

Vitreous haze as a novel marker for neurodegeneration in MS possibly indicating impairment of the retinal glymphatic system

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Introduction: Neurodegeneration in multiple sclerosis (MS) is associated with proteolytic breakdown of proteins. Clearance of such neurodegenerative waste products is driven by the glymphatic system of the brain. Recently we proposed that the glymphatic system of the brain extends to the retina. The retinal glymphatic system exits to the choroid and to the vitreous. Vitreous deposition of neurodegenerative waste (vitreous haze, VH) can be quantified from OCT raw data by a novel algorithm.

Objective: To investigate the relationship between VH and neurodegeneration in MS.

Methods: A cross-sectional study in 315 patients with MS and 87 healthy controls (HCs). The VH was quantified on OCT macular volume scans using an automated algorithm and all VH scores were log transformed after data extraction. Associations between VH and measures of neurodegeneration were investigated with generalized estimating equations.

Results: VH scores declined with age ($\beta=-0.007$, $p<0.001$) and longer disease duration ($\beta=-0.009$, $p=0.004$) in MS patients. After controlling for age, there was a significant relationship between VH and grey matter volume ($\beta=0.001$, $p<0.001$), white matter volume ($\beta=0.001$, $p=0.002$), macular ganglion cell – inner plexiform layer thickness ($\beta=0.008$, $p<0.001$) and peripapillary retinal nerve fiber layer thickness ($\beta=0.004$, $p<0.011$). In addition, patients with the highest level of disability showed less VH compared to patients with moderate disability (mean difference 0.16, $p=0.020$) and a trend towards lower levels of VH compared to patients with mild disability (mean difference 0.14, $p=0.053$). On a group level however, the VH scores between patients and HCs were similar (mean difference 0.03, $p=0.419$).

Conclusion: This study suggested that VH may be used as a novel biomarker to indirectly assess neurodegeneration in MS. There are two likely biological explanation for the consistent inverse relationship between VH and structural and functional metrics. There may

be progressive impairment of the retinal glymphatic system in MS or a burnt-out stage of neurodegeneration is reached.