Genetics in Eye Disease: From Discovery to Clinical Applications
Lucia Sobrin, MD, MPH

I. Introduction
   a. Mendelian Genetic Diseases
      i. Sequencing
   b. Complex Polygenic Diseases
      i. Genome-wide association Studies

II. Age-related macular degeneration
   a. Discovery in Genome-Wide Association Studies
      i. Discovery of Pathophysiologic Pathways
      ii. Genetic Testing in AMD
         1. Predictive Value
         2. Current recommendations
      iii. Drug development based on Findings
         1. Lampalizumab
   b. Pharmacogenetics
      i. AREDS Vitamins and Predicting Response to Treatment
      ii. Pharmacogenetics of Anti-VEGF Response and other medications

III. Retinal degenerations
   a. Sequencing as a tool for discovery of novel mutations
   b. Genetic testing for retinal degenerations
   c. Gene therapy clinical trials
      i. Leber’s Congenital Amaurosis
      ii. X-linked Retinoschisis

IV. Conclusions
   a. Increasing impact of genetic information in clinical practice for eye disorders
   b. Goal of personalized genetic medicine

The Evolution of In Vivo Confocal Microscopy for Quantitative Corneal Imaging
W. Matthew Petroll, Ph.D.

Overview
The optical sectioning ability of confocal microscopy allows high magnification images to be obtained from different depths within a thick tissue specimen, and is thus ideally suited to the study of intact tissue in living subjects. In vivo confocal microscopy has been used in a variety of corneal research applications on experimental animals since its development over 25 years ago. In recent years, the use of the confocal microscope on human patients has also expanded dramatically. Using confocal microscopy, the cellular details of fundamental biological processes such as inflammation, wound healing, toxicity, infection, and disease, which could previously be studied only under static or isolated conditions, can now be dynamically evaluated over time and
the effectiveness of treatment modalities determined. This presentation will review the evolution of confocal imaging technology, and provide examples of how advances in hardware and software have led to expanded clinical capabilities.

Outline of Presentation

I. In Vivo Confocal Imaging Systems: An overview of the different instruments used for in vivo confocal imaging will be provided, and their capabilities for quantitative corneal imaging compared.
   A. The TSCM
   B. The Confoscan 4
   C. The HRT-RCM

II. 3-D Corneal Imaging and Analysis: The development of confocal microscopy through focusing (CMTF) of the cornea will be described, and a range of clinical applications presented.
   A. Assessment of Corneal Sub-layer Thickness
   B. Evaluation of Stromal Haze
   C. Measurement of Corneal Keratocyte Density
   D. Volume Rendering

III. Quantitative Imaging of the Subbasal Nerve Plexus (SBNP): The evolution of advanced image acquisition, reconstruction and analysis procedures for assessing changes in the SBNP in response to surgery or disease.
   A. Morphometric Parameters
   B. Wide-field Reconstruction and Mapping of the SBNP
   C. 3-D Reconstruction of the SBNP
**Optic Neuritis**

- Andrew G. Lee, MD  
  - Chair Ophthalmology, Houston Methodist Hospital, Professor of Ophthalmology, Neurology, & Neurosurgery, Weill Cornell Medical College; Clinical Professor, UTMB Galveston; UT MD Anderson Cancer Center; Adjunct Professor, Baylor COM, U. Iowa & U. Buffalo SUNY

**Prototype for optic neuritis**

**Acute visual loss in young woman**

- 20 y/o white female  
- Acute unilateral visual loss (RE): 20/40  
- Mild relative central scotoma OD  
- OS exam: Normal  
- Pain with eye movement  
- Right RAPD  
- Normal fundus OU

**Overview**

- Typical optic neuritis  
- Optic neuritis treatment trial (ONTT)  
- Controlled high risk Avonex MS prevention study (CHAMPS) and other MS trials  
- Atypical optic neuritis including NMO

**Key questions: According to ONTT?**

- What is the diagnosis?  
  - Retrobulbar optic neuritis  
- What lab tests should be done?  
  - No labs needed for typical optic neuritis  
- Do you need a lumbar puncture?  
  - Not for typical optic neuritis?  
- Do you need an MRI & why?  
  - Yes, for prognosis for demyelinating disease  
- What treatment should be performed?  
  - None or IV steroids (but not oral steroids in std doses)

**Dad’s rule of duck**

- If it quacks like a duck, looks like a duck, and flies like a duck then it is likely to be a duck

