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Optical coherence tomography: A quantitative tool to measure neurodegeneration and facilitate testing of novel treatments for tissue protection in multiple sclerosis

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ABSTRACT

Optical coherence tomography (OCT) is a relatively new imaging technology that has been introduced as a powerful biomarker in neurological disease, including multiple sclerosis. In this review, OCT as an imaging technique, its reproducibility and validation in multiple sclerosis, application to other neurodegenerative diseases and future technological directions are discussed.

1. Background

It has long been established that demyelination alone is not the only pathological process at play in multiple sclerosis (MS). Inflammation and axonal degeneration also contribute to neurological damage, leading to clinical disability. This has been evidenced by temporal discordance between indicators of tissue damage on neuroimaging versus acquisition of clinical disability later in life. It is speculated that early on, patients have only limited disability due to functional compensation in the presence of demyelination and that much of the long term disability is due to axonal damage and subsequent neuronal death by retrograde degeneration.

MRI has thus far been the gold standard for measuring disease activity in MS and has been an outcome measure for almost all treatment trials to date. However, conventional MRI protocols, including T2 weighted sequences, although highly sensitive to inflammation based on water content, are not specific for or highly sensitive to detection of axon integrity. The inflammatory lesions seen on MRI may or may not lead to axonal damage and may or may not result in permanent disability. Consequently, conventional MRI has had a modest role in predicting clinical disability. Therefore, a clinical tool that may more accurately measure axonal and neuronal integrity would be an important complementary tool to MRI for understanding and predicting physical disability in MS.

The retina is composed of multiple layers of neurons starting with the outermost photoreceptors, which relay visual information through the bipolar layer to the retinal ganglion cells. The innermost layer of the retina is referred to as the retinal nerve fiber layer (RNFL) and is composed of unmyelinated axons that arise from the retinal ganglion cells and course along the retina, coalesce at the optic nerve head and pass through the lamina cribrosa where they become the myelinated optic nerve. The RNFL is unique in that it can be directly visualized through fundoscopic exam as the axons converge on the optic disc. As part of the anterior visual pathway, the axons in the RNFL relay information to the lateral geniculate nucleus in the thalamus and constitute a major white matter tract in the central nervous system.

Damage to the retinal nerve fibers and optic nerve have been observed in MS since the 1970s (Frisén and Hoyt, 1974) and modern autopsy studies of MS patients have shown retinal atrophy irrespective of disease duration (Green et al., 2010). As a portion of the central nervous system that is unmyelinated and simultaneously directly and non-invasively examined, the retina is a particularly good model for studying axonal and neuronal layer pathology in MS independent of the confound of colocalized myelin or myelin debris.

2. Technology

Optical coherence tomography (OCT) is a relatively new imaging technique that has rapidly developed over the last two decades. The machine is small, non-invasive, and inexpensive and can be used easily and efficiently in an office based setting. OCT technology is similar to ultrasound but uses near infra-red light instead of sound to measure back-

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scatter from a variety of media (biological tissues) to obtain micrometer resolution images. When applied to the retina this allows reconstruction of tomogram maps (Fig. 1) and accurate quantification of both the retinal nerve fiber layer (axons) and macular ganglion cell layer (neurons). These cell layers are part of the brain, relaying information to the thalamus. In other words, OCT is a quantitative ophthalmoscope which uses the eye as a window into the brain.

Over the last decade, OCT technology has expanded from an initial time-domain model to the more recent, spectral-domain (SD) model (also known as Fourier domain or fourth-generation). Time domain OCT analyzes the difference in time delay as a light is reflected off of the tissue as a function of depth versus a control echo using a mobile reference mirror. Spectral domain OCT is based on the mathematical Fourier transform equation and eliminates the need for a reference mirror. It is therefore a function of different light wavelengths rather than time echo delays and consequently is more rapid and with higher resolution (5 μm vs 10 μm) than its predecessor (Calabresi et al., 2015). Furthermore, the faster scanning speeds allow for much more information to be obtained in short periods of time, therefore SD-OCT enables imaging of the retina in 3 dimensions rather than two dimensions in TD- OCT. Both of these models have been used and validated in MS.

3. Reproducibility

As a new clinical assessment tool that has potential to be used in an office based setting, OCT has demonstrated excellent reproducibility in multiple circumstances including intra-rater, inter-rater, inter-visit and cross-center. An analysis of time-domain OCT in 396 MS patients and 153 healthy controls across 3 centers showed intraclass correlations ranging from 0.89 to 0.98. They also demonstrated mean RNFL thickness for MS patients and healthy controls varied by <3 μm across the three centers. (Cettomai et al., 2008) With the development of the SD OCT, this method was also validated with excellent reproducibility for RNFL thickness, macular thickness, and macular volume in 58 MS patients and 32 healthy controls. Similarly, intraclass correlations in this study ranged from 0.83 to 0.99 for intra-rater, inter-rater and inter-visit comparison (Syc et al., 2010).

