Optic Neuritis

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Objectives

• Be able to describe typical vs. atypical optic neuritis (ON) and the implications for testing and treatment
• Review data underlying evidence-based practices in the treatment of optic neuritis
• Compare and contrast idiopathic optic neuritis with neuromyelitis optica spectrum disorder (NMOSD) and anti-MOG associated optic neuritis
What is Optic Neuritis?

- Dysfunction of the optic nerve related to inflammation
Pathophysiology

- Characterized by inflammation and often demyelination
- Swelling of nerve tissue in area of demyelination
  - Followed by myelin sheath breakdown, then destruction of nerve fibers
Risk Factors for Acute Demyelinating Optic Neuritis

- Age 20-50
- Female gender
- History of multiple sclerosis (MS)
- Caucasian
Patient History

Pain

Pain in or around the affected eye **up to several days before vision loss**

Often worse with eye movement (92% in Optic Neuritis Treatment Trial [ONTT])

Pain usually a sign of orbital optic nerve involvement

• Pain much less frequent when orbital optic nerve segment spared (94% vs 32%)¹

Vision loss

Central vision affected in most cases

Color desaturation (colors muted, washed out, etc.)

Photopsias reported in 30% of patients

Typical Optic Neuritis
Natural History

- Vision worsens over several days to 2 weeks
- Visual recovery begins within 2-4 weeks following onset
- Further improvement possible up to 1 year or even longer from onset
- In ONTT, <10% had worse than 20/40 acuity in affected eye after 12 months
  - In ONTT, 56% of visual field defects resolved by 1 year, and 73% by 10 years
Examination

- Impaired visual acuity and contrast sensitivity
- Relative afferent pupillary defect (RAPD)
- Impaired color vision out of proportion to acuity
  - Ishihara color plate testing abnormal in 88% of affected eyes in the Optic Neuritis Treatment Trial (ONTT)
- Visual field defect
Examination

- Completely normal fundus, acutely in 2/3 of cases
- Optic disc pallor takes 4-6 weeks to be seen
- Optic disc edema present in about 1/3 of cases
- Peripapillary hemorrhages and exudates are rare
- Uveitis also uncommon in typical optic neuritis
Optic Neuritis

**Workup**

- MRI brain and orbits with contrast
  - Why brain AND orbits?
    - Brain MRI is best predictor of risk for MS in pts with optic neuritis
      - If at least one brain lesion, risk of MS is 72% over 15 years
      - If no brain lesions, risk of MS is 25% over 15 years
    - Optic nerve enhancement in 95% of cases (confirms diagnosis), orbital protocol is performed with orbital fat suppression
    - Helps rule out other causes of optic neuropathy
  - Further testing beyond MRI may not be needed for *typical* optic neuritis
Imaging Findings
Imaging

- Helpful in determining if MS is possible or likely
- AND what additional testing may be needed to diagnose MS (e.g., lumbar puncture)

- Optic neuritis is a clinical attack
- Dissemination in time and space needed for MS diagnosis
OCT in Optic Neuritis

Sensitive in detecting prior ON\(^1\)

- At least 3 months after attack, RNFL thinner by \(\geq 9 \, \mu m\) in 73% of ON eyes
- Ganglion cell /inner plexiform layer (GCL/IPL) thinner by \(\geq 6 \, \mu m\) in 96% of ON eyes (compared with unaffected contralateral eye)

GCL/IPL thins before retinal nerve fiber layer (RNFL)\(^2\)

- Thinning detectable between 1-3 months after onset

Visual Evoked Potentials

- Electrophysiological testing method for visual pathways
  - Not used as commonly as in the past, but also used in clinical trials

- P100 waveform is the basis for interpretation

- Latency of P100 is increased in optic neuropathy
  - Sensitive, not specific for ON
  - Often remains abnormal even after recovery from ON
Features of Typical Optic Neuritis

- Pain with eye movements (90+% of cases)
- Retrobulbar (no optic disc edema in 2/3 cases)
- Unilateral symptoms with central vision loss and RAPD
- Color vision loss out of proportion to acuity
- Vision improves substantially over weeks
Neuromyelitis Optica Spectrum Disorder (NMOSD)

- Attacks of optic neuritis and myelitis are typical, but not required for diagnosis
- Aquaporin-4 antibody test is very specific for NMOSD
- Distinct from MS
  - Interferon treatments effective for MS may worsen NMO
Diagnosis

- Optic neuritis, acute myelitis, or other typical NMOSD syndrome
- Detection of aquaporin-4 (AQP4) IgG antibodies is specific for NMOSD
  - Testing most helpful during an attack and before immunotherapy is given
  - Cell-based assays are the most sensitive (76.5%) and specific (99.9%) AQP4 test
    - Very rare false positives, very low threshold to send test
    - You can trust a positive result
NMOSD Differences in Treatment

