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PERSPECTIVE

Acute optic neuritis: a clinical paradigm for evaluation of neuroprotective and restorative strategies?

What makes the acute optic neuritis model unique in an era of trials for neuroprotective and myelin repair agents? Acute optic neuritis (AON) is a common, and often the earliest manifestation of central nervous system (CNS) inflammatory demyelinating disorders like multiple sclerosis (MS) and neuromyelitis optica (NMO). It affects at least half the patients with MS and is the presenting feature in 15–20% of patients. Vision loss in AON secondary to NMO tends to be more severe with less potential for recovery and greater axonal degeneration, as measured by optical coherence tomography (OCT) (Bennett et al., 2014). Several unique features of the afferent visual pathway (AVP) make the AON model an ideal system to study disease pathogenesis and evaluate potential neuroprotective and myelin repair strategies.

Recent advancements in technology have made precise structural, functional and electrophysiological characterization of the AVP possible, using sensitive and largely non-invasive methods. These techniques, now validated, have confirmed correlation of structural, functional and electrophysiological measures of the AVP (Balcer et al., 2015). Furthermore, investigations have established association of clinical and radiologic non-ocular disease activity in MS with accelerated loss of retinal nerve fiber layer (RNFL) and ganglion cell/inner plexiform layers (GCIPL) of the retina, as measured by OCT (Ratchford et al., 2013).

Since retinal changes in MS appear to reflect global CNS processes, it is reasonable to generalize lessons learnt from the AVP to the CNS as a whole in CNS inflammatory demyelinating disorders. The presence of axons and glia in the absence of myelin is a feature unique to the retina in the CNS. This allows for independent monitoring of the derivative elements of CNS inflammatory injury; demyelination, axon loss and neuronal degeneration. Cases with relative axon preservation, ideal candidates for myelin repair, can be differentiated from those with axon involvement that require reconstitution of axon circuitry before myelin repair is attempted. Similarly, neuroprotective and even regenerative capabilities can be detected and monitored longitudinally using sensitive techniques to quantify RNFL and GCIPL thickness. In this article, we describe the modern, high-precision, para-clinical tools that enable precise structural, functional and electrophysiological analysis of the AVP. This is followed by a discussion of the current and potential future applications of novel technology to study putative neuroprotective and myelin repair strategies, in an attempt to identify agents that preserve and repair tissue architecture, electrophysiology, and ultimately function.

Recent advancements in technology: On retinal imaging, the majority of AON cases develop RNFL edema at onset (lasting up to 3 months) followed at 3–6 months by loss of RNFL thickness secondary to axonal degeneration (Bennett et al., 2014). Analysis of retinal architecture can now be performed using OCT and scanning laser polarimetry (SLP); two techniques based on entirely different principles of physics (see **Figure 1**). The technology employed in OCT is based on interference patterns of backscattered near-infrared light while SLP relies on variations in birefringence, a property dependent on integrity of axon microtubules and neurofilaments. SLP appears to have immense potential in assessment of new therapeutic capabilities using the AON model. First, based on its underlying mechanism of variations in birefringence, which depend on axon integrity, it can be hypothesized that at the onset of AON, SLP is a superior technique for predicting axon integrity and visual prognosis. On the other hand, the technology in OCT does not detect axon integrity at presentation of AON. Second, unlike OCT, the technique in SLP is not influenced by water content; it can thus be expected to deliver a more accurate baseline RNFL thickness, not confounded by edema (Bennett et al., 2014). Kupersmith et al. (2013) showed that at the time of presentation of acute nonarteritic anterior ischemic optic neuropathy, measurements made by SLP are superior to OCT analysis in predicting permanent visual field deficits. However, in the AON model, it remains to be tested if measurements made by SLP are indeed more accurate than those of OCT in predicting long-term axon loss and visual prognosis. In an era of trials of myelin repair agents, sensitive means of early identification of ideal candidates who will experience relative axon preservation has become ever more relevant. Obtaining the 'true' baseline RNFL thickness, unbiased by edema, at the onset of AON is also of supreme importance in the longitudinal analysis of potential neuroprotective therapeutic strategies. Conversely, recent refinements in spectral-domain OCT technology have enabled high-precision retinal segmentation; if employed this might also yield 'true baseline measures' uninfluenced by edema at the onset of AON (Bennett et al., 2014).

Comparison of the two technologies in longitudinal studies of AON will ultimately clarify as to which technology is superior at the time of presentation in accurate baseline RNFL determination and prediction of axon integrity and visual prognosis over time. In any case, both OCT and SLP are sensitive and precise technologies, allowing small changes in retinal architecture to be detected reliably in prospective longitudinal studies. Using RNFL thickness as measured by OCT as an outcome measure, Henderson et al. (2010) estimated sample size for AON trials; only 75 patients per arm were needed to provide 90% power for a modest 40% effect size. Promising results from these small proof-of-concept studies using highly sensitive techniques can pave the way for larger scale, more traditional studies.

