Myelopathies: ‘Autoimmune and other mimickers of MS’

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DISCLOSURE

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None

Off Label Usage
Immunosuppressant use in NMO and paraneoplastic myelopathies
Learning Objectives and Lecture Outline

• **Diagnostic pearls in myelopathy:**
  - Myelitis in NMOSD
  - Other autoimmune & paraneoplastic myelopathies
  - Other myelopathies that mimic MS

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Neuromyelitis Optica

• Inflammatory autoimmune central nervous system disease with predilection for:
  - Optic nerve
  - Spinal cord
  - CVOs

• Aquaporin-4-IgG biomarker is 60-80% sensitive and >99% specific for diagnosis

• Pathogenic IgG binds to extracellular domain of astrocytic AQP4

*Sources:
Lennon et al. Lancet 2004
Apiwattanakul et al. Ann Neurol 2010
Popescu, Lucchinetti et al. Neurology 2011*
NMO and NMO Spectrum Disorders

• NMO Diagnostic criteria from 2006

Definite NMO
Optic neuritis
Acute myelitis
At least two of three supportive criteria
1. Contiguous spinal cord MRI lesion extending over ≥3 vertebral segments
2. Brain MRI not meeting diagnostic criteria for multiple sclerosis
3. NMO-IgG seropositive status

• NMOSD: AQP4-IgG (+) patients with single/recurrent ON, TM or other typical syndrome (e.g., intractable nausea and vomiting episode) who do not meet NMO dx criteria

NMO/NMOSD

• Typically relapsing
• Non-Caucasian ethnicity over-represented
• High frequency of co-existing autoimmunity
  • Personal/family Hx (e.g., SLE, MG)
• Brain MRI often normal at onset; CSF: OCB <30%
• Delay to Dx and Rx risks accumulation of attack-related disability
• MS meds may worsen NMO
  (fingolimod, IFN, natalizumab)
Transverse Myelitis in NMOSD: Symptoms & Signs

• Ascending numbness
  • Sensory level (symptom>sign)
• Pyramidal weakness (often severe)
  • Disability accumulates with attacks
• Bowel/bladder/sexual dysfunction
• Lhermitte’s sign/Uhthoff’s phenomenon
• Tonic spasms (NMOSD>MS)
• Pruritus/itch and intractable pain described

Wingerchuk et al. Neurology 1999
Kim et al. Arch Neurol 2012
Elsone and Jacob et al. MSJ 2012
Kanamori et al. Neurology 2011

Myelitis in NMOSD: ‘The Long and the Short of it’
Longitudinally Extensive Transverse Myelitis (LETM) in NMO/NMOSD

- MRI lesions characteristically are longitudinally extensive (≥3 vertebral segments)
- LETM prompts the physician to test for AQP4-IgG to confirm Dx
  - Seropositivity predicts recurrence
- ~58% of patients with idiopathic LETM are AQP4-IgG (+)
- ~89% of recurrent LETM AQP4-IgG-seropositive

**References**
- Lennon et al. Lancet 2004
- Wingerchuk et al. Neurology 2006
- Knibb et al. JAMA Neurol 2013
- Tobin et al. Curr Opin Neurol 2014
- Jiao and Pittock et al. JAMA Neurol 2014

Typical LETM lesions in NMO

![Typical LETM lesions in NMO](image)
T1 Hypointensity & bright-spotty T2 lesions

Segmental cord atrophy

Factors Influencing Lesion Length in NMOSD

• Timing of MRI in relation to symptoms:
  • Imaged too early – short
  • Imaged too late – short/discontinuous/resolved

• Immunosuppressant medications
Short Transverse Myelitis (STM)

• TM in MS is usually mild
• MRI lesions in adult MS cases are almost always <3 vertebral segments
  • may be long in pediatric MS
• STM is generally considered incompatible with NMO and a contraindication to AQP4-IgG testing
• AQP4-IgG was detected in only 1 of 22 STM cases in a reported study

Sheremata et al. Neurol Clin 2013
Banwell, Lennon and Pittock et al. Neurology 2008

Typical Short Transverse Myelitis in MS
Coalescence of multiple short MS lesions may resemble LETM; axial images informative

**Background:** Many consider STM to be incompatible with NMOSD

**Aim:** Assess frequency and characteristics of AQP4-IgG (+) STM

**Methods:** Searched Mayo Clinic database (MN, FL, AZ) for AQP4-IgG (+) STM

- Comparison groups:
  - Population based AQP4-IgG (-) STM
  - AQP4-IgG (+) LETM
Results

- 1st TM episode in AQP4-IgG (+) NMOSD is short in 14% (25/176)
  - 24% initially treated as MS with β-interferon which may worsen NMOSD
  - Attributes more common in AQP4 (+) STM compared to population-based AQP4-IgG (-) STM ($p<0.05$):
    - Nonwhite race
    - Tonic spasms
    - Coexisting autoimmunity
    - MRI (central T2-lesion, T1-hypointensity, brain lesions absent)
    - CSF lacking oligoclonal bands

