Objectives

- Revise the neuro-ophthalmic manifestations of multiple sclerosis
- Discuss the role of ONTT in diagnosis and management of patients with optic neuritis.
- Understand the principles and utility of retinal nerve fiber analysis in MS
Outline

- The afferent system
- Optic neuritis and ONTT
- Early treatment trials
- OCT in MS
- Conclusions

Case

- 45 year old with acute painful LOV OS
  - 4/15: develops left side “migraine headache with “spot” in front of the eye; progressively worsens
  - 4/17: eye pain worse with EOM; migraine headache resolves; vision worse
  - 4/18: sees PCP- oral steroids; pain better; vision worse.
  - 4/22: seen in clinic;
- PMH: RA
- FH: maternal GM, aunt and uncle with MS
Case

- VA: 20/20; 20/400
- Color: 12/12; 0/12
- Contrast: 36; 5
- VF: normal OD; diffuse loss OS
- Left RAPD

The afferent system
**MS presentation**

<table>
<thead>
<tr>
<th>Deficit reported</th>
<th>Presenting %</th>
<th>During course %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visual/oculomotor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paresis</td>
<td>42</td>
<td>88</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>41</td>
<td>82</td>
</tr>
<tr>
<td>Incoordination</td>
<td>23</td>
<td>63</td>
</tr>
<tr>
<td>Genitourinary/bowel</td>
<td>10</td>
<td>39</td>
</tr>
<tr>
<td>Cerebral</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>


**Afferent system**

- Retina, ON, OC and post chiasmal pathways
- Common visual complaints- visual blurring or distortion; “not right”, “tired eyes”, “night vision”; even with “20/20” (Ma, Kupersmith)

**Retro-orbital pathway**

- Optic chiasm: acute or chronic chiasmal neuritis
- Post chiasmal lesions: produce hemianopic field defects seen in fellow eyes of AON; relatively uncommon- ONTT
- Visual perception disorders: neglect, perseveration (palinopsia), agnosia depending on the site of lesion.
Retina

- Periphebitis: 10-25% of patients; clinically asymptomatic; does not seem to correlate with disease activity. (Rucker; Bamford; Birch; Hughes)
- Periphebitis in patients with ON associated with increased risk of MS (Lightman; Rodriguez)

ERG changes recorded in MS patients with/out optic neuritis indicates subclinical primary retinal damage (Gill; Kirkham)

Uveitis

- 10 times higher in MS population
- Pars Planitis:
  - Upto 48% have demyelinating lesions on MRI (Lassman; Hughes)
  - Risk of developing MS and/or ON: 20% (Malinowski)
- Anterior and posterior uveitis less common
Optic neuritis

- 3 types
  - Acute: ONTT
  - Chronic: Not uncommon; insidious and slowly progressive
  - Asymptomatic/subclinical:

ONTT

NEXT:
EARLY TREATMENT TRIALS
OC IN MS
CONCLUSIONS

ONTT- design

- Multicenter study; 457 patients
- Participants: 28-45y; acute UL ON ≤ 8d; no previous ON in affected eye; No other cause for ON except MS; No previous treatment with corticosteroids for MS or optic neuritis.
- Neurologic exams at baseline, 6m, annual (1y-4y), 5y and 10y
- Visual exam at baseline, 7 visits (0-6m), annual 1y-4y, 5y and 10y
- Baseline: Labs for syphilis, SLE, CXR for sarcoidosis, LP (optional) and brain MRI. Brain MRI repeated at 10y.
ONTT- design

- 3 treatment groups - Iv MP with oral steroids; oral prednisone; placebo x 14d; short oral taper
- 1st objective: assess safety and efficacy (degree and rate of visual recovery) of corticosteroids in treatment of ON;
- 6 month data used for 1st measure of visual outcome.
- 4 visual parameters used
  - Primary measure: Contrast sensitivity (Pelli-Robson)
  - Primary measure: Perimetry (HFA:30-2 and 2 isopters on Goldmann)
  - Secondary measure: Snellen acuity (B-L chart at 4m)
  - Secondary measure: Color vision (F-M 100)

ONTT- Baseline

- Pain reported by 92%
- Phosphenes: reported by 30%

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- Abnormal color vision: 88% (Ishihara); 94% F-M 100.
- Contrast sensitivity: 98% abnormal
- Optic disc:
  - 65% retrobulbar; 35% papillitis; hemorrhage 6% - uncommon
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- **Optic disc**:
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- **Visual fields**: variable
  - 48% diffuse loss; 52% focal- central defects 8%; Hemianopia- 5%

ONTT field categories

- Fellow eye abnormalities (subclinical)
  - Visual acuity- 14%
  - Contrast sensitivity: 15%
  - Color vision: 22%
  - Visual field: 48%
- Blood test, CXR, brain MRI, LP: **limited value in diagnosis of typical ON**
- MRI brain: 27% had ≥2 lesions ≥3mm size
- **CSF**
  - Pleocytosis (>5 cells): 36%
  - IgG synthesis increase: 44%; IgG ratio increase in 22%
  - OCB: 50%
ONTT - results

- IVMP + oral steroids:
  - Accelerated visual improvement; max 2-3 weeks when started within 1-2 weeks of onset
  - Reduced rate of CDMS for 2 years; especially those with abnormal brain MRI at baseline.
- Oral prednisone:
  - Rate and extent of recovery similar to placebo
  - Increased recurrence of ON at 5 years, probability of recurrence in either eye was almost 2-fold higher in prednisone group.