**Evaluation of typical optic neuritis**

- Optic Neuritis Treatment Trial (ONTT)  
- Randomized, controlled clinical trial  
- IV steroids vs. oral steroids vs. placebo  
- No labs necessary for typical ON  
- Lumbar puncture not necessary  
- No visual evoked potential needed
IV = more rapid recovery
All groups recover

Cumulative Probability of CDMS by Number of Brain MRI Lesions
- 51% ≥ 3 lesions
- 37% 1-2 lesions
- 16% No lesions

Probability of Recurrent Optic Neuritis in Either Eye by Treatment Group
- 41% Prednisone
- 25% Intravenous
- 25% Placebo

Cumulative Rates of Recovery of Normal Visual Field in First 6 Months
IV = more rapid
25% Methylprednisolone
15% Placebo
15% Prednisone
All groups recover

Cumulative Probability of CDMS by Treatment Group in First 2 Years
- 16.7% Placebo
- 14.7% Prednisone
- 7.5% Intravenous
P = 0.05 Prednisone vs Placebo
P = 0.05 Intravenous vs Placebo

Figure 1 Development of CDMS according to number of baseline brain MRI lesions
- 3 MRI Lesions (N=191)
- 2 MRI Lesions (N=191)
- 1 MRI Lesion (N=191)
US: Optic Neuritis Treatment Trial

- IV methylprednisolone (1000 mg/d) vs. oral prednisone (1 mg/kg) vs. placebo
- IV steroids sped rate of recovery but did not change final outcome
- Oral steroids increased attacks of ON
- No labs necessary for typical ON
- MRI prognostic for multiple sclerosis

What type of MRI

- ONTT: MRI head (T2 lesions for MRI)
- MR has improved over time since 1992 ONTT
  - Head
  - FLAIR
  - Fat suppression
  - Gadolinium
- Enhancing lesions (active disease)
- Greater than 9 MRI xT2 lesions, perpendicular, ovoid, corpus callosum, infratentorial, spine lesion

Beware bilateral ON enhancement especially intracranially (no pain)

Beware enhancing & enlarged

FAT SUPPRESSION POST GADOLINIUM

Beware enhancement outside of nerve itself...

http://rad.usuhs.edu/synapse/kiosk_image.html
**Fat sat**

- Suppress fat signal on T1
- Normal fat
- Shows enhancement of optic nerve
- If no T2 lesions and no enhancement beware of other etiologies for visual loss other than optic neuritis (e.g., retinal etiologies)

**FLAIR**

- Fluid attenuation inversion recovery
- Suppress normal CSF signal
- Only show pathologic white matter lesions

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**Table 1**

<table>
<thead>
<tr>
<th>Location of optic nerve enhancement</th>
<th>All patients (n)</th>
<th>All patients (%)</th>
<th>Patients with follow-up (n)</th>
</tr>
</thead>
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<tr>
<td>No enhancement</td>
<td>6</td>
<td>5.6</td>
<td>6</td>
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<tr>
<td>Orbit only</td>
<td>47</td>
<td>43.9</td>
<td>39</td>
</tr>
<tr>
<td>Canal only</td>
<td>10</td>
<td>9.3</td>
<td>9</td>
</tr>
<tr>
<td>Intracanal only</td>
<td>6</td>
<td>5.6</td>
<td>8</td>
</tr>
<tr>
<td>Orbit and canal only</td>
<td>21</td>
<td>19.6</td>
<td>18</td>
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<tr>
<td>Canal and intracanal only</td>
<td>7</td>
<td>6.5</td>
<td>4</td>
</tr>
<tr>
<td>All three segments</td>
<td>10</td>
<td>9.3</td>
<td>9</td>
</tr>
</tbody>
</table>


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**Figure**

Abnormal enhancement affected optic nerves

**Graph**

Years Post CIS Diagnosis

Risk of Conversion Based on Lesion Count at Presentation
Translation

- Should you tell a patient with optic neuritis who has a normal MRI that they don’t have MS?
  - No, ONTT 25% risk at year 15
- Should you tell a patient with optic neuritis who has an MRI with white matter lesions that they have MS?
  - No, ONTT 22% do NOT have MS at year 15

CHAMPS

- Controlled High Risk Avonex Multiple Sclerosis Prevention Study (CHAMPS)
- Monosymptomatic event (50% optic neuritis)
- MRI: demyelinating white matter lesions
- All received IV steroids
- Rx: Interferon beta 1-a vs. Placebo
- Outcome measures: CDMS & MRI

Results (CHAMPS)

- Three year pre-planned efficacy analysis
- Reduced risk of clinically definite MS: 45%
- Reduced # MR lesions, enhancing lesions