Orbital imaging has now been made possible through refinements in advanced magnetic resonance imaging (MRI) technology. Traditionally, formidable technical challenges including small size and mobility of the optic nerves along with confounding factors such as signal heterogeneity of surrounding structures have prevented the application of advanced MRI metrics to orbital imaging; mandating the application of rapid acquisition protocols in conjunction with high spatial resolution. In a recent AON study, axial diffusivity of the optic nerve as measured by diffusion tensor imaging technology (DTI) correlated with 6 month functional, structural and electrophysiological outcomes (Naismith et al., 2012). If these findings are confirmed by larger studies, application of DTI technology to the AON model might help predict the degree of expected axonal injury and thus identify candidates most likely to benefit from therapeutic strategies; particularly those targeting myelin repair. Neuroprotective capabilities can also potentially be assessed in longitudinal studies using DTI imaging of optic nerve.

Association of magnetization transfer ratios with time-linked visual evoked potential (VEP) latency following optic neuritis (Hickman et al., 2004) supports a role for MTR technology in detecting remyelination following AON. Altman et al. (2014) estimated sample size requirements for a placebo-controlled trial in MS using change in mean MTR of all T2 lesions as a primary outcome measure. Calculations suggest that 30% remyelination of T2 lesions could be detected with 80% power in 38 patients per arm based on the *in vivo* data, and in 66 per arm based on the *ex vivo* data. These sample sizes are in a range that makes MTR a feasible outcome measure for proof-of-concept trials of putative therapies achieving remyelination in MS lesions.

Pattern reversal VEP has traditionally been employed as an electrophysiological measure of AVP integrity; latency prolongation from conduction delay being the pathophysiological signature of demyelination. Conversely, reduction in amplitude of VEP signifies axonal injury (except in cases where significant demyelination can result in conduction block in a relative number of axons; thereby confounding the direct link between response amplitude and axonal integrity). In fact, conduction block in AON can result in a transiently undetectable VEP response, making it challenging to demonstrate changes in VEP latency from baseline in AON trials. On the contrary, multifocal VEP (mfVEP), which depicts global summed responses of the entire visual field, has far superior sensitivity in detecting topographic changes in