Results

- Among AQP4-IgG (+) NMOSD patients:
  - Delay to diagnosis was longer with initial STM than initial LETM (4.5 Vs 0 months, $p=0.01$)
  - Initial STM attacks were less severe than initial LETM attacks (15% Vs 56% needed gait aid at nadir, $p<0.001$)
  - Time from onset to MRI was similar for STM & LETM (15.5 Vs 14 days, $p=0.11$); hence timing unlikely to explain the reason for length difference
• STM was followed by LETM episode in 92%

Conclusions
• STM is not uncommon in AQP4 (+) NMOSD & when present delays diagnosis and treatment
• Clinical and radiologic characteristics identified in this study may help select those patients with STM at highest risk for AQP4-IgG (+) NMOSD

Asymptomatic TM in AQP4-IgG +ve Patients with extraspinal manifestations of NMOSD

• Case 1: 24/F (Cauc)
  • PMHx: MG Rx mycophenolate and low dose prednisone
  • Severe ON-poor recovery; ANA (+)

• Case 2: 18/F (Hispanic)
  • Antecedent intractable nausea/vomiting Diplopia; ANA (+) dsDNA-Ab (+)

• Case 3: 52/F (Af-Am)
  • PMHx: ON
  • HPI: severe bilateral ON
  • ANA (+) dsDNA-Ab (+); Rx IV steroids
  • MRI spine performed 3 wks later
NMO/NMOSD Treatment

**Acute:** IV MP x 5 days +/- PLEX

**Maintenance:**
- Corticosteroids (sometimes transitional)
- Azathioprine
- Mycophenolate
- Rituximab

**Novel investigational treatments:**
- IL-6 inhibitors (tocilizumab)
- Complement inhibitors (eculizumab)
- Anti-AQP4 monoclonal ab blocking therapy (aquaporinumab)
- Hematopoietic Stem Cell Transplantation
MOG-IgG associated myelopathy

- May be found in some seronegative NMOSD cases and cases of ADEM
- Compared to AQP4-IgG (+) NMOSD:
  - Male:female ratio equal
  - Younger
  - More often simultaneous ON and TM
  - Less often relapse
  - MRI spine: conus involvement
  - MRI brain: grey matter involvement

Case 1

- 54/F smoker
- Subacute progressive lower extremity weakness requiring gait aid
- Exam: spastic paraparesis
- CSF: WCC 93; protein 82; cytology normal
- CT chest: normal
- Paraneoplastic evaluation (serum and CSF) and NMO-IgG (serum) all negative
Case 1

- PET/CT: moderate uptake in lung nodes
- Trans-bronchial biopsy: small cell lung cancer
- Diagnosis: paraneoplastic myelopathy
- Tx: radiation and chemotherapy; remained dependent on gait aid 1 yr after onset
• 31 patients
• All had a progressive myelopathy
  • Rare reports of relapsing form
• In 67% myelopathy preceded cancer detection
  • Initially diagnosed with PPMS (7)
• CSF: protein↑(92%); WCC↑(63%); OCB(30%)
• MRI normal in 35%


Tractopathy in paraneoplastic myelopathy
Cancers and paraneoplastic autoantibodies

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung (small cell &gt; non small cell)</td>
<td>Amphiphysin</td>
</tr>
<tr>
<td>Breast</td>
<td>CRMP-5 IgG</td>
</tr>
<tr>
<td>Renal Cell</td>
<td>PCA-1</td>
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<tr>
<td>Melanoma</td>
<td>ANNA-1</td>
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<td>ANNA-3</td>
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<td>Endometrial</td>
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<td>Tonsillar</td>
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Paraneoplastic myelopathy: treatment and prognosis

- Cancer tx and immunotherapy are the mainstay
  - Target T-cell mediated process (corticosteroids and cyclophosphamide)
- Only a minority improve
- Most have moderate to severe disability
  - 87% required a gait aid at last follow up
• Lymphoma arising within the spinal cord
  • A variant of primary CNS lymphoma
• Present with progressive myelopathy
• CSF: ↑WCC (67%); ↑protein (100%); ↓glu (25%)
• MRI
  • Multifocal (spinal cord or brain)
  • Conus/cauda equina
  • Enhancing (often persistent)
• Dx by CSF or spinal cord biopsy
• Tx: IV Mtx; median survival 16 months
Distinguishing features

• Transverse myelitis (MS/NMO/idiopathic)
  • Clinical progression > 21 days
  • (CSF protein >100, WCC >50, ↓glucose)
  • Persistent enhancement
  • MS: resolves within 2 months in >96%
  • Cauda equina
  • PET

• Sarcoid (difficult)
  • Extra CNS disease

Lennon et al. Lancet. 2004
Polman et al. Annals of Neurology 2011
Cotton et al. Neurology 2003
Stern and Aksamit et al. Neurol Clin 2010

