Optical Coherence Tomography in Neurologic Diseases

Optical coherence tomography (OCT) provides tissue morphology imagery at much higher resolution than other imaging modalities such as MRI or ultrasound, and the machines are comparatively cheaper. It is an easy technique to perform, and it is non-ionizing, and therefore safe. These benefits are driving a rapid transformation of OCT, from its principal application as a research tool, into an extension of the "neurological examination" in routine office practice. Originally used in assessing the severity of tissue damage and prognosis of multiple sclerosis and various neuro-ophthalmic conditions, OCT is increasingly used in other neurological disorders such as Parkinson's disease, ALS and Alzheimer's disease.

This book is the first comprehensive review of the use of OCT in neurological diseases. The coverage includes a description of the technique and its utilization in a variety of neurologic conditions. It is essential reading for neurologists, neuro-ophthalmologists, and neuroradiologists wanting an introductory account of the clinical applications of OCT.

Other titles of interest

Imaging Acute Neurologic Disease: A Symptom-Based Approach
Edited by Massimo Filippi and Jack H. Simon
(ISBN 9781107035942)

Multiple Sclerosis Therapeutics, fourth edition
Edited by Jeffrey A. Cohen and Richard A. Rudick
(ISBN 9780521766272)

Pattern Recognition Neuroradiology
Neil M. Borden and Scott E. Forseen (ISBN 9780521727037)
The speaker and her research team have no financial interest in any of the tests or devices discussed in this presentation.

Dr. Balcer has received consulting fees from Biogen for work related to MS visual outcome measures.
It All Began With Our Patients...

- Said that their vision was “not right” despite 20/20 acuity on black and white eye chart
- Had to find a way to capture our patients’ symptoms
- Literature supported low-contrast vision, so used gray on white version of the ETDRS VA chart
Optic Neuritis Treatment Trial:
A First Look at Vision in MS

- Used Pelli-Robson contrast sensitivity (20/680 Snellen)
- Reduced contrast sensitivity and quality of life even years later

**Table 2. Visual Function at Time of Completion of NEI-VFQ**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Better Eye</th>
<th>Worse Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity ($N = 244$)</td>
<td>$-0.14 (-0.22, -0.06)$ [16%]</td>
<td>$-0.06 (-0.14, 0.04)$ [39%]</td>
</tr>
<tr>
<td>Contrast sensitivity ($N = 243$)</td>
<td>$15 (15, 16)$ [17%]</td>
<td>$14 (13, 15)$ [58%]</td>
</tr>
<tr>
<td>Visual field ($N = 225$)</td>
<td>$-0.05 (-1.40, 1.01)$ [12%]</td>
<td>$-1.41 (-3.92, -0.02)$ [33%]</td>
</tr>
<tr>
<td>Color vision ($N = 234$)</td>
<td>$55.00 (28.00, 87.00)$ [18%]</td>
<td>$85.50 (46.00, 159.00)$ [37%]</td>
</tr>
</tbody>
</table>

The First Studies in MS: Comparisons of Vision Tests

Odds ratio in favor of MS vs. control status (95% CI) for worse vision scores

- **High Contrast Acuity ~100%**
  - (1.3, 1.9)
  - $P<0.001$

- **Low Contrast Acuity 1.25%**
  - * (1.9, 3.1)
  - $P<0.001$

- **Contrast Sensitivity Pelli-Robson**
  - (1.5, 2.2)
  - $P<0.001$

- **Color Vision D15-DS**
  - (1.2, 1.8)
  - $P<0.001$

* Low contrast acuity best distinguished MS patients vs. controls, logistic regression models, accounting for age

MS Patients: n=130
Controls: n=90

The First Phase 3 MS Trial

Cumulative probability of worsening of scores from baseline

$P<0.001$

Hazard Ratio (HR) = 0.53 (95% CI: 0.36, 0.76)

Number of Patients at Risk

Placebo
- 307
- 301
- 287
- 278
- 272
- 266
- 255
- 247
- 242

Natalizumab
- 619
- 609
- 590
- 582
- 573
- 561
- 553
- 546
- 531

...High-Contrast Acuity Still Did Not Capture Vision in People with MS

Hazard Ratio (HR) = 0.65 (95% CI: 0.30, 1.43)
P = 0.28

Cumulative probability of worsening of scores from baseline

Time to study (weeks)

Placebo
Natalizumab

Number of Patients at Risk

Placebo
12  24  36  48  60  72  84  96  108  120
307  305  301  296  292  291  284  278  276

Natalizumab
619  616  605  602  597  589  586  580  571

Invited Review

Validity of low-contrast letter acuity as a visual performance outcome measure for multiple sclerosis

Laura J Balcer, Jenelle Raynowska, Rachel Nolan, Steven L Galetta, Raju Kapoor, Ralph Benedict, Glenn Phillips, Nicholas LaRocca, Lynn Hudson, Richard Rudick and Multiple Sclerosis Outcome Assessments Consortium

