Retrograde trans-synaptic degeneration in MS

A missing link?

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There has been substantial activity in recent years studying the visual pathways in patients with multiple sclerosis (MS). One of the driving forces has been the evolution of optical coherence tomography (OCT) as a highly accessible test that allows precise quantification of retinal structures. Pertinent to neurology, OCT gives us the ability to measure the thickness of retinal layers containing neuronal cell bodies (the ganglion cell layer) and unmyelinated axons (the peripapillary retinal nerve fiber layer [RNFL]) of the first-order (anterior) sensory neurons of the visual pathway. Other features of the visual system that make it a particularly appealing model are the availability of sensitive and reliable clinical outcome measures, such as low-contrast visual acuity and visual evoked potentials for detection of functional changes related to axonal loss or demyelination; related to this, optic neuritis can serve as a "natural experiment" that helps us understand the working of the visual system. The ultimate goal of studying a single functional system is to determine structure–function correlations, facilitating broader understanding of how the CNS is affected by and adapts in MS.

With OCT as a tool to measure the first-order neurons (within the retina) and MRI as a tool to measure the second-order neurons (within the brain), the visual pathways are proposed as an ideal model to study trans-synaptic degeneration—the degeneration of neurons that connect to the initially affected neurons. One could conceptualize trans-synaptic degeneration as occurring in an anterograde (optic neuritis causing subsequent degeneration of posterior visual pathways) or retrograde (lesion in optic radiation causing ganglion cell and axon degeneration) direction. Trans-synaptic degeneration carries broader interest because, although it is less easily quantified outside the visual system, it may be a key mechanism underlying progressive disability and brain atrophy in MS. A model that accurately quantifies trans-synaptic degeneration could be used to test drug efficacy in clinical trials of neuroprotection.

In this issue of *Neurology*®, Klistorner et al.[1] report their study examining the effect of posterior visual pathway pathology on the retina, finding an association between MRI measures of optic radiation integrity and retinal integrity measured by temporal quadrant RNFL thickness using OCT. This finding supports the occurrence of trans-synaptic degeneration in MS, in this case in a retrograde direction. The authors evaluated the posterior pathways with 2 methods—lesion analysis and diffusion tensor imaging—with each yielding similar results, increasing confidence in the results and exposing both lesional and nonlesional pathology. In this cohort, with optic neuritis–affected eyes specifically excluded, posterior visual pathway pathology accounted for as much as 35%–40% of the atrophy of the RNFL. There was also an association between posterior visual pathway integrity and low-contrast letter acuity.

Although retrochiasmal lesions may not lead to persistent visual field defects in MS,[2] awareness of their importance has been greatly facilitated by OCT (figure). The contribution of retrochiasmal lesions to retinal degeneration and impairment of low-contrast letter acuity has received more attention since an elegant study by Reich et al.[3] The time course of retinal trans-synaptic neurodegeneration has recently been described following stroke[4] and for patients with MS.[5] The study reported here builds on this prior work, with some unique features. Specific exclusion of eyes with a history of optic neuritis aids the ability to study the effect of posterior visual pathway lesions selectively. Use of spectral-domain OCT allows more reliable quantitation of individual quadrants of the peripapillary RNFL than older time-domain OCT. The authors also vigilantly evaluated for retrochiasmatic presynaptic lesions (in the optic tract), which were very uncommon in this cohort.

Whether trans-synaptic degeneration is a "missing link" between focal tissue damage early in MS and progressive disability occurring in progressive forms of the disease remains to be proven, although some available evidence supports this theory. Atrophy of the thalamus (the lateral geniculate nucleus, relay station of the visual pathway, is part of this structure) occurs early in MS and is disproportionate to atrophy of other gray matter structures.[6] Trans-synaptic degeneration is one possible mechanism for accelerated thalamic degeneration in MS, given that structure's highly interconnected

See page 2165

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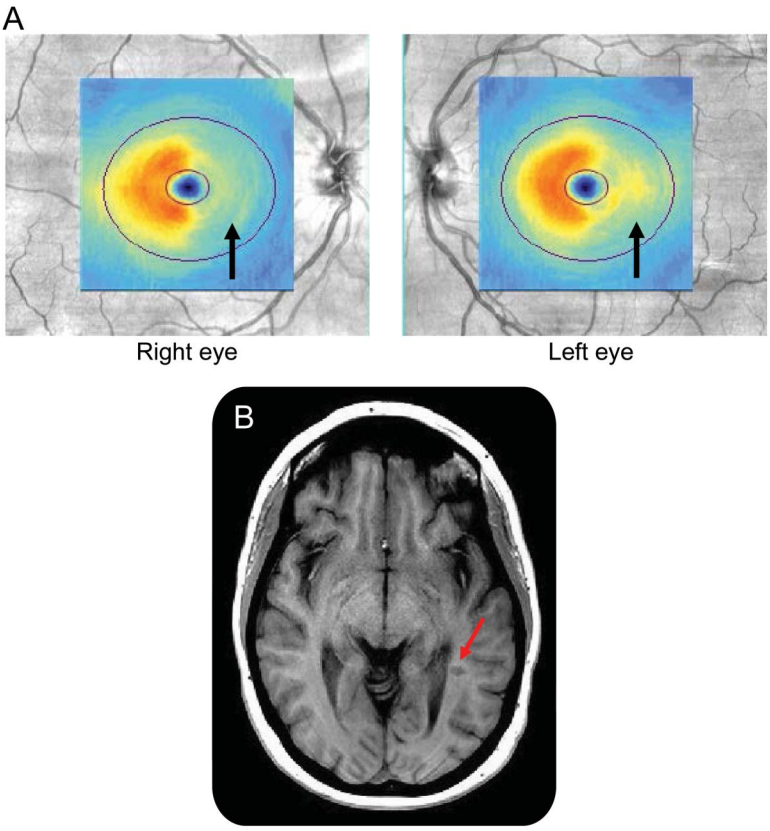
Figure Optical coherence tomography and MRI



(A) Color-coded thickness map (red = thicker, blue = thinner) of retinal ganglion cell + inner plexiform layers (GCL + IPL) from optical coherence tomography (OCT) of a 37-year-old patient with multiple sclerosis shows loss of left homonymous hemiretinal GCL + IPL thickness (black arrows), consistent with remote posterior visual pathway lesion. Axial T1-weighted MRI (B) from same patient shows T1-hypointense black hole in the left optic radiation, possibly contributing to homonymous GCL/IPL thinning seen on OCT.

nature.[7] Retrograde trans-synaptic degeneration is one of the potential mechanisms explaining RNFL loss that occurs over time in MS, even in the absence of optic neuritis.[8] Questions also remain, such as whether this truly is a domino effect, which would result in severe brain atrophy, or whether intrinsic checks exist, such as degeneration halting in the first synaptic neuron or being compensated by multiple synaptic afferents.[9] The ultimate test is whether therapies preventing trans-synaptic degeneration will be able to prevent disability accumulation and disease progression.

MRI and OCT, when used in conjunction, are powerful tools to study pathway-specific structure–function relationships. We must always recognize, however, that we are only seeing to the limits of our detection. The authors of this study are right to acknowledge the potentially underappreciated role of subclinical optic neuritis, cortical MS lesions, and other potential (unknown) pathologies to which our current techniques are insensitive. Intrinsic repair and recovery mechanisms are of particular interest but are more likely to be appreciated by functional and molecular imaging than by anatomical imaging techniques. Multimodal imaging studies, especially if further validated through large-group longitudinal studies, hold great promise to understand the mechanisms underlying disability and study treatments to augment recovery in MS.

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