Seeing through the eyes of a child: Optical coherence tomography and visual metrics in pediatric MS

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Objectives

1. Review the clinical features of optic neuritis in children and adolescents
2. Present high- and low-contrast letter acuity, and OCT data in pediatric MS
3. Discuss likelihood of confirmation of MS following ON in the pediatric populations
4. Consider future directions in pediatric treatment trials
Incidence per 100,000 children (under 19 years) in Canada

Presenting Phenotypes

Funded by the Multiple Sclerosis Scientific Research Foundation
Case Presentation: 1

- 14 year old male
- Previously well
- Hepatitis B vaccination, 3 months earlier

- Presents with
  - Loss of vision in right eye over 4-5 days
  - Pain with ocular movement

- Examination
  - Swelling of right optic disc
  - RAPD
  - VA :finger counting OD, 20/20 OS

MRI Optic Nerves
Case Presentation: 2

- 7 year old female
- previously well
- acute, bilateral visual loss
- VA: 20/400 bilat., loss of colour vision, no pain with ocular movements
- Tx: IV methylpred, oral pred. Taper
- Full visual recovery over 6 months
- Bilat optic disc pallor
- Neurologically normal for last 2 years
MRI: case 2

Concepts of ON in children

- More likely to have bilateral onset
- Less likely to have ocular pain
- Unilateral involvement: more likely to develop MS
- Visual prognosis excellent
- Risk of MS: variable reports in literature, likely due to variable follow-up
Optic Neuritis in Children (Lucchinetti, 1997)

- 79 patients, onset ON under age 16 years
- median age onset was 11 years (2-16)
- M/F 1:1.6
- 36% preceding infection, 37% ocular pain, 36% headache
- 39% unilat ON; 57% bilat
- 19% diagnosed with MS (median observation 16 years (5-35)
- Kaplan Meier analysis of MS risk:
  - 13% by 10 yrs; 19% by 20 yrs; 22% by 30 yrs; and 26% by 40 years

Optic Neuritis: Visual acuity

<table>
<thead>
<tr>
<th>Visual acuity at presentation</th>
<th>ONTT N=patients (%)</th>
<th>Pediatric Cohort N=eyes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/40 or better</td>
<td>162 (35.4)</td>
<td>8 (17.8)</td>
</tr>
<tr>
<td>20/50-20/190</td>
<td>129 (28.2)</td>
<td>9 (20.0)</td>
</tr>
<tr>
<td>20/200 or worse</td>
<td>166 (36.3)</td>
<td>28 (62.2)</td>
</tr>
</tbody>
</table>

- More children than adults present with optic disc swelling.
- Most children recover quite well.
  - Visual acuity improved to 20/40 or better at the time of the last follow-up examination in 96% of affected eyes.

Pediatric ON at SickKids

- 36 children
  - Female: male ratio = 1.6
  - Ages 2.2 to 17.8 years
  - Mean age 12.2 years
  - Mean follow-up 2.1 years
  - Unilateral ON: 58%, Bilateral ON: 42%
  - Variable severity of deficits, but VA was worse than 20/200 in 69%
  - MRI brain showed white matter lesions separate from optic pathways in 54% (19 of 35 children who underwent brain MRI)
Outcome to Date

- 13 children have clinically definite MS (36%)
- 1 child has Devic’s disease

- MS group (n=13)
  - 58% had bilateral ON (mean age 12.2 yr)
  - 42% had unilateral ON (mean age 14.4 yr)

- ON group as whole:
  - 47% of bilateral ON group (mean 11.5 yr) diagnosed with MS
  - 24% of unilateral ON group (mean 12.7 yr) diagnosed with MS

- MRI group
  - 86% with abnormal brain MRI diagnosed with MS
Meta-analysis of ON data in children


29% of the patients have been diagnosed with MS to date (mean observation 6.3 years)

• Risk with abnormal brain MRI, after adjusting for age
  OR 28.0, p<0.001, CI 6.27, 125.13
Standardized MRI evaluation of children with acute demyelination

- N=302 children (<16 years) enrolled at 23 centers & followed for 5 years
- Standard imaging protocol with centralized quality control
- Consensus between 2 raters trained on the tool blinded to clinical presentation & Dx

Lead Site

1st Clinical Attack

<table>
<thead>
<tr>
<th>Protocol B: Lead Site N=124</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 scans per patient</td>
</tr>
<tr>
<td>8 MS visit scans</td>
</tr>
<tr>
<td>1,000 scans</td>
</tr>
</tbody>
</table>

