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Characterizing retinal structure injury in African-Americans with multiple sclerosis

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ABSTRACT

To examine retinal structure injury in African-Americans (AA) with Multiple Sclerosis (MS) compared to Caucasians (CA) with MS, we used spectral domain optical-coherence tomography (OCT) in this cross sectional study. The peripapillary retinal nerve fiber layer (pRNFL) and macular volume of 234 MS patients (149 CA; 85 AA) and 74 healthy controls (60 CA; 17 AA) were measured. Intra-retinal segmentation was performed to obtain retinal nerve fiber (RNFL), ganglion cell (GCL), inner plexiform (IPL), inner nuclear (INL), outer plexiform (OPL), outer nuclear (ONL), retinal pigment epithelium (RPE), and photoreceptor (PR) layer volumes. Study was approved by IRB, and informed consent obtained from all participants. We found that pRNFL was thicker in AA v. CA healthy controls (100.9 vs 97.00 μm, $p=0.004$). Compared to HC, MS patients demonstrated thinner pRNFL ($p<0.0001$), and lower TMV ($p<0.001$), macular RNFL ($p<0.0001$), GCL ($p<0.0001$), and IPL ($p<0.0001$). AAMS patients had thinner pRNFL (87.2 vs 90.0 μm, and lower TMV (8.2 vs 8.4 mm^3, $p=0.0001$), RNFL (0.73 vs 0.79 mm^3, $p=0.0001$), and GCL (0.94 vs 0.98 mm^3, $p=0.007$) than CAMS patients. Sub-analysis of patients without history of AON showed thinner pRNFL (88.9 vs 93.1 μm) and TMV (8.2 vs. 8.5 mm^3, $p<0.0001$) in AAMS compared to CAMS patients. In conclusion, this cross-sectional study provides evidence supporting greater retinal structure injury in AAMS compared to CAMS patients, irrespective of history of AON. Our findings are consistent with other studies demonstrating a more severe CNS tissue injury in AAMS patients.

1. Introduction

African-American MS (AAMS) patients appear to have a more aggressive disease course than Caucasian Americans (CAMS) patients (Cree et al., 2004; Kister et al., 2010; Weinstock-Guttman et al., 2003). Relative to CAMS, AAMS patients experience increased occurrence of multifocal symptoms, a shorter time from symptom onset to gait impairment, increased cognitive impairment, and more rapid accumulation of disability (Cree et al., 2004; Kister et al., 2010; Weinstock-Guttman et al., 2003). These findings were supported by observations that show more severe attacks followed by incomplete recovery, more frequent pyramidal system involvement, greater cerebellar dysfunction, and often a higher number of relapses in AAMS patients compared to CAMS patients (Cree et al., 2004; Kister et al., 2010; Weinstock-Guttman et al., 2003).

Over the past decade, several studies demonstrated that tissue injury visualized by MR imaging is worse in AAMS than CAMS patients (Weinstock-Guttman et al., 2010; Khan et al., 2015; Howard et al., 2012). Furthermore, AAMS patients appear to respond less favorably to disease-modifying therapy (DMT) than CAMS patients (Cree et al., 2005; Klineova et al., 2012). Visual dysfunction due to acute optic neuritis (AON) and retinal structure injury commonly occur in MS (Balcer, 2006). It has been reported that AON in AAMS patients results in more severe visual loss both at onset and a year after observation than CAMS patients (Phillips

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et al., 1998; Kimbrough et al., 2014). These observations highlighting the differences between AAMS and CAMS patients, have been summarized in a review suggesting that ethnicity may affect disease biology in MS (Khan et al., 2015).

Tracking optic nerve changes in patients with MS historically was limited to contrast sensitivity testing, visual evoked potentials and hand held ophthalmoscopic fundus examinations (Phillips et al., 1998; Bennett et al., 2014; Sergott, 2007; Gilbert and Sergott, 2007). However, advances in technology allow for rapid, non-invasive *in-vivo* visualization of the layers of the retina at a micron level with the use of Optical Coherence Tomography (OCT) (Saidha and Calabresi, 2014; Sergott et al., 2007), which uses near-infrared light to create cross-sectional or 3D images of the retina. This allows for quantitative objective estimation of axonal integrity by tracking the changes of unmyelinated axons in the retina. The early principal focus of OCT imaging in MS has been on the retinal nerve fiber layer (RNFL), which is the innermost layer of the retina that consists of unmyelinated axons originating from the ganglion cell neurons that enters the neural retinal rim of the optic disc, and subsequently coalesces as the optic nerve (Petzold et al., 2010). The RNFL is significantly thinner in patients with MS, with or without a history of AON, as compared to healthy controls (Petzold et al., 2010; Frohman et al., 2006).

