CDR (as determined by spectral domain OCT) is abnormal in MS and correlates with visual function. OCT-derived CDR and related optic nerve head metrics may represent an objective measure by which to monitor disease progression, and potentially neuroprotection, in therapeutic MS trials.

1. Introduction

Cup to disc ratio (CDR) is conventionally assessed by ophthalmologists in the diagnosis and monitoring of glaucoma [1,2]. Prior studies have also demonstrated increases in CDR following optic neuritis, as measured with time-domain OCT (Stratus-3) [3]. Further, optic nerve head changes, such as disc cupping, have also been observed in patients with ischemic and compressive optic neuropathies, as well as in patients with anterior visual pathway trauma [4–8]. These findings highlight that optic nerve head abnormalities, including increased CDR, may not exclusively result from glaucoma and may also result from non-specific optic nerve injury. Despite the extremely high predilection of the MS disease process to afflict the optic nerves (94–99% of MS patients have detectable optic nerve lesions at *post-mortem*), CDR and related optic nerve head measures remain largely unexamined in MS with spectral domain optical coherence tomography (OCT)[9,10]. The majority of OCT research in MS to date has primarily focused on evaluation of retinal nerve fiber layer (RNFL) thickness.

OCT uses non-invasive, low-coherence interferometry to obtain high-resolution tomographic images of retinal structures [11]. OCT-derived measures of RNFL thickness have been shown to correlate with brain volume, low-contrast visual acuity function, optic nerve atrophy (measured by both conventional and non-conventional MRI techniques), and clinical history of optic neuritis [12–20]. Quantification of retinal structures by OCT may provide an objective and precise method by which to characterize and monitor disease progression in MS, in an eloquent, accessible, and frequently afflicted tissue target of the disease process [21–23].

In this study, we used spectral domain Cirrus-HD OCT (Carl Zeiss Meditec Inc, Dublin, California) to determine if CDR and related optic nerve head measures differ between MS patients and healthy volunteers, evaluate their association with visual function, and determine their relationships with validated objective OCT-derived measures of retinal architecture including RNFL thickness.

2. Methods

The Johns Hopkins University (JHU), University of Pennsylvania (UPenn), and University of Texas-Southwestern (UTSW) Institutional Review Board approval was obtained for all study protocols. Written

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0022-510X/$ – see front matter
doi:10.1016/j.jns.2010.12.011

informed consent was obtained from all study participants before study procedures were initiated. Participants were excluded if they had a known history of ocular disease, glaucoma, diabetes, and/or a refractive error of greater than ±6 diopters. Participants between the ages of 18 and 65 were recruited to join the study. Patients of all MS subtypes were included. All OCT scans were performed by experienced OCT technicians on undilated pupils.

A total of 105 MS patients and 88 age-matched healthy controls (HC) were recruited to the study (JHU: 40 MS, 40 HC; UPenn: 32 MS, 21 HC; UTSW: 33 MS, 27 HC). Interrater reproducibility was determined in an independent cohort of 25 healthy volunteers and 25 MS subjects at JHU.

Retinal imaging was performed using Cirrus-HD OCT. Peri-papillary RNFL thickness measures were obtained using the Optic Disk Cube 200×200 protocol which utilizes 200 horizontal scans lines (each composed of 200 A-scans) to generate a 6 mm square grid. This scan protocol provides mean RNFL thickness (for 360° around the optic disc) and RNFL quadrant thickness measurements. Optic nerve head measures were obtained from the Optic Disk Cube 200×200 protocol using analysis software included in Cirrus-HD Version 5.0. Optic nerve head measures assessed included CDR (the average cup to disc ratio; square root of the cup to disc area ratio), disc area (total area within the disc margin, mm^2), cup volume (total volume of the cup, mm^3), integrated rim (area of the neuro-retinal rim, mm^2), and vertical CDR. The vertical CDR is a linear ratio of the diameter (Fig. 1).

Visual acuity measures (high- and low-contrast letter acuity) were assessed in a darkened room using retro-illuminated eye charts, with subjects wearing their habitual corrective long distance spectacles/contact lenses. Both Early Treatment Diabetic Retinopathy Study (ETDRS) charts and Sloan charts (2.5% and 1.25% contrast) were used [24]. The number of letters read correctly (letter acuity) was recorded in 77 MS patients.