Other Sites

1st Clinical Attack

<table>
<thead>
<tr>
<th>Protocol A: Other Sites N=178</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 scans per patient</td>
</tr>
<tr>
<td>20 MS visit scans</td>
</tr>
<tr>
<td>732 scans</td>
</tr>
</tbody>
</table>

2nd Clinical Attack

| 6 mos | 1 yr | 2 yrs | 3 yrs | 4 yrs | 5 yrs | 2nd Clinical Attack* |

*MS diagnosis scan is acquired at MS-defining attack, any time ≥ 28 days after acute demyelination

Verhey, Banwell et al, Lancet Neurology 2011

MRI Predictors of MS

0 of 2 parameters
0 of 2 parameters
1 of 2 parameters
2 of 2 parameters

Log Rank (Mantel Cox) p<.001

Time After Acute Demyelinating Episode (years)

Verhey, Banwell et al, Lancet Neurology 2011
Evaluation of ON in children

One eye or two?

- Monocular testing
  - Captures unilateral visual dysfunction
  - May not represent the overall visual function of the patient
- Binocular testing
  - Overall visual functioning relies upon the use of both eyes simultaneously
  - Other clinical outcome measures in MS capture overall visual function (i.e. ambulation status)
  - Visual function is often highly-correlated
Binocular Summation and Inhibition

- Do binocular scores reflect the better eye, worse eye, or a value in between?
- Binocular summation
  - Improved visual acuity (more letters read correctly) when using both eyes compared to either eye
  - Decreased in conditions such as amblyopia
- Binocular inhibition
  - Occurs in patients with large inter-ocular differences in contrast sensitivity
  - The score using both eyes together is less than that of the better eye alone
- Mechanism poorly understood
  - Related to neural interactions of input from both eyes within the post-geniculate visual pathway

High- and Low-Contrast Letter Acuity

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children</td>
</tr>
<tr>
<td>High Contrast (monocular score)</td>
<td>64 ± 4</td>
</tr>
<tr>
<td>High Contrast (binocular score)</td>
<td>66 ± 4</td>
</tr>
<tr>
<td>Low-contrast (2.5%, monocular)</td>
<td>33 ± 8</td>
</tr>
<tr>
<td>Low-contrast (2.5%, binocular)</td>
<td>42 ± 6</td>
</tr>
<tr>
<td>Low-contrast (1.25%, monocular)</td>
<td>22 ± 8</td>
</tr>
<tr>
<td>Low-contrast (1.25%, binocular)</td>
<td>34 ± 6</td>
</tr>
</tbody>
</table>

High contrast (ETDRS) charts - Snellen equivalent:
20/25 = 55 letters, 20/20 vision = 60 letters, 20/16 = 65 letters, 20/12.5 = 70 letters
High and Low Contrast Letter Acuity in Children

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls</th>
<th>MS without ON</th>
<th>MS with ON</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children</td>
<td>Children</td>
<td>Children</td>
</tr>
<tr>
<td>High Contrast (monocular score)</td>
<td>64 ± 4</td>
<td>62 ± 6</td>
<td>61 ± 13</td>
</tr>
<tr>
<td>High Contrast (binocular score)</td>
<td>66 ± 4</td>
<td>67 ± 4</td>
<td>65 ± 4</td>
</tr>
<tr>
<td>Low-contrast (2.5%, monocular)</td>
<td>33 ± 8</td>
<td>31 ± 8</td>
<td>25 ± 11</td>
</tr>
<tr>
<td>Low-contrast (2.5%, binocular)</td>
<td>42 ± 6</td>
<td>41 ± 4</td>
<td>36 ± 12</td>
</tr>
<tr>
<td>Low-contrast (1.25%, monocular)</td>
<td>22 ± 8</td>
<td>18 ± 8</td>
<td>11 ± 9</td>
</tr>
<tr>
<td>Low-contrast (1.25%, binocular)</td>
<td>34 ± 6</td>
<td>32 ± 5</td>
<td>26 ± 12</td>
</tr>
</tbody>
</table>

• For MS children without ON, only monocular LCLA different compared to controls
• Monocular scores for ON eyes significantly differed from controls using LCLA 2.5% and 1.25% contrast
• ON scores for binocular 2.5% contrast vs. controls: p=0.0581
• Among MS patients, monocular scores differed between the groups for 2.5% and 1.25% contrast (p=0.0432 and 0.0108, respectively) but did not differ for binocular scores.

