Neuro-Ophthalmic Imaging
For Demyelinating Diseases
Like Multiple Sclerosis
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Conflicts of Interest
None

Disclosures
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UT Southwestern Clinical Center for Multiple Sclerosis
• Chaired by Dr. Elliott Frohman, MD, PhD
• 7 full time fellowship trained MS physicians
• 4 Physician Assistants and 1 Nurse Practitioner
• 5 Registered Nurses (2 Dedicated Research Nurses)
• 2 Neuro-Ophthalmic Imaging Specialist
• 2 Social Workers
• MS Society Fellowship Program
• Combined MS and Neuro-Ophthalmology Fellowship
• Physician, Physician extender and Nurse MS Training Program
• Over 1000 have attended training program
• More than 6000 patients
• Bio Repository and Brain Bank

Children’s Hospital of Dallas Pediatric Demyelinating Disease Clinic
• Directed by Benjamin Greenberg, MD
• Deputy Director Donna Graves, MD
• Nurse, Physician Assistant, Neuro-Ophthalmic Imaging Specialist, Social Worker, Physical Therapy, Psychology, Cognitive Testing, School Liaison
• Dedicated Neuro-Ophthalmic lab with Spectralis OCT
• First Pediatric Demyelinating Disease fellow starting in July
• Inpatient and Outpatient Electrophoresis (PLEX)

Collaborative Research
UT Southwestern is part of unique research collaboration conceived by Dr. Frohman. The MS Centers at UTSW, Penn, Johns Hopkins, and UCSF combine our fund raising, resources, data, and publishing. Instead of competing, we work together. Twenty Nine peer reviewed papers published in just the past two years.

Elliot Frohman, MD, PhD		Peter Calabresi, MD
Laura Balcer, MD, MSCE		Ari Green, MD
Penn Medicine		UCSF Medical Center

Multiple Sclerosis
• Estimated 400,000 people in the United States and 2.5 million worldwide
• Medically described in Holland in the 14th century.
• Seminal description by Charcot in 1868
Multiple Sclerosis Types

Multiple Sclerosis
- Relapsing Remitting
- Primary Progressive
- Secondary Progressive
- Progressive Relapsing
- Clinically Isolated Syndrome
- Radiological Isolated Syndrome

MS Borderline Diseases

Idiopathic inflammatory demyelinating diseases
- Neuromyelitis optica (Devic’s Disease)
- Transverse myelitis (TM)
- Acute disseminated encephalomyelitis (ADEM)
- Other “Mimics” like Sarcoidosis and Lupus

A major role of the MS Specialist is separating MS from all the “Mimics”.

Multiple Sclerosis And The Eye

- Problem (Optic Neuritis or Internuclear Ophthalmoplegia INO)
- Up to 80 percent of patients with Optic Neuritis will eventually be diagnosed with Multiple Sclerosis
- 75 percent of MS patients will have at least one episode of optic neuritis in their lifetime
- Post mortem analysis shows 90 percent of MS patients have some form of optic nerve involvement

Importance of Neuro-ophthalmic Imaging in Multiple Sclerosis

- Since the eye is part of the central nervous system, it can be a good indicator of what going on in the brain
- Can provide a model for developing new imaging techniques and testing drug therapies
- Quantifiable data can be obtained for testing neuro-protective and neuro-regenerative drugs

MS MRI Findings

Yellow Arrows are inflammation along blood vessels not visible on 3T MRI's
Classic MS Lesions at 7 Tesla's in the periventricular area of the brain.

7 Tesla MRI Images of MS

NYU Physician winter 2008–2009. Gina Shaw, p. 16-17
Not every vision problem in an MS patient is caused by MS.

Quantitative Visual Acuity

Neuro-Ophthalmic Testing Structure and Function

Retinal nerve fiber layer is associated with brain atrophy in multiple sclerosis

Axonal Demyelination in MS Lesions

The ability to combine structure and function together into one test so that the specific areas of the eye and their function are known.

Retinal nerve fiber layer is associated with brain atrophy in multiple sclerosis

• Quantified Vision (HC and LC)
• Color Vision
• Visual Fields (30-2 and 10-2)
• Infrared Pupillometry
• Infrared Oculography
• Electrophysiology

• Fundus Photography
• Infrared Fundus Photography
• OCT
• MRI

Reduction in RNFL thickness correlates positively with poor visual function when low-contrast letter acuity (2.5% contrast) is tested in a MS cohort

Elliot M. Frohman, Laura J. Balcer and Peter A. Calabresi (2010)
Can retinal imaging accurately detect optic neuritis?

Nat. Rev. Neurol.
doi:10.1038/nrneurol.2010.13
Color Vision Testing

Visual Field Test

Infrared Binocular Pupilometry

Relative Afferent Pupillary Defect

Infrared Binocular Oculography

Internuclear Ophthalmoparesis (INO)
7 Tesla MLF Identification

Optic Neuritis
- Optic neuritis is inflammation of the optic nerve.
- Typically resolves on its own in 2 or 3 weeks even if untreated
- High contrast vision typically returns to near normal usually within 3 months after the attack of optic neuritis but color and low contrast vision can be diminished long-term
- OCT rnf thickness after optic neuritis is typically normal or above normal due to optic nerve swelling
- Over the next 3 to 6 months rnf thickness will decrease between 10 and 40 microns in 75% of pts

Disk At Risk (DAR)
- No or small physiological cup
- Small compact nerve
- Vessels crowded together
- Risk factor for Acute Ischemic Optic Neuritis (AION)
- Often confused for optic neuritis and worked up for MS

Optic Neuritis

Optic Nerve – Disc At Risk

Ocular Coherence Tomography
- Has already proven to be a reliable biomarker not only for MS but for other neurological disorders including Alzheimer's and Parkinson's
- May be useful in head trauma, concussion, and other brain atrophy studies since there is a correlation between brain volume and rnf
What has OCT shown us so far?