Abstract: Low-contrast letter acuity (LCLA) has emerged as the leading outcome measure to assess visual disability in multiple sclerosis (MS) research. As visual dysfunction is one of the most common manifestations of MS, sensitive visual outcome measures are important in examining the effect of treatment. Low-contrast acuity captures visual loss not seen in high-contrast visual acuity (HCVA) measurements. These issues are addressed by the MS Outcome Assessments Consortium (MSOAC), including representatives from advocacy organizations, Food and Drug Administration (FDA), European Medicines Agency (EMA), National Institute of Neurological Disorders and Stroke (NINDS), academic institutions, and industry partners along with persons living with MS. MSOAC goals are acceptance and qualification by regulators of performance outcomes that are highly reliable and valid, practical, cost-effective, and meaningful to persons with MS. A critical step is elucidation of clinically relevant benchmarks, well-defined degrees of disability, and gradients of change that are clinically meaningful. This review shows that MS and disease-free controls have similar median HCVA, while MS patients have significantly lower LCLA. Deficits in LCLA and vision-specific quality of life are found many years after an episode of acute optic neuritis, even when HCVA has recovered. Studies reveal correlations between LCLA and the Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC), retinal nerve fiber layer (RNFL) and ganglion cell layer plus inner plexiform layer (GCL + IPL) thickness on optical coherence tomography (OCT), brain magnetic resonance imaging (MRI), visual evoked potential (VEP), electroretinogram (ERG), pupillary function, and King-Devick testing. This review also concludes that a 7-point change in LCLA is clinically meaningful. The overall goal of this review is to describe and characterize the LCLA metric for research and clinical use among persons with MS.
What About Structure to Validate Low-Contrast Acuity?

- The MS back-story from 2001
- Permanent axonal loss even without acute optic neuritis

Control autopsies (n=8)  MS (n=8, only 4 with ON)

Optical Coherence Tomography: More to Follow in Next Talk...

- RNFL = retinal nerve fiber layer (axons)
- GCL+IPL = ganglion cell layer (neurons)

A First Look at OCT in MS: RNFL Thinning in the Absence of Acute Optic Neuritis

MS Eyes: n=180
Disease Free Control Eyes: n=72

RNFL thickness (microns)

Overall average
Temporal
Superior
Nasal
Inferior

P < 0.001 for ON vs. non ON eyes, P = 0.03 for MS non ON vs. control eyes, GEE models accounting for age and within-patient, inter-eye correlations

Vision-Specific QOL: Even 20/20 is Not as Good as We Once Thought!

**Quality of Life Scores (mean)**

- **NEI-VFQ-25**
  - Disease-Free Controls: 98.5 ± 1.8
  - ON-20/40 or better (p<0.001 vs. controls): 84.0 ± 14.7
  - ON-20/50 or worse (p<0.001 vs. controls): 73.3 ± 15.9

- **Neuro-Ophthalmic Supplement**
  - Disease-Free Controls: 96.8 ± 5.0
  - ON-20/40 or better (p<0.001 vs. controls): 74.4 ± 17.8
  - ON-20/50 or worse (p<0.001 vs. controls): 67.7 ± 21.0

*P*-values from linear regression models, accounting for age

VEP: Remyelination May Save Axons and Neurons?

- Patients with acute unilateral ON (n=21)

<table>
<thead>
<tr>
<th></th>
<th>Mean VEP Latency (milliseconds)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>&gt; 20% RNFL Loss at 6 months</td>
<td>123.0± 17.2 n=6</td>
</tr>
<tr>
<td>&lt; 20% RNFL Loss at 6 months</td>
<td>111.9 ± 13.1 n=12 P=0.146</td>
</tr>
</tbody>
</table>

Primary endpoint: Recovery of FF-VEP latency*

Adjusted mean change in optic nerve conduction latency (measured by FF-VEP) in the affected eye compared with the unaffected fellow eye at Baseline. PP: placebo, n=36; anti-LINGO-1, n=33. ITT: n=41, both groups.
More Cutting Edge Electrophysiology: Melanopsin Mediated Pupillary Response

The Efferent Side: Rapid Number Naming Scores in MS

...are worse in patients compared to controls

...and reflect vision-specific quality of life

Rapid Number Naming in MS
...Digitized!

Slower times in patients compared to controls

Increased numbers of saccades and inter-saccadic intervals in MS

Hainline, Rucker et al. Submitted.
MULES Test of Rapid Picture Naming

Disease-free controls: 38.6 ± 7.3 seconds (range 29.4 – 53.4 sec)

Patients with MS: (range 44.4 – 86.3 sec)

Patients with NMO: (range 40.1 – 97.7 sec)

The Next Big Project!

- Establish criteria for defining optic nerve lesion in MS by OCT and vision data
- New and ongoing IMSVISUAL project to determine thresholds of inter-eye differences in RNFL and GCL thickness
- These thresholds will be determined from RENEW ON trial and IMSVISUAL controls
- IMSVISUAL MS patients = validation cohorts
The Role of Vision in MS

- Greater than two decades of data show both afferent and efferent systems are affected.
- Vision is a unique system that correlates structure, function, electrophysiology, QOL.
- Simple performance measures continue to have great value and sensitivity in MS.
- Goal: establish criteria that accurately predict an optic nerve lesion in MS.