• What not to do
  • Interferon-β used to treat MS can exacerbate NMOSD\textsuperscript{1}
  • Fingolimod, alemtuzumab, natalizumab, and dimethyl fumarate are suspected to be ineffective in NMOSD based on case reports and series

\textsuperscript{1}Kim SH et al. Mult Scler 2012; 18:1480–1483.
NMOSD Differences in Treatment

• What to do
  • Acute exacerbation
    • 1000 mg daily IV methylprednisolone x 3-5 days
    • If inadequate response to steroids within 5 days, then plasmapheresis
  • Maintenance treatment
    • Azathioprine, rituximab, mycophenolate mofetil have been mainstays of treatment
    • Newer treatments include
      • Eculizumab – C5 inhibitor, absolute risk reduction (ARR) of 33%
        • Weekly infusion x 4 weeks, then every other week
        • Need meningococcal vaccine and daily antimicrobial prophylaxis
        • Restricted use in the United States
      • Inebilizumab – anti-CD19, ARR 27%
        • Trial stopped early due to efficacy, longer-term followup needed
        • Infusion x 1, then repeated 2 weeks later, then every 6 months
      • Satralizumab – IL-6 receptor blocker, AR 23% (32% in AQP-4 + cases)
        • Subcut. Injection every 2 weeks x 3 doses, then every 4 weeks
      • Tocilizumab – IL-6 receptor blocker, superior to azathioprine in reducing relapse rate
        • IV infusion every 4 weeks

Distribution of AQP4 Receptors

• Note the relative lack of receptors in the brain parenchyma
  • Brain lesions more rare than in MS

• Cluster of receptors near area postrema (AP)
  • Attacks involving AP can cause hiccups and intractable nausea and vomiting
Anti-MOG Antibodies

- Antibody against the myelin oligodendrocyte glycoprotein expressed on the outer lamella of the myelin sheath
- Positive in ~5% of patients with optic neuritis (by comparison, ~3% have anti-aquaporin-4 antibodies, with NMO)
MRI Features of anti-MOG Optic Neuritis

- Often involves a long, anterior portion of optic nerve, **as well as ON sheath and surrounding orbital fat**
- There is often bilateral optic nerve involvement
Table 1. Typical characteristics of optic neuritis in MS, AQP4-IgG-positive NMOSD, and MOG-IgG-associated disorder

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MS</th>
<th>AQP4-IgG</th>
<th>MOG-IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>20s</td>
<td>40s</td>
<td>30s + children</td>
</tr>
<tr>
<td>Sex</td>
<td>Female &gt; male</td>
<td>Female &gt;&gt; male</td>
<td>Female ~ male</td>
</tr>
<tr>
<td>Optic neuritis characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Bilateral ON</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Severe vision loss at nadir</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Risk of recurrent ON</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Steroid dependent</td>
<td>Rare</td>
<td>Rare</td>
<td>++</td>
</tr>
<tr>
<td>Risk of blindness (&lt;20/200)</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Other CNS involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADEM</td>
<td>Rare</td>
<td>Rare</td>
<td>++</td>
</tr>
<tr>
<td>Brainstem</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Diencephalic symptoms</td>
<td>Rare</td>
<td>++</td>
<td>Rare</td>
</tr>
<tr>
<td>LETM</td>
<td>Rare</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Conus medullaris</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>MRI optic nerve enhancement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length and location</td>
<td>Short</td>
<td>Long and posterior</td>
<td>Long and anterior</td>
</tr>
<tr>
<td>Perineural enhancement</td>
<td>Rare</td>
<td>Rare</td>
<td>++</td>
</tr>
<tr>
<td>Optic chiasm involvement</td>
<td>Rare</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

Rare or less than 5%; + infrequent; ++ frequent; +++ very frequent; ADEM, acute disseminated encephalomyelitis; AQP4, aquaporin-4; CNS, central nervous system; IgG, immunoglobulin G; LETM, longitudinally extensive transverse myelitis; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; MS, multiple sclerosis; ON, optic neuritis.
MOG-IgG optic neuritis

- IV 1000mg methylprednisolone x 3-5 days followed by PO prednisone taper over 1-3 months
- If severe and no significant improvement at 1-2 weeks, consider plasma exchange or IVIG

Single attack, Full recovery

- Observe

Recurrent attacks, steroid dependent, incomplete recovery

- Consider chronic immunotherapy: rituximab, mycophenolate, azathioprine, or monthly IVIG
Anti-MOG Antibody Testing