Retinal nerve fiber layer thinning (RNFL) reflects MS related optic nerve neurodegeneration.


Peripapillary nerve fiber layer

Although non-specific, Average Macular Thickness is also reduced in MS eyes. Burkholder et al. Ann Neurol 2006, Pulicken et al. Neurology 2007

Primary focus of OCT research in MS to date

The retinal nerve fiber layer

Although non-specific, Average Macular Thickness is also reduced in MS eyes. Burkholder et al. Ann Neurol 2006, Pulicken et al. Neurology 2007

Gilenya Induced Macular Swelling

Gilenya was immediately stopped. Sent to Retina Clinic same day

A proper OCT for Neurology needs both Optic Nerve and Macula.

Patient who has had 2 attacks of ON in the same eye

A little damage in the PMB goes a long way

This patient’s High Contrast vision is 59 (almost 20/20) but the 2.5 is 18 and the 1.25 is 10

OCT Retinal Segmentation

Why is there an interest in being able to quantify the neural components of the retina in MS?

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

Why is there an interest in being able to quantify the neural components of the retina in MS?

GCL + IPL Segmentation

GCL + IPL thickness better correlates with vision and function than RNFL after ON

MS Micro Cyst in GCL+IPL

Published this year in Brain by Dr. Green’s group at UCSF
• Results have been duplicated at UT SW and Johns Hopkins
• Call into question whether MS is primarily a demyelinating disease
• May be very common if you know what to look for
• Blood brain barrier studies needed (Fluorescein Angiography, Fluorophotometry)

Other systemic diseases like diabetes may have inflammation as their primary early damage mechanism
Electrophysiology

- Perform each test in a step by step method the same way each time
- Follow generally accepted guidelines (ISCEV)
- Get training from people who actually perform the test
- Performing a high quality test does not require you to know how to interpret the test
- Newer test are combining structure and function.
- Studies are using electrophysiology again

Electrophysiology Multiple Sclerosis

- VEP (Visually Evoked Potential)
  - Measures cortical response to visual stimulus of about 20 to 30 degrees
- mfVEP (Multi-Focal Visually Evoked Potential)
  - Measures cortical response to specific areas of retina. Usually 60 to 120 hexagons. Gives you about 60 degrees of retina
- mfERG (Multi-Focal Electroretinogram)
  - Measures direct scotopic retinal responses
    - Time (Latency)

Demyelination Effect on Action Potential

- becomes diminished, resulting in either slowing of conduction velocity, or inability to sustain repetitive impulse discharges, or conduction failure

Gelfand JM, et. al. Brain (2012)
Visually Evoked Potential (VEP)

The Multifocal VEP

Multi-Focal Visually Evoked Potential (mFVEP)

The Multifocal ERG

Multi-Focal Electroretinogram (mfERG)

Fig. 1
Focal stimulus evokes local dipole source in the retina. When action potentials reach the optic nerve head a second dipole source is generated there. Source 2 is delayed relative to source 1. The delay is proportional to the fiber length connecting the stimulated patch with the nerve head.

Sutter, E. Encyclopedia of the Eye. 2010

Slide Courtesy of Dr. Erich Sutter

Optic Nerve Head Component

Interesting Case MS Patient Optic Neuritis?

Caucasian Female
31 yo
5’6” 437lbs
BP 140/80
Obstructive Sleep Apnea (CPAP user)
MS dx in 2007
RRMS type on Rebif
Blurry vision OS for 3 months. No pain or headaches.
Spinal Tap opening pressure was 24

Vision and Pupils
HC  OD  88 OS 81 OU 79
2.50 OD  38 OS  0 OU 39
1.25 OD  9 OS  0 OU 11
APO OS

Notice that the GDX scan on the right since it works by birefringence does not show swelling.
Interesting Case Macular Scans

Interesting Case 120 Sector mfVEP

Interesting Case 103 Hexagon mfERG

Interesting Case Was it ON, Papilledema, or Pseudo-tumor?
No new enhancing lesion or ON enhancement OU on MRI
Opening Pressure on Spinal Tap 24
2 Weeks of Diamox and Steroids

Pre and Post treatment images.

ONHC 150 Days After AON

Neuro Protective and Neuro Regenerative Agent Trials

- **BIIB033 (Anti Lingo 1)**
  - Ready for human trials
  - SD-OCT and mfVEP will be two of the primary outcomes
  - Shown to promote axonal integrity and spinal cord remyelination in mouse model.

  *Nature Medicine 13* Published online: 30 September 2007 | doi:10.1038/nm1664

- Two other studies still in animal stages

  Structure and Function
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