In-vivo detection of deep retinal neuronal layer changes following acute optic neuritis

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Multiple sclerosis (MS)

- MS is an immune-mediated demyelinating disorder of the Central Nervous System (CNS) with both inflammatory and degenerative components.

- MS commonly involves the optic nerves; acute optic neuritis (AON) is the presenting feature in ~20% of patients, while 50% experience it at some point during the course of their disease.

- Autopsy studies demonstrate that optic nerve pathology is present in the majority of MS patients even in the absence of overt clinical involvement.


Retinal histology

Microscopic cross-sectional view through the optic nerve including the retinal layers

http://hubel.med.harvard.edu
Optical coherence tomography (OCT)

- OCT is a technique that employs low coherence interferometry of near-infrared light.
- It is used to generate *in-vivo* high-resolution (< 5 µm), cross-sectional images of the retina.
- Because of the depth-resolving capacity of OCT, it enables visualization of retinal tissue structures similar to tissue sections under a microscope.

Evidence that retinal neuronal loss occurs in MS

- Ganglion cell dropout (79% of MS patient eyeballs)
- Inner nuclear layer neuron dropout (40% of MS patient eyeballs)

\[\text{Green et al. Brain 2010; 133: 1591-601}\]

- Retrograde neurodegeneration is thought to culminate in drop out of retinal ganglion cells.
- Our group has previously shown using macular segmentation that thinning of the composite ganglion cell + inner plexiform (GCIP) layers occurs following AON¹.
- However, comprehensive longitudinal *in-vivo* assessment of deep retinal neuronal layers following ON remains largely unexplored.

**Objectives**

- To determine whether objective changes in INL and ONL thicknesses occur following AON.

- To explore whether these changes may be temporally related to thickness changes of the composite ganglion cell + inner plexiform layer thickness (GCIP).

**Methods - Participants**

- 34 patients diagnosed with acute unilateral demyelinating ON.

- Baseline evaluation was performed with a mean delay of 14 days from onset (SD 8.8, range: 1-33 days).

- A comparison cohort of 34 MS patients, who did not develop AON, were matched 1:1 based on age, sex, and duration of OCT follow-up.
Demographic and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients presenting with AON at baseline</th>
<th>Patients with MS who did not develop AON at baseline or during follow-up</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>36.4 (9.4)</td>
<td>35.9 (9.1)</td>
<td>0.83a</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>30 (88)</td>
<td>30 (88)</td>
<td>1.00b</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIS</td>
<td>7 (20.6)</td>
<td>0 (0.0)</td>
<td>0.01b</td>
</tr>
<tr>
<td>RRMS</td>
<td>26 (76.5)</td>
<td>33 (97.1)</td>
<td></td>
</tr>
<tr>
<td>SPMS</td>
<td>1 (2.9)</td>
<td>1 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Eyes with a previous history of AON, n (%)</td>
<td>12 (17.6)</td>
<td>19 (27.9)</td>
<td>0.15d</td>
</tr>
<tr>
<td>Follow-up duration, months, median (IQR; range)</td>
<td>22.5 (12.6-34.2)</td>
<td>22.9 (14.2-36.4)</td>
<td>0.65c</td>
</tr>
</tbody>
</table>

Abbreviations: AON = Acute optic neuritis; MS = multiple sclerosis; CIS = clinically isolated syndrome; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; IQR = inter-quartile range.


Retinal imaging

- Patients underwent Cirrus-HD OCT imaging, with automated intra-retinal layer segmentation, at each study visit.

- Two macular segmentation methods were used to obtain measures of retinal layer thickness:
  1. Manufacturer’s algorithm
  2. Graph-based, open-access method
Statistical analysis

- Time was taken as a continuous variable starting at the onset of AON symptoms.
- Comparisons between clinically affected and fellow eyes, at set time intervals, were done using mixed-effects linear regression accounting for within-subject inter-eye correlation.
- Multilevel linear spline models were used to analyze the course of OCT measure changes over time.
- Breakpoints (allowing for changes in slope to occur) were positioned, according to the best fit to the data.

Abbreviations: GCIP = ganglion cell+innerplexiform layer; INL = inner nuclear layer; OPL = outer plexiform layer; ONL = outer nuclear layer; PRL = photoreceptor layer
### Table 2: Estimated rates of change in average retinal layer thicknesses in clinically-affected eyes after ON

<table>
<thead>
<tr>
<th>OCT measure</th>
<th>Baseline to 3 months</th>
<th>3 to 6 months</th>
<th>6 to 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate of change (µm/month)</td>
<td>p-value</td>
<td>Rate of change (µm/month)</td>
</tr>
<tr>
<td>RNFL</td>
<td>-9.85 &lt;0.001</td>
<td>-0.91</td>
<td>0.713</td>
</tr>
<tr>
<td>GCL+IPL</td>
<td>-3.68 &lt;0.001</td>
<td>0.17</td>
<td>0.668</td>
</tr>
<tr>
<td>Graph-based</td>
<td>-2.70 &lt;0.001</td>
<td>0.11</td>
<td>0.731</td>
</tr>
</tbody>
</table>

Abbreviations: ON = optic neuritis; GCIP = ganglion cell layer + inner plexiform layer; RNFL = retinal nerve fiber layer.

### Table 3: Estimated rates of change in average retinal layer thicknesses in clinically-affected eyes after ON

<table>
<thead>
<tr>
<th>OCT measure</th>
<th>Segmentation method</th>
<th>Baseline to 3 months</th>
<th>3 to 6 months</th>
<th>6 to 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate of change (µm/month)</td>
<td>p-value</td>
<td>Rate of change (µm/month)</td>
<td>p-value</td>
</tr>
<tr>
<td>INL+OPL</td>
<td>Manufacturer</td>
<td>0.71 &lt;0.001</td>
<td>-0.31</td>
<td>0.103</td>
</tr>
<tr>
<td></td>
<td>Graph-based</td>
<td>0.11 0.417</td>
<td>-0.26</td>
<td>0.061</td>
</tr>
<tr>
<td>ONL+PRL</td>
<td>Manufacturer</td>
<td>2.18 &lt;0.001</td>
<td>-1.34 &lt;0.001</td>
<td>-0.17</td>
</tr>
<tr>
<td></td>
<td>Graph-based</td>
<td>1.37 &lt;0.001</td>
<td>-0.65</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Abbreviations: ON = acute optic neuritis; INL = inner nuclear layer; OPL = outer plexiform layer; ONL = outer nuclear layer; PRL = photoreceptor segments layer.
Relationship between GCIP loss and ONL thickening at the 4±1 month visit

Take home messages

- Ganglion cell layer thinning following AON appears to be most rapid in the early months.

- OCT segmentation demonstrates a transient increase in ONL thickness that appears to be proportional to the degree of GCIP loss in affected eyes.

- This raises the possibility of biological trans-synaptic changes occurring in the deep retinal neuronal layers and may help us understand the cellular response to injury in MS.
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