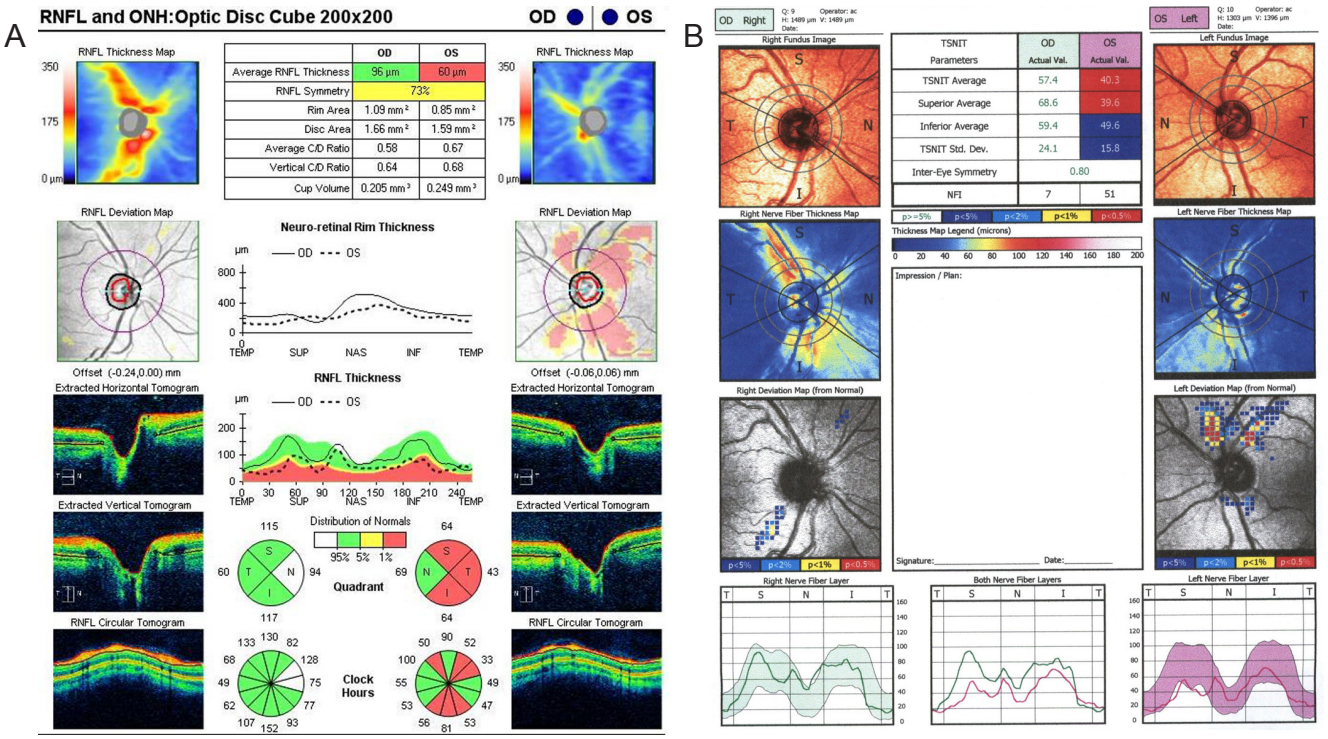

Figure 1 Technologies for analysis of retinal architecture.
(A) Optical coherence tomography. Spectral domain optical coherence tomography scan from a patient at University of Texas Southwestern with unilateral optic neuritis affecting the left eye. OD: Right eye; OS: left eye; RNFL: retinal nerve fiber layer.
(B) Scanning laser polarimetry. Scanning laser polarimetry scan from the same patient (as IA) in University of Texas Southwestern with unilateral optic neuritis affecting the left eye. OD: Right eye; OS: left eye; TSNIT Average (TSNIT stands for Temporal - Superior - Nasal - Inferior-Temporal): average retinal nerve fiber layer thickness; NFI: nerve fiber indicator.

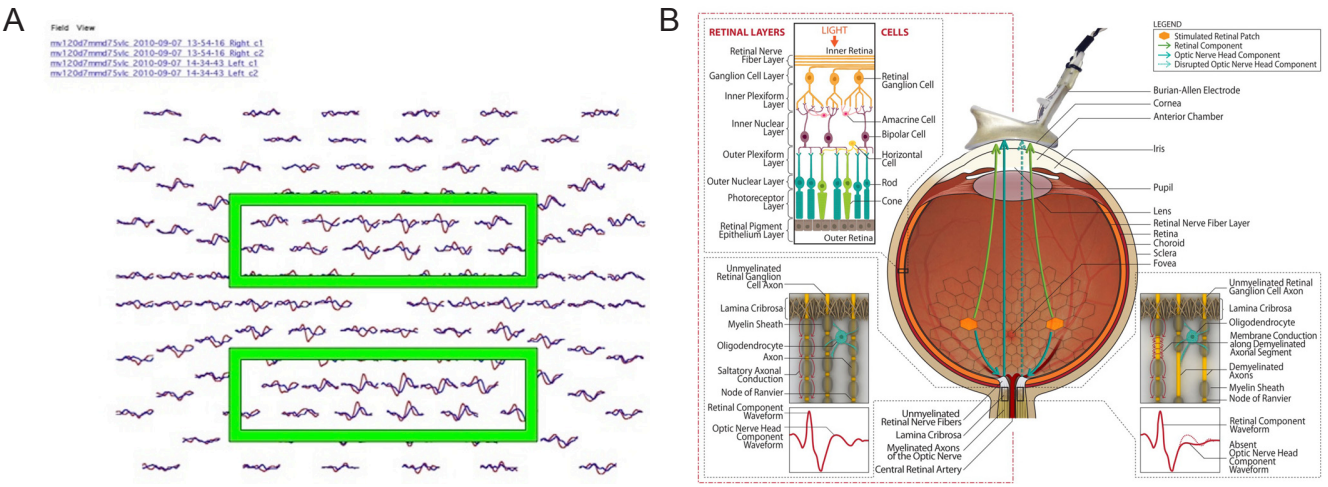

Figure 2 Technologies for electrophysiological analysis of the afferent visual pathway integrity.
(A) Multifocal visual evoked potential. Multifocal visual evoked response at very low Michelson-contrast (14.2%), using pattern-reversal stimulation. Responses in the right (red) and left (blue) eyes, from a patient with a history of left optic neuritis; notice both timing response prolongation and amplitude attenuation in the left (blue) eye. Reproduced from Frohman et al. (2012).
(B) Optic nerve head component. Using two interleaved global flashes in the multifocal electroretinography stimulation protocol, two induced waveforms are evoked: the retinal component and the optic nerve head component (ONHC). The ONHC is believed to be generated at the point of conversion from membrane to saltatory conduction, as retinal nerve fibers traverse the lamina cribrosa and acquire a myelin sheath. Disorders resulting in damage of retinal ganglion cells or their axons; or impairing the acquisition of myelin in retrolaminar region may result in abnormal or absent ONHC responses. Reproduced from Frohman et al. (2013).