Natural History of MS

Clinical and MRI Measures


**At least 3 of the following:**
- ≥1 Gd-enhancing brain or spinal cord lesion or ≥9 T2 hyperintense brain and/or spinal cord lesions of ≥3 mm in size if none of the lesions are Gd-enhancing
- ≥1 brain infratentorial lesion or spinal cord lesion ≥3 mm in size
- ≥1 juxtacortical lesion ≥3 mm in size
- ≥3 periventricular lesions ≥3 mm in size

**At least 1 of the following:**
- 2nd clinical episode
- Gd-enhancing lesion ≥3 months after onset of initial clinical event located at different site
- New T2 lesion detected any time after a reference scan that was performed at least 30 days after onset of initial clinical event
- A first attack plus changes on MRI may be enough

**European MAGNIMS multicenter collaboration have been incorporated (Swanton et al. Lancet Neurol 2007;6:677-686; J Neurol Neurosurg Psychiatry 2006;77:830-833.)**

**Dissemination in time:** New T2 or gadolinium-enhancing lesion on a follow-up MRI, with reference to baseline scan, regardless of when obtained
- Previously reference scan > 30 days after initial event
- Dissemination in space: At least one T2 lesion in at least two out of four areas: periventricular, juxtacortical, infratentorial, or spinal cord
- Need not be gadolinium enhanced

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**Revised McDonald Criteria 2010**
- European MAGNIMS multicenter collaboration have been incorporated (Swanton et al. Lancet Neurol 2007;6:677–686; J Neurol Neurosurg Psychiatry 2006;77:830–833.)
- Dissemination in time: New T2 or gadolinium-enhancing lesion on a follow-up MRI, with reference to baseline scan, regardless of when obtained
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- Need not be gadolinium enhanced
What is NMO? ... Dad’s rule of ducks

What is different about Arabian Peninsula compared with Western world for MS/NMO?

Why does earlier diagnosis & treatment matter in NMO?

Five indications for ordering NMO

- Affects women
- Disproportionately affects African-Americans and Asians
- Asian form of MS more like NMO
- Most NMO patients are misdiagnosed initially as MS

NMO

Optic neuritis (bilateral, sequential or simultaneous)

Transverse myelitis (longitudinal > 3 segments)

NMO IgG

Optic neuritis (but not typical)

Tends not to recover

Bilateral

Brain MRI either normal or not typical white matter lesions for MS

LP pleocytosis (> 50 WBC)
Typically normal or not convincing for MS
Over time lesions can develop however
Transverse myelitis (spine MR) abnormal
Optic nerve enhancement in acute cases

1. Non-recovering optic neuritis (<20/200)
2. Bilateral simultaneous or sequential ON
3. Recurrent ON & MRI brain not typical for MS
4. Atypical MS: MR negative & LP > 50 WBC CSF cells
5. Transverse myelitis (kids/adults)

For acute therapy
IV methylprednisolone 1 gram for 3 to 5 days followed by an oral taper
If minimal response to corticosteroid therapy and vision < 20/200
Then plasma exchange for a total of 3 to 5 exchanges
Rituximab
Rationale for treatment

- NMO attacks = disability from attacks
- MS attacks = relapse/remit then progressive disability

What difference does it make?

- MS
  - Immunomodulatory therapy
  - Recovers, Relapses, Remits
- NMO
  - Immunosuppressive therapy
  - Doesn’t recover as well
  - Unpredictable course
  - Immunomodulatory may be worse for NMO

Chronic therapy for NMO

- Azathioprine
- Mycophenolate mofetil
- Rituximab
- IV gamma globulin (IVIg)
Prognosis of NMO

- Unpredictable, relapsing course
- Attacks occurring months or years apart
- Disability cumulative (from attacks)
- Moderate degree of permanent limb weakness from myelitis common
- Death most often caused by respiratory complications from myelitis attacks
- Cumulative survival is decreased in NMO

Summary: Optic neuritis

- Typical optic neuritis
- Optic neuritis treatment trial (ONTT)
- Controlled high risk Avonex MS prevention study (CHAMPS) and other MS trials
- Atypical optic neuritis including NMO

Summary

- NMO is likely a separate disease from MS
- Looks different
- Acts different
- NMO attacks lead to disability
- Immunosuppression not immunomodulatory
- NMO = biomarker (no biomarker for MS)
- Start treatment if NMO positive

Thanks for your time and attention

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When do I order NMO antibody

1. Non-recovering optic neuritis (<20/200)
2. Bilateral simultaneous or sequential
3. Recurrent ON & MRI brain not typical for MS
4. Atypical MS: LP > 50 WBC CSF cells
5. Transverse myelitis in adults