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In Vivo Characterization of Retinal Microvascular Network in Multiple Sclerosis

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Multiple sclerosis (MS) is an inflammatory demyelinating disorder of the central nervous system featured with progressive neurodegeneration. Current management aims to reduce the inflammation through immunomodulation. However, the effectiveness of these treatments for preventing degeneration is unclear. Vascular alterations, which may be caused by inflammatory cerebral endotheliopathy,¹ could play a role in neurodegeneration. Indeed, increased incidence of ischemic stroke and diffuse hypoperfusion in normal appearing white and gray matter have been reported in MS patients.¹ Thus, studying cerebral microvascular changes may reveal the underlying pathophysiology that connects inflammation and neurodegeneration. Since the retina is an extension of the brain, the cerebral and retinal vasculature shares similar anatomical and physiological features. Furthermore, retinal nerve fiber layer (RNFL) thinning and ganglion layer (GCL) thinning are ocular biomarkers of neurodegeneration in MS.² Therefore, characterizing retinal microvascular changes in MS may help ascertain the role of vascular dysfunction in neurodegeneration. Direct measurement of the retinal vascular function can occur through the transparent ocular media. We have developed a method to quantitatively analyze non-invasive capillary perfusion maps (nCPMs) obtained by the Retinal Function Imager (RFI, Optical Imaging Ltd, Rehovot, Israel).³ The present study was done to determine the macular microvascular network changes in patients with relapsing and remitting MS (RRMS).

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We recruited 17 RRMS patients and 17 age-and-gender-matched controls (Table 1; available at www.aaojournal.org). Subjects with high refractive errors of more than +6.0 or –6.0 diopters (due to the limit of the imaging device), with any history of eye disease, or have been on systemic corticosteroids within 3 months prior to the study were excluded. Patients with a history of cerebral cardiovascular disease, hypertension, diabetes, or kidney disease were also excluded. The institutional review board approved this study and every subject signed informed consent. Each MS patient had an ophthalmic examination, including optical coherence tomography (OCT) imaging (Cirrus, Carl Zeiss Meditec, Dublin, CA) of the peripapillary RNFL (200 × 200 scan protocol). The nCPMs at the macular region of one eye from each subject was imaged using RFI. Image processing was performed to separate microvessels (width < 15 μm) from nCPMs and fractal analysis (box counting, D_{box} = vessel density) was performed in different annular and quadrantal zones (Fig. 1; available at www.aaojournal.org). We analyzed the relationship between the microvascular results and clinical manifestations and evaluated the receiver operator curve (ROC).

The D_{box} of retinal microvessels in the fovea-centered, circular zone (diameter = 3.6 mm) was significantly lower in MS patients in comparison to controls (Fig. 2). Quadrantal analyses indicated that the significant microvessel loss in MS patients was most evident in the superior quadrant ($P < 0.05$). Analyses of annular zones showed significant microvessel loss in 4 out of 6 total annular zones in MS patients when compared to the same zones in controls ($P < 0.05$). There were no significant differences between the two groups in the large vessel network ($P > 0.05$). The area under the ROC curve was 0.73 ($P = 0.03$) for microvessel D_{box} in the annular zone from 2.1 to 3.6mm. In the MS group, the D_{box} of microvessels in the 3.6 mm circular zone was not related to expanded disability status scales ($r = 0.1$, $P > 0.05$), disease duration ($r = 0.20$, $P > 0.05$), RNFL thickness ($r = -0.04$, $P > 0.05$), or mean arterial pressure ($r = 0.04$, $P > 0.05$).

We found that the retinal microvasculature in MS patients was impaired as delineated by its decreased density. This is in agreement with previously documented cerebral vasculopathies in MS.^{1,4} The microvasculature changes were located in almost all annular zones up to the diameter of 3.6 mm, with the more severe changes found in the superior quadrant. We hypothesize that a diffusive retinal microvascular loss occurs in MS patients. Direct microvascular damage could be related to inflammation since pathological studies showed retinal perivascular inflammation and fibrotic changes in vessels during various stages of MS.⁵ It has also been established that retinal volume loss (neurodegeneration) correlates with brain atrophy.² Thus, microvascular loss may also be partially attributed to the decreased metabolic demands due to the retinal neuronal loss.

Cerebral hypoperfusion is considered to be a major step in inducing the energy failure status in MS patients.¹ Therefore, understanding the relationship between microvascular changes and neurodegeneration may reveal the underlying pathogenesis of MS. Interestingly, no correlation was established between RNFL thickness and microvascular network loss. It might be because GCL thickness has a stronger correlation with cerebral neuronal damage.² Alternatively, this may be simply due to the small sample size in the present study. A longitudinal study with a larger sample size and GCL thickness measurements may yield more information. Nevertheless, this study demonstrates that retinal microvasculature

analysis could provide a promising approach for detecting microvasculature impairment in MS patients. To the best of our knowledge, this is the first MS study that quantitatively analyzed nCPMs after the separation of large vessels. These novel quantitative analyses of the retinal microvasculature may help increase knowledge of the fundamental pathophysiology of neurodegeneration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 2. Retinal microvessel network analysis in MS and controls

The D_{box} in the fovea-centered, circular zone (diameter = 3.6 mm) was significantly lower in MS patients in comparison to controls (A). Among the quadrantal zones, the D_{box} in the superior zone (B) was significantly lower in the MS group ($P=0.02$). Among the annular zones (C), the D_{box} of MS groups was significantly lower in the 1.1-1.6 mm and 2.1 – 3.6 mm annular zones in comparison to the control group in the same zones ($P < 0.05$). The area under the curve of the ROC (D) was 0.73 ($P = 0.03$) with a cut-off value of 1.5 for microvessel fractal dimension (D_{box}) in the 2.1 to 3.6mm annular zone. This provides a sensitivity of 77% and a specificity of 70% for predicting MS microvasculature impairment.