The Neuro-ophthalmology of Multiple Sclerosis

Leonard V. Messner, OD, FAAO
Professor & Vice President for Patient Care Services-Illinois College of Optometry
Executive Director-Illinois Eye Institute

Lorraine Lombardi, PhD

Disclosures

- Carl Zeiss Meditec (speakers bureau)
- King Devick Technologies (scientific advisory board)
- Illinois Society for the Prevention of Blindness (clinical research grants)
### Key Points

- Diagnostic criteria for MS
- Pathogenesis & Classification of MS
- Neuro-ophthalmic manifestations of MS:
  - Afferent system:
    - Optic neuritis
  - Efferent system:
    - Brainstem motility disorders
    - Nystagmus
    - Cranial neuropathies
- Visual biomarkers of disease activity

### 2010 Revised MacDonald Diagnostic Criteria for MS

- Evidence of damage (clinical attacks and/or lesions) in 2 or more separate areas of the CNS (including the brain, spinal cord, and optic nerves), plus evidence that the damage happened 1 or more months apart, plus evidence that the damage did not happen because of another disease.

---

![Diagram showing 2010 Revised MacDonald Diagnostic Criteria for MS](image-url)
Pathogenesis of MS

- Auto-immune attack against myelinated axons
  1. Acute inflammation
  2. Demyelination
  3. Axonal destruction
  4. Fibroglial remodeling


The Immunopathogenesis of Multiple Sclerosis: T-Cell Involvement

- Attacking virus with surface amino acids (epitope) that resemble myelin oligodendrocyte glycoprotein (MOG)
- Activated T cells “introduced” to antigens by Ag presenting cell (APC)
  - Tissue macrophage
  - CNS dendrite
- Sensitized T cells react to both viral and myelin epitopes (molecular mimicry)

Freedman M. NARMS 2007

Immunopathogenesis cont.

- Primed and activated immune cells cross blood-brain barrier via integrin molecules (e.g. matrix metalloproteases) and attack MOG epitopes
- As myelin is destroyed, new antigens are released resulting in inflammation and perpetuation of the disease process
T-cell exposure to viral trigger

T-cells become "primed" in regional nodes

Activated T-cells cross BBB (via integrin proteins)

T-cells attack myelin (MOG)

Myelin is destroyed & new antigenic proteins are released

B-Cell Involvement in MS

Lehman-Horn K, et al. Ther Adv Neurol Disord 2013

FDA approves new drug to treat multiple sclerosis

Release
Pathogenesis-Based MS Treatments (cont.)

- INF-β derivatives stabilize the BBB through inhibition of MMP (also some potential anti-viral activity)
- GA affects antigen presentation and thereby reduces the inflammatory effect directed against myelin
- Anti-alpha-4 integrin natalizumab (NTZ) inhibits transport across BBB
- Fingolimod (FTY720) entraps activated T-cells within regional lymph nodes
- Teriflunomide inhibits the proliferation of activated T-cells.
- Dimethyl fumarate blocks pro-inflammatory cytokine production.
- Anti CD20 (ocrelizumab) depletes B-cells and in turn the ability of B-cells to regulate APC pathways for T-cell activation.

The recent development of monoclonal antibody-based treatments has resulted in improved efficacy of anti-MS therapy but with significant complications of immunosuppression and opportunistic CNS infections (notably progressive multifocal leukoencephalopathy (PML)). This is particularly true of individuals who are sero-positive for the JCV virus.

Fingolimod (Gilenya)-Associated Macular Edema

- Analysis of phase 2 & 3 fingolimod studies revealed CME in 19 cases out of 2,615 patients (0.7%)
- 68% within first 4 months of treatment
- Increased risk of CME if pre-existing diabetes or uveitis

Recommendations:
- Baseline retinal exam/OCT for patients planned for fingolimod then at 3-4 months (closer surveillance if underlying diabetes or uveitis)
Classification of MS

- Relapsing-remitting (85%)
- Secondary-progressive
- Primary-progressive
- Progressive-relapsing
Neuro-ophthalmic Manifestations of MS