Statistical analysis was completed on the right eye of all study participants to avoid bias due to inter-eye correlations. As the MS patients and healthy controls were age-matched, two-sample t-tests were used to analyze optic nerve head measures between the groups. Multivariate regression, accounting for age and gender was performed using Stata 11.0 (StataCorp, College Station, TX) to assess the relationship between CDR measures, RNFL thickness, and visual acuity scores. Partial correlation coefficients (r) and their associated p-values were determined. Intraclass correlation coefficients (ICCs) were calculated to assess the interrater reproducibility of the quantitative optic nerve head measures. ICCs were computed in SPSS Version 12.0 (SPSS Inc, Chicago, IL) using a two-way random model for absolute agreement. An ICC calculates the proportion of variance attributed to between group differences and can be used to determine the correlation between two members of one group. The greater the ICC (maximum value = 1), the greater the agreement between measures.

3. Results

A total of 105 MS patients and 88 healthy controls were recruited across the three academic centers (Table 1). The mean ages of MS patients and healthy controls were similar and comparable across all centers. Of the 105 patients, 34% (36 MS patients; 12 from each study site) had a history of optic neuritis (ON). Most participants had relapsing–remitting MS (Table 1).

Interrater reproducibility analysis of optic nerve head measures revealed excellent reproducibility for all measures (HC: ICCs 0.94–0.99, MS: 0.96–0.99). Analysis of MS patients and healthy controls was comparable, with narrow 95% confidence intervals across all measures in both cohorts (Table 2).

Average CDR was increased in MS patients when compared to healthy controls (MS: 0.49 ± 0.16, HC: 0.42 ± 0.18, $p = 0.007$). The average vertical CDR (MS: 0.48 ± 0.16, HC: 0.40 ± 0.18, $p = 0.001$) was also increased in the MS cohort, while rim area (MS: 1.28 ± 0.27, HC: 1.38 ± 0.22, $p = 0.005$) and RNFL thickness (MS: 83.3 ± 14.2, HC: 94.8 ± 10.2, $p < 0.001$) were decreased in our MS population. No difference was seen between the MS patients and healthy controls in disc area or cup volume or volume (Fig. 2A). In MS participants with a history of ON, the average

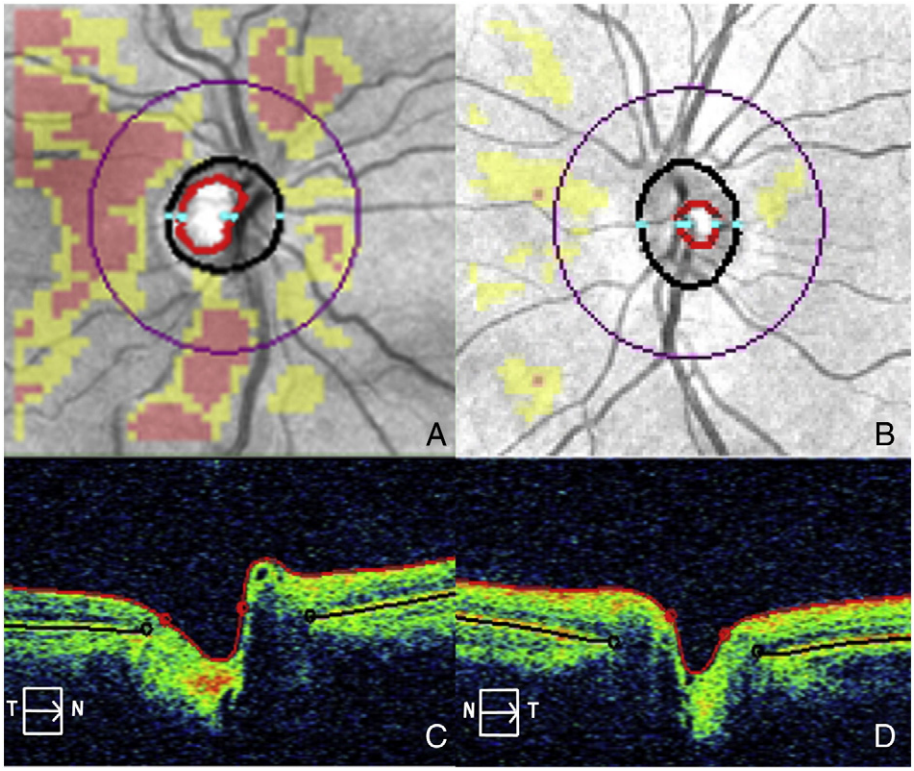

Fig. 1. Optic nerve images. RNFL deviation Map (Image A) and horizontal tomogram (Image C) of a MS patient (CDR: 0.59, RNFL: 59 μm). RNFL deviation Map (Image B) and horizontal tomogram (Image D) of a healthy volunteer (CDR: 0.42, RNFL: 96 μm). The cup is bounded by the red outline and the disc by the black outline in images A and B.