4. Validation in multiple sclerosis

OCT has been applied to a variety of diseases including glaucoma, macular degeneration and more recently, multiple sclerosis. Initial studies in MS patients with acute optic neuritis noted an initial period of swelling and a subsequent reduction in retinal nerve fiber layer thickness 3 to 6 months after the event (Costello et al., 2006). This study also showed that patients with incomplete visual recovery demonstrated more pronounced RNFL loss.

Further analyses went on to suggest that RNFL thinning is present even in the absence of a history of optic neuritis (Pulicken et al., 2007), inferring that there was ongoing axonal pathology even in the absence of an acute demyelinating event in the optic nerve and further studies have corroborated these findings (Syc et al., 2012). It has also been further elaborated that not only is there subclinical thinning of the RNFL, an axonal layer, but there is also thinning of the ganglion cell and inner plexiform (GCIP) layer, the neuronal layer that gives rise to the RNFL axons. Whether this is due to local microscopic inflammation or just dying back neurodegeneration is unclear. This in vivo study using OCT to show thinning of the GCIP was consistent with autopsy studies of retinal pathology in MS that revealed neuronal drop out in 79% of people with MS (Green et al., 2010).

But what is the clinical manifestation of these microscopic changes detected on OCT? Subtle visual impairments are often not apparent on visual acuity testing with *high* contrast letter charts used in most clinical practices. However, Balcer and Frohman (2010) showed that reduced retinal nerve fiber layer (RNFL) thickness measured by OCT correlated with reduced *low* contrast visual acuity in MS patients. This clinical correlate with low contrast vision using 1.25% and 2.5% Sloan eye charts has been echoed in multiple follow up studies (Pulicken et al., 2007; Saidha et al., 2011; Villoslada et al., 2012) and is now used as a standardized visual clinical correlate in MS. Additional studies have shown evidence of association with color vision changes with Hardy-Rand-Rittler plates (HRR) and Lanthony D15 tests (Villoslada et al., 2012). Thus OCT changes are biologically relevant and correlate with more subtle visual disability and loss of visual quality of life (Walter et al., 2012).

Initial research on OCT in MS had examined primarily cross sectional data, with limited longitudinal research beyond a 6–12 month follow up period in the setting of acute optic neuritis. In 2010, Talman et al.[12] studied longitudinal findings using OCT in MS patients for up to four years of follow up. This study followed almost 300 patients using OCT and low contrast visual acuity measures, with a mean follow up time of 18 months, 109 of which had follow up at >2 years and 41 had follow up at >3 years. They showed progressive RNFL thinning over time in the absence of acute optic neuritis, which was associated with clinically detectable visual loss. This again reiterated the hypothesis that there is ongoing axonal degeneration in MS independent of acute inflammatory demyelinating disease.

Beyond visual changes, OCT evidence of thinning of the RNFL and GCIP have been found to correlate with measures of overall clinical disability. Toledo et al. (2008) showed in a 2008 study that RNFL atrophy correlated with cognitive impairment by symbol digit modality test and with physical disability on neurological exam. Poor vision in multiple sclerosis has also been linked with overall physical fatigue (Chahin et al., 2015).

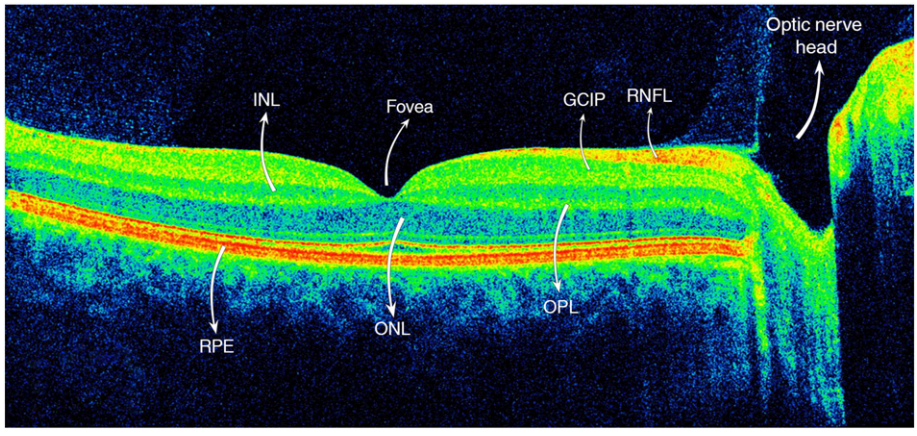

Fig. 1. Image from a high definition OCT scan depicting the retinal architecture. Cell layers are labeled as follows: INL = inner nuclear layer; GCIP = ganglion cell and inner plexiform layer; RNFL = retinal nerve fiber layer; RPE = retinal pigment epithelium; ONL = outer nuclear layer; OPL = outer plexiform layer.