- Optic neuritis
- Brainstem motility disorders
- Nystagmus
- Cranial neuropathies

Optic Neuritis

15 y/o AA Female

- Acute vision loss OD x 2 days
- BVA:
  - 20/200 OD
  - 20/20 OS
- + RAPD OD
- No pain on eye movement
Neuroretinitis

• Infectious / parainfectious autoimmune optic neuropathy
• Common etiologies:
  – Infectious: cat scratch disease (Bartonella henselae), Lyme disease & syphilis
  – Post viral illness (Leber’s idiopathic stellate neuroretinitis)
• Acute papillitis with macular scar
• Resolution x 6–12 months
• Treatment of underlying infectious disease (if known)
• Does not evolve to MS

Demyelinating Optic Neuritis

• A focal inflammatory / demyelinating event of the optic nerve that may be idiopathic and localized to the optic nerve or may be or become associated with other systemic illnesses, notably multiple sclerosis.
Classification of Demyelinating Optic Neuritis

- Anterior (Papillitis)
- Retrobulbar

Retrobulbar Optic Neuritis
75%

Anterior Optic Neuritis
25%
No Blood!
Clinical Features of Optic Neuritis

- Abrupt vision loss
  - variable (average 20/60 x ONTT)
  - APD
  - Dyschromatopsia (> VA loss)
  - Decreased brightness
  - Nadir x 2 weeks
  - Gradual recovery (albeit with sustained color and brightness loss)
  - Pain (>90%)

29 Y/O AA Woman

- Acute vision loss – OD
- "Everything looks dark & dim."
- Pain behind OD on movement
- +APD OD
- BVA:
  - 20/400 OD
  - 20/20 OS
Visual Field Defects (affected eye)

- Diffuse (48.2%)
- Localized (51.8%)
  - centro/centro-ecal (8.3%)
  - arcuate/altitudinal (20.1%)
  - hemianopic (4.2%)

Fellow Eye Visual Field Defects

- Visual acuity (13.8%)
- Contrast sensitivity (15.4%)
- Color vision (21.7%)
- Visual fields (48.8%)

30-y/o woman
c/o vision “dark & dim”
OS x 5 days (getting worse)

VA = 20/20

+ APD
+ Pain

VA = 20/80
25-y/o woman c/o decreased vision, OD x one week (getting worse)

VA = 20/40
+ APD
+ Pain

VA = 20/20
MRI Characteristics

- T1WI post Gd
  - Enhancement of acute lesions
  - Hypointense axonal atrophy ("black holes") with chronic lesions
- T2WI
- FLAIR  
  - Hyperintense with acute & chronic lesions
42 y/o Caucasian Woman

- Recent onset vision loss OS
- BVA:
  - 20/20 OD
  - 20/60 OS
- RAPD OS
- Pain on eye movement OS
56 y/o White Man

• C/o decreased vision, OD x 3 days
• BVA:
  – 20/40 OD
  – 20/20 OS
• RAPD OD
• Pain on eye movement
ONTT Protocol

• Patients 18 to 45 years with acute (8 days or less) optic neuritis randomized to:
  – oral prednisone (1mg/kg/day) x 11 days, 4 day taper
  – IV methylprednisolone (1000mg/day) x 3 days followed by oral prednisone (1mg/kg/day) x 11 days, 4 day taper
  – oral placebo x 14 days


ONTT Results (6 months)

• Quicker recovery with IV steroids
• Visual recovery excellent for ALL groups
• Increased # of new attacks with oral prednisone alone


The Effect of Corticosteroids for Acute Optic Neuritis on the Subsequent Development of Multiple Sclerosis

Roy W. Bond, Patricia A. Creech, Jonathan I. Teale, David J. Kaufman, Dan L. Kappel, Ronald W. Hoyt, C. Theodore Brown, and the Optic Neuritis Blind Group

The NEW ENGLAND JOURNAL OF MEDICINE
ONTT Results (2 years)
• Development of MS
  – Oral prednisone (14.7%)
  – Placebo (16.7%)
  – IV steroids (7.5%)