To date, we are aware of only one published study that compared retinal structural injury in AAMS and CAMS patients (Kimbrough et al., 2014). This study identified accelerated retinal structure injury in AAMS patients, characterized by increased thinning of the peripapilllary RNFL (pRNFL) and of the combined ganglion cell and inner plexiform layers (GCL+IPL). These findings correlated with impaired high contrast visual acuity at baseline and with greater loss of low contrast visual acuity over time; thereby suggesting that ethnicity exerts differential effects upon retinal tissue injury in MS. Our current work further explores the integrity of retinal tissue in AAMS and CAMS patients using high-definition, spectral domain OCT.

2. Materials and methods

This was a cross sectional case-control study. The local Institutional Review Board approved the study and written informed consent was obtained from all participants.

2.1. Patient population

Patients with a relapsing form of MS based on the McDonald 2010 Criteria (Polman et al., 2011) were enrolled by convenience from the Multiple Sclerosis Center between 2013 and 2015. History of AON was determined using medical records documenting the diagnosis of AON. Clinical characteristics including age at the time of the OCT, disease duration, EDSS score, and duration of exposure to disease modifying therapy (DMT) were obtained from the MS Clinic database. Subjects with prior history of ophthalmologic disorders including retinal disease, glaucoma, diabetes and uncontrolled hypertension, or a clinical attack of optic neuritis in the past 30 days from time of their OCT scans, were excluded. The age/sex matched healthy controls were recruited from the family members of the patients, as well as the volunteers from our office staff.

2.2. Imaging technique

A trained OCT technician obtained all images using a single Heidelberg SPECTRALIS SD-OCT with N-Site Analytics platform, software version 6.0 (Heidelberg Engineering, Inc. Heidelberg, Germany). To evaluate the thickness of the pRNFL, a single line circular B-scan with a radius of 3.4 mm from the center of the papilla was used, with average automatic real time (ART) of 80.

The total macular volume (TMV) was measured as the volume between the inner limiting membrane and the boundary of the retinal pigment epithelium within a 6mm diameter circle centered on the fovea. A system built in macula scan was used (30×20 mm^2 area consisting of 61 B-scans, average ART of 9). All macula scans, including all MS patients and healthy control subjects, were analyzed using automated segmenting software (Heidelberg Engineering, version 6.0). Volume layer thickness was individually measured using the standard 1 mm, 3 mm, 6 mm ETDRS grid. The final volumes were measured within the 6 mm circle. The following layers were automatically segmented; Retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), photoreceptor layer (PR) and retinal pigment epithelium (RPE). Layers were not combined. All images were examined for misalignments to avoid potential segmentation errors as outlined in the OSCAR IB criteria (Tewarie et al., 2012). Specifically, all images were assessed for homogeneous reflectivity of the outer plexiform layer. Furthermore, after image acquisition, measurement of pRNFL and intra-retinal segmentation was conducted blinded to the race of the study participants.

2.3. Statistical analysis

Statistical analyses were performed using the STATA v. 13.1 (StataCorp, College Station Texas, USA). Evaluation of group differences was performed using Mann–Whitney *U* test. Mixed effect Multivariate Analysis of Variance (MANOVA) was performed with pRNFL thickness, macular volume, and segmented macular retinal layers (GCL, IPL, INL, OPL, ONL, PR, PRE) as dependent variables. The model included diagnosis (healthy controls, MS without history of AON, and MS with history of AON) and ethnicity as main effects, with an ethnicity-by-diagnosis interaction term. We also included age, gender, and disease duration as covariates. The F-values were divided by the interocular correlation coefficient to avoid conflation of statistical significance from use of paired biological data from the same subject (i.e. pair of eyes) (Rosner and Milton, 1988). The effect of ethnicity on the individual retinal layers and pRNFL thickness (global, as well as individual quadrants) was investigated using generalized estimating equation (GEE) with normal distribution and an identity link function (Hanley, 2003). Independent variables were modeled similar to that of the MANOVA analysis, i.e. ethnicity and diagnosis as main effects, with an interaction term of diagnosis-by-ethnicity. Age, gender, and disease duration were modeled as covariates. *P* value less than 0.05 were considered as statistically significant.

3. Results

Four hundred and sixty eight eyes from 234 MS patients and 147 eyes from 74 age-matched healthy controls (HC) were included for pRNFL assessment and intra-retinal macular segmentation. Twenty eyes were excluded for comorbidities, including macular edema, microcystic macular edema, glaucoma, high refractory error over 6 diopters, and poor image quality. Only one participant had a single eye included because of the inability to focus, rendering the other eye OCT data with sub-optimal quality data to be excluded from the study. No images were excluded due to misalignments.

Baseline characteristics of all participants are summarized in Table 1. The AA healthy control subjects were older than CA healthy controls (0.04). However, there was no significant difference in age between the AAMS and CAMS patients ($p=0.06$). The