Case 2

• 55 yr old man
  • Referred for ? transverse myelitis

• Rapid quadriplegia (90 mins) –legs resolved later

• MRI spine – signal change and enhancement

• Diagnosed with transverse myelitis; AQP4-IgG (–)

• PMHx: coronary artery disease s/p 2x stents, HTN, hyperlipidemia

• SHx: current smoker (40 pk yr Hx)
Is it an owl or a snake?
Case 1

• Additional investigations
  • APTT elevated
  • Beta-2-glycoprotein-1 antibodies & lupus anticoagulant found & persisted (>12 wks)

• Diagnosis: **Anti-phospholipid syndrome**
  • Vertebral artery occlusion
  • Hypoperfusion of anterior spinal artery -> watershed infarction anterior horn cells

• Treatment
  • Anticoagulation and smoking cessation

**Definition of owl/snake eye sign**

• Bilateral T2-hyperintensities: anterior horn cells
• Distinguish from tractopathies
• Typically ≥2 images (exclude artifact)
• Usually ischemic in etiology
Owl/snake eye lesions

- Vascular (primary or secondary)
- Inflammatory/autoimmune
  - NMO
  - Paraneoplastic motor neuropathy
- Hirayama disease (brachial monomelic atrophy)
- Hopkins syndrome
- Infectious
  - (polio, west nile virus, enterovirus)

Spondylotic myelopathy (SM)

- Commonest cause of myelopathy
  - 23.6% of non-traumatic myelopathies
- Treatable!
- MRI: spondylosis, stenosis, cord compression
- Occasional atypical MRI features:
  - T2-signal abnormalities (15%)
  - Gadolinium enhancement (7%)
  - May suggest tumor or inflammation
Specific Pattern of Gadolinium Enhancement in Spondylotic Myelopathy

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Objective: To highlight a specific under-recognized radiological feature of spondylotic myelopathy often resulting in misdiagnosis.

Methods: Patients evaluated between January 1, 1996 and December 31, 2012 who met the following criteria were included: (1) spondylotic myelopathy was suspected, (2) gadolinium enhancement was detected, and (3) spinal surgery was performed.

Results: Fifty-six patients (70% men) whose median age was 53.5 years (range = 24-80) were included. Spinal cord magnetic resonance imaging (cervical in 55, thoracic in 4) revealed longitudinal spindle-shaped T2 signal hyperintensity (100%) and cord enlargement (79%) accompanied by a characteristic pancake-like transverse band of gadolinium enhancement in 41 (72%), typically immediately caudal to the site of maximal spinal stenosis. Forty (71%) patients were initially diagnosed with neoplastic or inflammatory myelopathies, and decompressive surgery was delayed by a median of 11 months (range = 1-64). Spinal cord biopsy in 6 did not reveal any alternative diagnosis. Ninety-five percent were stable or improved. Gadolinium enhancement persisted in 75% at 12 months, raising concern about the accuracy of the initial diagnosis. Twenty patients required a gait aid (36%) at last follow-up (median = 60 months, range = 5-172). The need for a gait aid was preoperatively (p = 0.005), but not delay of surgery, predicted the need for a gait aid at final follow-up.

Interpretation: Transverse pancake-like gadolinium enhancement associated with and just caudal to the site of maximal stenosis and at the rostral-caudal midpoint of a spindle-shaped T2 hyperintensity suggests spondylotic is the cause of the myelopathy. Persistent enhancement for months to years following decompressive surgery is common. Recognition is important to prevent inappropriate interventions or delay in consideration of a potentially beneficial decompressive surgery.

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‘Pancake-Like’ or ‘Transverse-Band’ enhancement

D1 D2 E1 E2
‘Circumferential’ Enhancement of White Matter Sparing Gray Matter

Identification of Pancake-like Pattern

1. Transverse band (width>height)

2. Location:
   - Just below site of max stenosis
   - Middle of spindle shaped T2-hyperintensity

3. Axial circumferential pattern sparing gray matter
Spinal cord sarcoidosis

- May mimic NMOSD (Long lesions in ~75%)
- Often initial manifestation of sarcoid
- Gad enhancement pattern:
  - More intense than NMO
  - Dorsal linear subpial (not pathognomic)
  - Persists (>2 mos)
- CT/PET chest to dx
- Dx: biopsy (preferably lung)
- Tx: Prolonged high dose oral steroids +/- steroid sparing/TNF-alpha inhibitors
**Dural arteriovenous fistula**

- Progressive or stepwise myelopathy
- Acute worsening with valsalva
- Conus often involved
- Worse with steroids
- Dx: spinal angio
- Tx: surgical disconnection/endo vascular occlusion

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**Neoplastic and Sarcoid Myelopathies**
Inflammatory Myelopathies

Summary of T2 patterns

MS (dorsal/lateral column)
Ischemic (snake eyes)
Spondylosis/NMO/Sarcoid
NMO/Sarcoid
Dural AVF
Paraneoplastic/B12/Copper
Summary of Enhancement Patterns

Persistence >3 months

Spondylosis

Dural AVF

Lymphoma

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