ONTT Results (2 years)
• Abnormal MRI (2 or more WML's 3mm or greater in diameter)
  – Placebo (36%)
  – IV steroids (16%)

Trobe JD. Arch Ophthalmol 1994

RISK OF DEFINITE MS BY TREATMENT GROUP

Placebo
Prednisone
Intravenous

% with Definite MS

Years of Follow-Up
ONTT Results (3 years)

- MRI / MS Correlation
  - 3 or more plaques (43.1%)
  - Normal MRI (9.3%)

- MS by TX Group
  - IV steroids (24.7%)
  - Oral prednisone (29.8%)
  - Placebo (29.8)

Beck RW. Arch Ophthalmol 1995

ONTT Results (15 years)

- Conversion to MS:
  - Overall = 50%
  - Normal MRI at baseline = 25%
  - Abnormal MRI at baseline = 72%

- Lowest risk of MS:
  - Males
  - Profound disc swelling
  - No pain
  - NLP

- If no MS at 10 yrs, only 2% CDMS at 15 yrs. If normal MRI at baseline

Optic Neuritis Study Group Arch Neurol 2008

ONTT Results (15 years)

- Visual function:
  - 92% affected eyes 20/40 or better
  - 97% fellow eyes 20/40 or better
  - 1% < 20/200 (ea. eye)
  - Poorer VA associated with slightly higher conversion to MS
  - Majority of subjects reported residual visual dysfunction that impacted QOL (NEI VFQ-25)

Optic Neuritis Study Group Arch Neurol 2008
ONTT Results (15 years)

- Visual acuity and contrast sensitivity both significantly reduced in African Americans as compared to other race/ethnic groups


ONTT Results (15 years)

- Expanded Disability Status Scale (EDSS):
  - 66% < 3
  - 13% \( \geq 6 \)
- Degree of disability not related to # of baseline MRI lesions

Optic Neuritis Study Group Arch Neurol 2008

What have we learned from ONTT?
ONTT Summary

• Visual recovery is excellent (>90% 20/40 or better @ 15 year)
• Poorer visual outcomes among African Americans
• IV corticosteroids may speed visual recovery (no effect on final vision)
• Abnormal baseline MRI is a strong predictor of MS (mild EDSS)
• Unlikely conversion if normal baseline MRI & no MS @ 10 YRS.

Can MS be prevented in patients with “high-risk” optic neuritis?

CHAMPS

• Controlled High-Risk Avonex® Multiple Sclerosis Prevention Study
• Combined corticosteroids / interferon beta-1a (Avonex®)
CHAMPS - Patient Enrollment

• 50 clinical centers (US & Canada)
• 383 patients - first acute demyelinating event
  – eye (optic neuritis)
  – spinal cord (incomplete transverse myelitis)
  – brainstem/cerebellar syndrome
• Abnormal brain MRI at baseline

CHAMPS – Treatment Protocol

• All patients given IV corticosteroids with oral taper within 14 days of symptoms (ONTT protocol)
• 50% given weekly IFN beta-1a (Avonex®) x IM injection within 27 days of symptoms
• 50% given weekly placebo injection within 27 days of symptoms

CHAMPS (3 year results)

• Development of MS significantly reduced for Avonex® group
  – 35% Avonex
  – 50% placebo
• Reduction in size and number of new brain lesions among Avonex® patients
  – 53% Avonex
  – 82% placebo

Early Treatment of MS Study (ETOMS)

- Weekly injections of interferon beta-1a (Rebif®) vs. placebo for high-risk MS patients
- 2-year MS conversion:
  - Rebif: 34%
  - Placebo: 45%
- Fewer new lesions & T2 volume with Rebif


Betaferon/Betaseron in Newly Emerging Multiple Sclerosis for Initial Therapy (BENEFIT Study)

- Evaluation of every other day injections of interferon beta-1b for patients with first demyelinating event & abnormal MRI
- Conversion to MS (2-year results):
  - 45% with placebo
  - 28% with IFN-b-1b


PreCISe Study

- Glatiramer acetate (Copaxone®) 20 mg subQ qd
- 2-year results:
  - 45% reduction in MS
  - 57% reduction in new T2 lesions
  - 66% reduction if optic neuritis as first presenting sign

Is there a penalty for delay in treatment?