Binocular Summation

High-contrast letter acuity scores (ETDRS) in children and adults

- Binocular
- Better Eye
- Worse Eye
Binocular summation

Low-contrast letter acuity scores (1.25%) in children and adults

One eye or two?

- Low contrast letter acuity captures monocular vision impairment
- Children have a greater capacity than adults for binocular summation
- If binocular acuity is incorporated into trials or studies, a clinical effect may be masked
- Binocular inhibition infrequently occurs in children with optic neuritis
- Mechanism?
Measuring Axonal Loss: Optical Coherence Tomography

- Non invasive, high resolution
- Near infrared (820 nm)
- Analogous to ultrasound
- Quantitative, reproducible
- Scans take ~15 seconds
- Captures anterior visual pathway axonal loss

OCT Parameters in MS

- Retinal nerve fiber layer (RNFL) thickness = non-myelinated ganglion cell axons
- Macular volume = primarily ganglion cell bodies
Retinal Nerve Fiber Layer Thickness in Pediatric Demyelinating Diseases

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean (SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control eyes</td>
<td>88</td>
<td>110 (12)</td>
<td>N/A</td>
</tr>
<tr>
<td>All disease eyes</td>
<td>108</td>
<td>100 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ON eyes</td>
<td>20</td>
<td>81 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fellow eyes</td>
<td>10</td>
<td>109 (12)</td>
<td>0.824</td>
</tr>
<tr>
<td>Non-ON eyes</td>
<td>78</td>
<td>104 (14)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Non-ON eyes by disease subtype

<table>
<thead>
<tr>
<th>Disease Subtype</th>
<th>N</th>
<th>Mean (SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRMS</td>
<td>30</td>
<td>109 (11)</td>
<td>0.554</td>
</tr>
<tr>
<td>ADEM</td>
<td>22</td>
<td>105 (19)</td>
<td>0.336</td>
</tr>
<tr>
<td>TM</td>
<td>18</td>
<td>101 (10)</td>
<td>0.012</td>
</tr>
<tr>
<td>NMO</td>
<td>4</td>
<td>93 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CIS</td>
<td>2</td>
<td>93 (0.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

RNFL thickness was compared for each group to control eyes, accounting for within-patient, inter-eye correlations.

Non = optic neuritis, RRMS = relapsing remitting MS, ADEM = acute disseminated encephalomyelitis, TM = transverse myelitis, NMO = neuromyelitis optica, CIS = clinically isolated syndrome.

Retinal Nerve Fiber Layer Thickness in Children and Adults

<table>
<thead>
<tr>
<th>Group/Eyes</th>
<th>Pediatrics¹</th>
<th>Adults²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>109</td>
<td>105</td>
</tr>
<tr>
<td>MS without Optic Neuritis</td>
<td>109</td>
<td>92</td>
</tr>
<tr>
<td>MS fellow eye (of patients with unilateral ON)</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>MS and Optic Neuritis</td>
<td>86</td>
<td>85</td>
</tr>
</tbody>
</table>

- Greatest reductions in RNFL thickness are seen in eyes with a history of acute optic neuritis
- In adults, MS non-ON eyes have less RNFL thickness than controls, suggesting the occurrence of chronic axonal loss separate from acute attacks in MS patients
- These results also suggest a role for ocular imaging techniques such as OCT in trials that examine neuroprotective and other disease-modifying therapies

Relation between LCLA and OCT

Among children with all demyelinating diseases, a 1-line (5 letter) decrease in LCSLC score was associated with a decrease in RNFL thickness by 2.2 µm using both 2.5% and 1.25% charts ($p=0.004$ and $p=0.018$, respectively).

A 5-letter difference using high-contrast letter charts was not associated with RNFL thinning ($p=0.62$).

Comments

The relationship between function and structure of the anterior visual pathway using low-contrast letter acuity and OCT, respectively, has been explored extensively in adults.

Binocular summation and inhibition should be considered for studies using binocular data (as well as monocular data).

Additional pediatric data is needed to establish whether axonal loss is present in the RNFL.

Correlations between RNFL thickness and MRI measures and cognitive scales are also needed to validate axonal loss, if present.
The relation between unilateral vs. bilateral presentation of acute optic neuritis may be dependent upon age
Unilateral optic neuritis is more common in older children
MRI at presentation is the greatest predictor of risk of MS
Prospective collaborative studies and clinical trials are needed