Optic Neuritis in the Era of Biomarkers

Presenter:
John J. Chen, M.D., Ph.D.
Associate Professor of Ophthalmology and Neurology

Department of Ophthalmology
at Mayo Clinic, Rochester, Minnesota
Disclosures

- None

Optic Neuritis

- Optic neuritis = inflammation of the optic nerve
- Most common cause of optic neuropathy in young patients (<50yo)
- Subacute monocular vision loss
  - 90% pain with eye movements
  - Dyschromatopsia
- 2/3 the disc is normal (retrobulbar optic neuritis)
Optic Neuritis Treatment Trial

- Vision improves over 1-3 months
  - 92% improve to 20/40 or better
  - 3% with 20/200 or worse
- 1g IV methylprednisolone x 3-5 days +/- PO prednisone taper
  - Speeds recovery but does not change visual outcome
  - Low dose PO prednisone alone increased recurrence rate

Differential of Optic Neuritis

- Multiple sclerosis
- Neuromyelitis optica (NMO)
- MOG-IgG associated disorder
- Inflammatory/autoimmune
  - Sarcoid, lupus, granulomatosis with polyangiitis
- Infectious
  - Lyme, syphilis, TB
- Idiopathic
Risk of Multiple Sclerosis After Optic Neuritis

• Overall 50% at 15 years
  • 25% if no white matter lesions on MRI
  • 72% if white matter lesions at time of optic neuritis

Neuromyelitis Optica (NMO)

• Initial series described Devic and Gault in 1894
  • Classic symptoms are severe optic neuritis and longitudinally extensive transverse myelitis

Right eye          Left eye                   Left optic neuritis

Only able to count fingers

No lesions on FLAIR

NMO transverse myelitis
MS transverse myelitis
Neuromyelitis Optica (NMO)

- NMO antibody to aquaporin4 (AQP4) was discovered in 2004 at the Mayo Clinic (Lennon et al., 2004)
  - AQP4: Water channel protein in astroglial foot processes
    - Expressed in brain, spinal cord, optic nerves
  - Binding of AQP4-IgG to AQP4 causes complement activation and astrocytic injury

Neuromyelitis Optica Spectrum Disorder (NMOSD)

- Core clinical characteristics
  - Optic neuritis
  - Transverse myelitis (LETM)
  - Area postrema syndrome
    - Unexplained hiccups or vomiting
  - Acute brainstem syndrome
  - Symptomatic narcolepsy
  - Symptomatic cerebral syndrome

**NMOSD Features**

- NMOSD-optic neuritis vs MS-optic neuritis
  - More severe, less recovery (~50% ≤ 20/200)
  - More relapses, bilateral involvement, and chiasmal lesions
- Transverse myelitis can lead to paraplegia
- Brainstem and diencephalon lesions can cause refractory hiccups, N/V, respiratory failure
- Mortality 6-32%
  - Higher in earlier studies. Lower now with better treatment

**NMOSD Treatment**

- Acute attacks:
  - IV corticosteroids and PLEX for acute attacks
- Maintenance therapy w/ chronic immunosuppression:
  - Rituximab is typically first line. Alternatives include azathioprine and mycophenolate
  - A recent randomized double blind placebo controlled trial found eculizumab (a C5 complement inhibitor) is very effective in NMOSD
  - Most MS medications are not effective and some may increase relapse rate in NMO (contraindicated)
AQP4-IgG Testing at Mayo

- AQP4-IgG testing is done at the Mayo Clinic with a fluorescence activated cell sorting (FACS) live cell based assay
  - AQP4-IgG ab: 76% sensitivity, 99% specificity
    - Serum>CSF sensitivity

Myelin Oligodendrocyte Glycoprotein (MOG)

- MOG is a transmembrane protein found on the surface of oligodendrocytes and myelin
- In the early 2000's, MOG antibody was erroneously thought to be a marker of MS
- New cell based assays have shown that MOG-IgG is a biomarker for a distinct demyelinating disease process: MOG-IgG associated disorders

Mayo MOG-IgG Live Cell Based Assay (FACS)

Positive MOG-IgG patient

Negative MOG-IgG patient

IgG Binding Index = \frac{\text{Median fluorescence GFP} \times \text{Population}}{\text{Median fluorescence GFP} \times \text{Population}}

IgG Binding Index of negative patient; 162/147 = 1.1
IgG Binding Index of positive MOG-IgG; 40,593/477 = 85.1

Index > 2.49 = positive

Diseases Associated with MOG-IgG

- Optic Neuritis (single/recurrent)
- Transverse myelitis (single/recurrent)
- NMOSD-like phenotype (AQP4-IgG seronegative NMOSD)
  - Explains ~1/3 of AQP4-IgG negative NMOSD
- Acute disseminated encephalomyelitis
  - Multifocal CNS disorder plus widespread inflammation on head MRI
  - Predominantly affects children
- MOG-IgG is almost never positive in patients with AQP4-IgG-positive NMOSD or classic MS
Features of MOG-IgG Optic Neuritis

- Recurrent optic neuritis
  - 50-75% recurrent
- Bilateral in 50%
- Disc edema
  - Up to 86% at onset
  - Can be severe with peripapillary hemorrhages
- 50% have enhancement that also involves the sheath
- Similar relapses and initial severity to AQP4-IgG optic neuritis, but better recovery and final visual outcomes
  - Only 6-10% ≤ 20/200 (vs 50% for AQP4-IgG)

Treatment of MOG-IgG Optic Neuritis

- Acute Attacks
  - IV methylprednisolone for 3-5 days followed by PO prednisone taper (1mg/kg/day) over 2-3 months
  - Consider plasma exchange or IVIG if severe and no recovery after 1-2 weeks
- Chronic immunotherapy for relapsing disease with residual deficits
  - Typical first line agents are rituximab, azathioprine, and mycophenolate
  - Monthly IVIG may be more efficacious for severe relapsing disease
**When Do I Test for AQP4-IgG and MOG-IgG?**

- Atypical optic neuritis
  - Severe visual impairment
  - Bilateral or recurrent optic neuritis
  - Poor visual recovery
  - Prominent disc edema
  - Perineural optic nerve enhancement
  - Coexisting extra-optic nerve CNS demyelinating lesions suggestive of MOG-IgG or AQP4-IgG

![Optic neuritis diagram](image)
Thank you.