CHAMPS In Ongoing Neurological Surveillance (CHAMPIONS)

• Open label extension of immediate treatment (IT) and delayed treatment (DT) groups in CHAMPS
• 5-year results:
  – 36% of IT group developed MS
  – 49% of DT group developed MS
• 10-year results:
  – 58% of IT group developed MS
  – 69% of DT group developed MS
• 2X annualized relapse rate in DT group

Summary of Optic Neuritis

• Excellent visual prognosis
• Natural history suggests that CIS patients with positive MRIs will progress to CDMS
• Corticosteroids followed by immunomodulatory therapy should be strongly considered for high-risk patients.
• Long-term studies suggest there is a neurological penalty for not starting immunomodulatory therapy at onset
Brainstem Motility Disorders

The Internuclear Ophthalmoplegias
- Internuclear ophthalmoplegia (INO)
- Bilateral internuclear ophthalmoplegia (BINO)
- Wall-eyed bilateral internuclear ophthalmoplegia (WEBINO)
- One-and-one-half syndrome
Internuclear Ophthalmoplegia

- Lesion of MLF
- Ipsilateral adduction deficit
- Abducting nystagmus in fellow eye (+/-)
- Convergence abolished = midbrain (anterior INO)
- Convergence spared = pons (posterior INO)

26 y/o Woman with INO owing to MS

- Left adduction deficit on right gaze
- Right abducting nystagmus
- Skew deviation
  - Hyper eye (OS) = intorted
  - Hypo eye (OD) = extorted
- Convergence spared
The Internuclear Ophthalmoplegias

- Internuclear ophthalmoplegia (INO)
- Bilateral internuclear ophthalmoplegia (BINO)
- Wall-eyed bilateral internuclear ophthalmoplegia (WEBINO)
- One-and-one-half syndrome

Bilateral Internuclear Ophthalmoplegia

- Bilateral MLF lesion
- Bilateral adduction deficits
- Contralateral abducting nystagmus (+/-)
- Convergence abolished = midbrain
  Convergence spared = pons
36 y/o Man with BINO Owing to MS

- Bilateral adduction deficits (with contralateral abducting nystagmus)

The Internuclear Ophthalmoplegias

- Internuclear ophthalmoplegia (INO)
- Bilateral internuclear ophthalmoplegia (BINO)
- Wall-eyed bilateral internuclear ophthalmoplegia (WEBINO)
- One-and-one-half syndrome
Wall-Eyed Bilateral Internuclear Ophthalmoplegia

- Bilateral internuclear ophthalmoplegia with pronounced exotropia
- Abolished convergence (midbrain)
- Involvement of convergence pathways / MR subnuclei of CN III

32 y/o Woman with WEBINO Owing to MS

- Bilateral adduction deficits
- Pronounced EXO deviation
- Abolished convergence
The Internuclear Ophthalmoplegias

- Internuclear ophthalmoplegia (INO)
- Bilateral internuclear ophthalmoplegia (BINO)
- Wall-eyed bilateral internuclear ophthalmoplegia (WEBINO)
- One-and-one-half syndrome

One-and-One-Half Syndrome

- Lesion of CN VI nucleus & ipsilateral MLF
- Complete gaze palsy to side of lesion (One)
- INO on gaze away from the lesion (1/2)

29 y/o Hispanic Woman

- Recent onset diplopia when looking to the left
S/P IV Methylprednisolone

28 y/o Woman with Recent-Onset Diplopia

- Prior history of left ET (now left XT)
- Gaze palsy on right gaze
- Right INO on left gaze
Follow-up X 3 months

- Resolution of diplopia
- Re-establishment of left ET

Nystagmus

Common Types of Nystagmus with MS

- Found in approximately 30% of MS patients
  - Acquired pendular
  - Periodic alternating
  - Gaze-evoked
Gaze-Evoked Nystagmus (a.k.a. Gaze-Paretic Nystagmus)