ONTT - results

- Natural history (placebo group):
  - Visual recovery begins rapidly (79% by 3 weeks & 93% by 5 weeks) and improves for up to 1 year; most improve completely by 5-6 weeks.
  - Once recovered and stable (1 year follow up) after the initial episode of ON, vision remains stable over follow up.
- At 1 year, no difference in 4 visual parameters between groups.

ONTT - visual prognosis (6m)

- Persistent visual symptoms in 56%
- Visual acuity: 69% had 20/20
- Color vision: 40% abnormal
- Contrast sensitivity: 56% abnormal
- Visual field: 32% abnormal
- RAPD: 54%
- Optic atrophy: 63%.
ONTT- MRI brain

- **Initial MRI** if abnormal with WMD was the single most important predictor of the future risk of MS
  - 25% with no MRI lesions developed MS
  - 50% with ≥1 lesions developed MS in 5y
  - 72% with ≥1 lesions developed MS in 15y.

ONTT- 15 year visual outcome

<table>
<thead>
<tr>
<th>Table 4. Visual Function at 15 Year Follow-up According to Multiple Sclerosis Status</th>
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<tbody>
<tr>
<td><strong>MRI</strong> (n=44)</td>
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<tr>
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<tr>
<td><strong>Height (mm)</strong></td>
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<tr>
<td><strong>Vasculature (mg)</strong></td>
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<tr>
<td><strong>Disc hemorrhage (mg)</strong></td>
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<tr>
<td><strong>Retinal edema (mg)</strong></td>
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<tr>
<td><strong>Optic nerve edema (mm)</strong></td>
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ONTT- 15 year Neurological Outcome

- Risk of developing MS was highest within 5y of onset
- Low risk of CDMS if normal MRI with severe disc edema, disc hemorrhage, retinal edema, absence of pain, NLP vision
- Pts who developed CDMS had a relatively benign course (2/3rd had EDSS<3) irrespective of MRI lesions at baseline (ONTT group)
To treat or not treat

- IVMP: accelerates initial recovery but not outcome; decreases relapses and CDMS up to 2 years
- Oral steroids should be avoided: increases chances of recurrence in either eye.
- Optic neuritis- precursor vs. CIS

Case

- 45y
- UL vision loss with RAPD
- Pain with EOM
- Diffuse vision loss
- Papillitis
- Admitted
- IVMP + steroids
- MRI brain and orbits
- LP

Case

- Blood work normal
- CSF:
  - CSF cells: 4
  - Normal glucose and protein
  - IgG synthesis rate: 0
  - IgG index: 0.4
  - OCB: absent
  - MBP: 0.8

6/7/2011
Case

- Was MRI orbits needed?
- Was LP needed?
- Were steroids needed?
- Can results of ONTT be used in this patient?
- Atypical features- PMH of RA; MRI brain normal; MS panel normal
- What next?

Early treatment trials
CHAMPS
- Randomized double blind, placebo controlled
- Weekly IFN-β1a (Avonex) vs. placebo
- Patients: First demyelinating event + brain MRI lesions
- Primary endpoint: CDMS
- Secondary endpoint: MRI lesion
- Follow up: 3 years
- Results
  - Treatment decreased conversion to CDMS 35% vs 50%
  - IFN-β1a (Avonex) significantly reduced lesion load (T2 and T1-Gd)
  - 15% drop out

CHAMPIONS
- 5 year open label extension of CHAMPS
- All patients offered IFN-β1a (Avonex) at enrolment
- CHAMPS placebo group- delayed treatment arm
- CHAMPS Treatment group- immediate treatment arm
- Results at 5y
  - 53% completed 5 years follow up
  - CDMS probability lower in immediate treatment group (36% vs 49%)
  - Decreased numbers of active relapsing disease in the immediate treatment group
  - No difference in EDSS scores between early and delayed treatment; very few patients with major disability

ETOMS
- Randomized double blind, placebo controlled
- Weekly low dose IFN-β1a vs. placebo
- Primary outcome: development of CDMS
- Patients: 309 patients with CIS, abnormal neurologic exam and MRI lesions
- Duration: 2 years
- Results:
  - Treatment decreased conversion to CDMS 34% vs 45%
  - Treatment increased the time to conversion
  - Treatment decreased lesion burden
  - No EDSS change in the 2 groups