latency/amplitude of VEP responses. Frohman et al. (2012), showed that sensitivity of the mfVEP may be further enhanced by employing variable contrast pattern reversal stimuli, allowing for detection of mild injury or even occult damage in the so called unaffected eye (see **Figure 2A**). Another promising electrophysiological signature of myelination is the optic nerve head component (ONHC), a discrete late-response waveform of multifocal electroretinogram, which represents the transformation of slow membrane conduction in unmyelinated axons of the retina to fast saltatory conduction as they traverse the lamina cribrosa and acquire a myelin sheath (see **Figure 2B**) (Frohman et al., 2013). A history of AON is associated with abnormal or absent ONHC response and correlates with structural, functional and electrophysiological measures of the AVP. If confirmed and validated by larger studies, variable contrast mfVEP and ONHC response have the potential to be exquisitely sensitive outcome measures that allow even small proof-of-concept trials of AON to detect neuroprotective and myelin repair capabilities that can then be further tested in larger studies.

Emerging myelin repair and neuroprotective therapies: One of the finest examples of the application of recent technology to the AON model in the design of trials for myelin repair agents is the recently concluded phase II trial for Anti-LINGO-1 (BIIB033). This is a humanized monoclonal antibody targeting LINGO-1, a protein that serves to developmentally arrest oligodendrocyte progenitors. RENEW (www.clinicaltrials.gov; NCT01721161) was a randomized, double-blind, placebo-controlled study evaluating the effect of anti-LINGO-1 treatment *versus* placebo following AON (n = 82). The primary end point was change in conduction velocity of the affected optic nerve, measured using full field VEP (FF VEP) at week 24. The baseline was taken to be the initial measurement from the unaffected eye; as discussed before VEP response in the AON eye can be transiently absent due to conduction block at presentation. Secondary outcome measures included changes in the RNFL and GCIPL thickness as measured by spectral-domain OCT at week 24. Again, the baseline was taken to be the initial measurement from the unaffected eye; likely because edema can confound measurements in the affected eye. Results (Kapoor et al., 2015) were remarkable for a significantly improved latency recovery as measured by the primary endpoint of FF VEP, among anti-LINGO-1 participants, compared with placebo (P = 0.05). Further recovery of latency was observed at the time of the last measurement at week 32 (P = 0.01). In a subgroup of 39 cases with mfVEP studies, findings were consistent with the overall group. No significant effects were observed with secondary outcome measures. At least, in this study no neuroprotective effects were detected; not unexpected since anti-LINGO-1 mechanistically is a remyelinating agent. Any neuroprotective effects secondary to remyelination will likely require more time before they can be detected.

In a randomized AON study initial treatment with systemic corticosteroids *versus* placebo showed no significant differences in optic nerve atrophy (as measured by MRI imaging of optic nerve using short tau inversion recovery sequences) at 6 months (Hickman et al., 2003). An ongoing phase IV trial of neuroprotection using the AON model compares the anti-inflammatory and neuroprotection effects of adrenocorticotropic hormone (ACTH) *versus* methylprednisolone. The primary outcome measure is average RNFL thickness at 6 months, while the secondary outcome measure is RNFL swelling at 1 and 3 months. Tertiary outcome measures include changes in mfVEP, ONHC responses, and pupillary response metrics. A predefined exploratory outcome is GCIPL thickness at 6 months (www.clinicaltrials.gov; NCT01838174).

Clemastine fumarate, an approved anti-histamine agent, has been shown to have remyelinating potential and is currently being studied in a phase II trial in relapsing remitting MS patients with latency delay on VEP (> 125 ms) in at least one eye (www.clinicaltrials.gov; NCT 02040298). The primary objective is to evaluate the efficacy of clemastine relative to placebo for reducing P100 latencies on FF VEP.

Future directions: These and other ongoing investigations will undoubtedly create the framework for the establishment of the AON clinical paradigm as a surrogate for CNS inflammatory demyelinating disorders, in clinical and translational research, to gain insights into disease mechanisms and identify potential treatment strategies. The exquisitely sensitive techniques being developed will allow detection of even modest myelin repair and neuroprotective capabilities in small proof-of-concept trials of putative agents; promising therapies can then be escalated to larger scale phase III efficacy trials. Ultimately, development of multi-parametric models combining outcome measures from various CNS systems, in studies powered to detect clinically meaningful changes are needed to evaluate potential myelin repair and neuroprotective strategies.

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