Consequential timeline of optic nerve and retinal changes compared with functional imaging assessments in autoimmune demyelination

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Background

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system that commonly causes optic neuritis. While people with MS can initially recover from optic neuritis, over one-third of these patients have abnormal visual function later in disease. Previous studies have also shown retinal nerve fiber layer thinning and retinal ganglion cell (RGC) loss in patients with MS and the disease model experimental autoimmune encephalomyelitis (EAE). This suggests that optic nerve demyelination and the resultant axonal damage eventually leads to permanent loss of retinal ganglion cells. There are, however, no studies assessing the temporal relationship between optic nerve myelin and axonal damage with regard to RGC loss.

Objective

The goal of this study is to define the consequential timeline of histopathological changes in the optic nerve and retina compared to longitudinal visual imaging and functional assessments.

Methods

EAE was induced in 8-week-old C57BL/6J male mice and continued for 15, 35, or 60 days post-EAE induction. Myelin and axonal integrity were evaluated by immunohistochemistry and confocal imaging. Brn3a+ RGCs were counted in twelve representative fields of one flat-mounted retina per mouse. Visual evoked potentials (VEPs) were measured using the LKC ganzfeld system. Spectral Domain-Optical Coherence Tomography imaging was performed using an Envisu OCT system and InVivoVue software from Bioptigen.

Results

Our immunohistochemical data show that demyelination and axonal injury is evident in the optic nerve as well as the spinal cord in C57BL/6J mice 35 days post EAE induction. At this time point, a statistically significant reduction in Brn3a+ RGCs is also observed. Furthermore, there is a delay in VEPs by day 15 that is sustained at day 35 post EAE induction. Retinal thinning measured by OCT, on the other hand, is not apparent until day 35, consistent with pathological data demonstrating a loss of RGCs.

Conclusion

These data suggest that demyelination and axonal injury in the optic nerve precede RGC loss. Therefore, preventing optic nerve damage early in MS may be an important therapeutic strategy against retinal degeneration and visual impairments in later stages of the disease.