Filippi M. Lancet 2004
BENEFIT
- Randomized double blind, placebo controlled
- Alternate day IFN-β1b (Betaferon) vs. placebo
- Primary outcome: time to CDMS and McDonald MS
- Patients: 468 patients with CIS and MRI lesions
- Duration: 2 years; 5y long term study with open enrolment
- Results: 76% completed 5y follow up
  - At 2y: treatment decreased conversion to CDMS (28% vs. 45%)
  - At 3y: early treatment decreased conversion to CDMS (37% vs. 51%)
  - At 3y: early treatment delayed disability progression by 40%
  - At 5y: early treatment decreased conversion to CDMS (46% vs. 57%)
  - At 5y: no difference in EDSS progression in early and late treatments; absolute risk reduction 4% with early treatment

PreCISe
- Randomized double blind, placebo controlled
- Daily Glatiramer acetate vs. placebo
- Primary outcome: time to CDMS
- Secondary outcome: MRI lesions
- Patients: 481 patients with CIS and MRI lesions
- Duration: 2 years; 5y long term study with open enrolment
- Results:
  - At 2y: treatment decreased conversion to CDMS (25% vs. 43%); 45% risk reduction with treatment; NNT was 5.5
  - Treatment delayed conversion to CDMS
  - Treatment group had decreased lesion load on MRI

To treat or not treat
- Early treatment delays conversion to CDMS as well as the lesion load on MRI brain (all trials)
- No significant difference in EDSS progression in early and delayed treatment groups noted at 5y (CHAMIONS and BENEFIT).
- No reliable way to predict progression of CIS to CDMS- any role for “watchful waiting”?
- Costs and side effects of treatment??
- Close follow up with examination and MRI in 3-6 months?
Case

- Isolated optic neuritis
- No lesions on MRI brain
- No DMT yet
- How do we follow-up? Clinical, MRI brain, other markers?

Ocular Coherence Tomogram in Multiple Sclerosis

What is OCT

- Principle of low-coherence interferometry
- Similar to USG- light instead of sound
- Measures echo time delay and intensity of reflected/ backscattered light to produce a cross-sectional image.
Reflectance pattern is processed, presented as grayscale (8-bit) or false color image (24-bit).

Axial resolution: OCT 3-15 μ; USG 150 μ.

Image processing algorithms identify interfaces between tissues.
Automated segmentation techniques extract quantitative values used to measure tissue thickness.
At present, segmentation and thickness analysis can be done for total retinal thickness, RNFL.
Normative database can be established for patients deemed normal by clinical and other established methods.
Retinal nerve fiber layer in MS

- Clear pathological correlate: Axonal loss causes disability and RNFL looks at CNS axons!!
- RNFL loss may reflect global neurodegeneration
- Proposed pathogenesis:
  - Direct effect of acute optic neuritis
  - Chronic/subclinical lesions of anterior visual pathways.
  - Effects of retrograde axonal degeneration from trans-synaptic degeneration from lesions of retro-geniculate pathways.

*Budenz, Ophthalmology 2008

OCT in MS results

- MS-ON eyes vs. healthy controls: (14 studies n=2063)
  - Average RNFL thickness loss: -20.38 μm (Range: 5–40 μm)
- MS without ON eyes vs. healthy controls (15 studies n=3154)
  - RNFL loss is -7.08 μm
- MS- affected eyes vs. "unaffected eye" (27 studies n=4199)
  - Estimated RNFL loss: -14.57 μm

*Petzold, Lancet Neurol 2010
RNFL and functional correlates

- RNFL loss was associated with reduced visual acuity in many studies.
- RNFL loss was associated with reduced contrast sensitivity (using 1.25% chart) in many studies.
- RNFL loss was associated with visual field loss at 3-6m after ON. Prognosis for visual recovery poor if RNFL thickness < 75 μm. (Costello 2006).
- RNFL loss was associated with poor EDSS scores in a few studies with correlation increasing for those without MSON.

Petzold, Lancet Neurol 2010

Limitations of OCT

- Test- Retest variability for RNFL scan varies between 5-7 μm (to be significant Fast scan mean RNFL would be expected to change by no more than 9.5 μm- 95% of the time*)
- Resolution- Stratus OCT axial <10 μm, more transverse, SD-OCT 5-7 μm commercially and 2-3 μm in research.
- Ocular changes that may also give rise to decreasing NFL thickness- retinal disease, optic nerve disease including glaucoma.
- Factors that may affect data acquisition- inability of patient to sit for scan, poor signal strength, dense cataracts, media opacities.

Case

- Follow up 5/20
  - Visual acuity: 20/20; 20/50
  - Color: 12/12; 8/12
  - Contrast: 36; 25
  - VF: normal OD; central scotoma OS
  - Left RAPD
Case

![Eye Image]

Conclusion

- Multiple sclerosis can affect various parts of the afferent visual pathways.
- The ONTT was critical in establishing the natural history of optic neuritis.
- Early treatment trials have shown a clear benefit in delaying progression of CIS to CDMS, but not EDSS.
- Retinal NFL assessment using OCT correlates with clinical measures and can be used as a marker for disease progression.
- Integration of Retinal NFL thickness assessment using OCT into research (and clinical setting) could allow better structure function correlation.