- Unlike with AQP4 antibodies in NMOSD
  - Anti-MOG antibodies have lower specificity than AQP4 (98% vs ~ 99.9% for AQP4)
    - Makes an important difference in the positive predictive value of the test (PPV 72% for MOG, PPV 95% for AQP4)
  - MOG + patients are sometimes observed without treatment

- Testing all optic neuritis patients for MOG is not useful
  - There can be false positives and not all MOG patients need immunosuppression

- Testing best reserved for patients with features suggesting MOG optic neuritis
  - Bilateral or recurrent optic neuritis
  - Prominent optic disc edema
  - Severe vision loss at nadir
  - Perineural enhancement on MRI

Atypical Optic Neuritis

- Characteristics include:
  - Progressive vision loss, poor visual recovery, painless, hemorrhages or exudates on fundus exam, severe vision loss, and relapse after steroid withdrawal
  - Some believe visual outcomes may be poor if left untreated
  - Relapse after steroid withdrawal treated with slower withdrawal of steroids and starting immunosuppressive agent
  - Atypical features should prompt testing for AQP-4 and MOG antibodies and a neuro-ophthalmology referral
• 457 patients with acute optic neuritis (≤ 8 days symptoms)

• Randomized to 3 groups
  • 250 mg IV methylpred q6 hrs x 3 days, oral steroid taper x 11 days
  • 1 mg/kg day oral prednisone x 14 days
  • Oral placebo x 14 days

• Visual field and contrast sensitivity primary outcomes
  • Visual acuity and color vision secondary measures

• Outcomes assessed at various intervals, including 6 months

• Visual function recovered faster in IV steroid group than in placebo group

• Oral prednisone alone associated with increased risk of optic neuritis recurrence
ONTT Take Home Messages

• From this trial and some of the follow-up analyses, we learned:

• It is acceptable to give or withhold IV steroids in cases of acute optic neuritis

• Later studies\(^1\) show no improvement in long term visual outcome with steroids, but accelerated recovery

• Steroids do not affect the long-term risk of development of MS

• There is no role for moderate-dose oral steroids (1 mg/kg/d) alone in the treatment of typical acute demyelinating optic neuritis

Treatment of Typical Optic Neuritis with High-Dose Corticosteroids

Factors that may decrease the risk: benefit ratio
- Onset < 8 days
- White matter lesions on brain MRI
- Significant pain
- Significant vision impairment
- Features of atypical optic neuritis

Factors that may increase the risk: benefit ratio
- Higher potential for adverse reaction
  - History of poorly controlled diabetes
  - History of adverse reaction to steroids
  - Potential for significant harm from common steroid side effects

When Does Optic Neuritis Need Rx?

In typical demyelinating optic neuritis, treat if the patient’s vision is sufficiently impaired to justify the risks.

Treatment is with mega dose steroids +/- oral taper.

Do not treat with moderate dose (1 mg/kg) oral steroids alone. May increase risk of recurrence.

Mega dose steroids hasten recovery from optic neuritis, but do not affect final vision outcome.
Megadose Oral Steroids?

- 55 optic neuritis patients within 14 days of symptom onset
- Randomized to 3 days of 1000 mg IV methylprednisolone daily vs. 3 days of 1250 mg oral prednisone with no oral taper
- No difference between the two groups in primary end point of P100 latency on VEP at 6 months, or secondary end points of high and low-contrast visual acuity at 1 and 6 months
Megadose Oral Steroids Implications for Clinical Practice

• A major benefit of oral steroids is ease of administration and cost savings
  • 1250 mg oral prednisone can be given as 25 50 mg pills, which can be blended into a smoothie

• Still does not address
  • Ideal timing of initiation of therapy
  • Who benefits from corticosteroid treatment

• Still no evidence that IV or PO treatment of typical optic neuritis impacts long-term vision outcomes
Oral Steroid Taper

- Oral steroid taper was part of the ONTT (11 days of 1 mg/kg/day prednisone, then tapered off) after 3 days of mega dose IV steroids
- No effect on short or long-term outcomes in MS\(^1\)
- Some clinicians include the taper after mega dose steroid treatment, others do not

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
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<tbody>
<tr>
<td>Faithful to ONTT trial design</td>
<td>No effect on outcomes in MS</td>
</tr>
<tr>
<td>Could be beneficial, no trial has compared ON treatment with vs. without taper</td>
<td>Extra cost and potential for side effects in susceptible patients</td>
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Pediatric Optic Neuritis

In other words, pediatric optic neuritis is more typically atypical

• How is it different from adult optic neuritis?
  • More often bilateral and/or severe vision loss
  • Most often presents with funduscopic abnormalities, such as retinal exudates and disc edema
  • Recover faster and higher percentage of secondary causes than in adults
  • Typically treated with high-dose IV steroids, followed by 2-6 week oral taper
Questions?