- Lesion of nucleus prepositus hypoglossi / medial vestibular nucleus (neural integrator)
- Tonic deviation away from the lesion with fast catch-up toward the side of the lesion
- Frequently seen with ethanol / CNS depressants

Gaze-Evoked Nystagmus – Clinical Features

- Medium intensity horizontal jerk nystagmus with gaze ipsilateral to side of lesion
- Does not improve when eyes are brought back 15 degrees (differentiation from physiologic end-position nystagmus)
- Asymmetric when shifting from left to right gaze
- Presence of rebound on primary gaze refixation
Gaze-Evoked Nystagmus in 27 y/o Woman with MS

Gaze-Evoked Nystagmus in 71 y/o Woman with Acute Oscillopsia & Vestibular Dysfunction
Gaze-Evoked / Rebound Nystagmus in 34 y/o Man with MS

Cranial Neuropathies
Cranial Neuropathies

- Nuclear or fascicular lesion
  - CN III
  - CN IV
  - CN VI

“The Signature” of CN VI Paresis

- Eso which increases in the action of the paretic eye

Etiology of CN VI Palsy

Mayo Clinic Study of Olmstead Co, MN USA from 1978-1992 (n = 137)

- Undetermined: 26%
- Hypertension: 19%
- HTN & diabetes: 12%
- Trauma: 12%
- MS: 7%
- Neoplasm: 5% (complicated)
- Diabetes (alone): 4%
- CVA: 4%
- s/p neurosurgery: 3%
- Aneurysm: 2% (complicated)
- Other: 8%

40 y/o woman

Acute horizontal diplopia greater at distance and on left gaze

Recent onset paresthesias R > L
Ocular Structure & Functional Biomarkers in Multiple Sclerosis

- Optical coherence tomography (OCT)
- Low contrast acuity testing
- Visual-motor dysfunction (rapid number naming / KD test)

OCT Findings in MS

- Acute optic neuritis associated with RNFL thinning of 20% - 40% X 3 months
- Thinning of RNFL & GCL+IPL occurs over time with MS in the absence of optic neuritis (thinning of 12%)
- Incorporation of OCT, low-contrast acuity measurement & vision-specific QOL measures incorporated into MS clinical trials
• Longitudinal study of ganglion cell/inner plexiform layer (GCIP) layer q 6 months in 164 MS patients (59 health controls)
• Exclusion if development of optic neuritis
• Faster rates of GCIP thinning if:
  – Relapses (42% faster, p = 0.007)
  – New gad-enhancing lesions (54% faster, p < 0.001)
  – New T2 lesions (36% faster, p = 0.002)
• Highest annual rates of GCIP thinning if combination of new gad-enhancing lesions, new T2 lesions & disease duration < 5 yrs. (70% faster in patients with all three characteristics vs. without, p < 0.001)

Ratchford JN, et al. Neurology 2013

Low Contrast Acuity Testing in MS

• Low contrast charts (2.5% and 1.25%) compared to high contrast (100%) ETDRS/Snellen letters
• Comparison of LCA to OCT, QOL and standard neurology-based MS outcome measures (e.g. EDSS, MRI, cognitive performance)
Visual-Motor Dysfunction in MS / Impaired Saccades

- Evaluation of rapid number naming (King Devick test), low-contrast acuity, OCT and QOL measures in 81 MS patients vs. healthy controls
  - K-D time scores significantly higher (worse) for MS patients vs. health controls (p = 0.003)
  - Higher K-D scores associated with poorer QOL with NEI VFQ-25 (p < 0.001) & 10 item Neuro-Oph Supplement (p < 0.001)
  - Higher K-D scores correlated with reduced LCA (p < 0.001) & reduced NFL thickness (p = 0.002)


Key Points

- Diagnostic criteria for MS
- Pathogenesis & Classification of MS
- Neuro-ophthalic manifestations of MS:
  - Afferent system:
    - Optic neuritis
  - Efferent system:
    - Brainstem motility disorders
    - Nystagmus
    - Cranial neuropathies
- Visual biomarkers of disease activity
Thanks!