Longitudinally Extensive Transverse Myelitis

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Regional MS Summit

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MS Center at Swedish
Transverse myelitis

Diagnostic Criteria for Transverse Myelitis*

Inclusion criteria for diagnosis of transverse myelitis (idiopathic or disease associated)
Development of sensory, motor or autonomic dysfunction attributable to the spinal cord
Bilateral symptoms
Clearly defined sensory level
Exclusion of compressive aetiology by MRI or CT myelography
Spinal cord inflammation demonstrated by CSF pleocytosis or elevated IgG or gadolinium enhancement
Progression to clinical nadir between 4 hours and 21 days from onset of symptoms

Exclusion criteria for diagnosis of transverse myelitis (idiopathic or disease associated)
History of radiation to the spine within 10 years
Clear arterial distribution clinical defect consistent with anterior spinal artery occlusion
Abnormal flow voids on the surface of the cord consistent with AVM

Exclusion criteria for idiopathic transverse myelitis
Serologic or clinical evidence of connective tissue disease (sarcoidosis, Behcet’s disease, Sjogren’s syndrome, SLE, mixed connective tissue disorder)
CNS manifestations of syphilis, Lyme disease, HIV, HTLV-1, Mycoplasma, other viral infection.
Brain abnormalities suggestive of MS
History of clinically apparent optic neuritis

Longitudinally Extensive Transverse Myelitis

BRIEF COMMUNICATIONS

Neuromyelitis Optica IgG Predicts Relapse after Longitudinally Extensive Transverse Myelitis

Brian G. Weinshenker, MD, FRCP(C)1
Dean M. Wingerchuk, MD, FRCP(C),2
Sandra Vukusic, MD,3 Linda Linbo, RN,1
Sean J. Pittcock, MD,1 Claudia F. Lucchinetti, MD,1 and Vanda A. Lennon, MD, PhD1,4,5

Ann Neurol 2006;59:566–569
LETM beyond NMO
LETM beyond NMO: Compressive myelopathy

Among 668-683 patients with cervical spondylotic myelopathy in Japan:
- 7.3% have gadolinium enhancement (Ozawa H. et al. Spinal Cord. 2010 May;48(5):415-22.)

- 56 pts with LE T2H on MRI
- 40 (71%) associated enhancement: “pancake-like”
Pancake-like enhancement pattern

Flanagan E. et al, Accepted for publication in Annals of Neurology, 2014
Pancake-like enhancement: axial

Flanagan E. et al, Accepted for publication in Annals of Neurology, 2014
Pancake-like enhancement may persist even after the decompression.

Flanagan E. et al, Accepted for publication in Annals of Neurology, 2014
LETM beyond NMO: Sarcoidosis

- Sarcoidosis
  - Myelopathy is typically subacute
  - 50% have leptomeningeal enhancement
  - CSF ACE has high false negative rate

Flanagan E. et al, Accepted for publication in Annals of Neurology, 2014
Letm beyond NMO

- Paraneoplastic myelopathy
  - Subacute or progressive myelopathy
  - 47% LETM
  - 50% symmetric tract involvement
    - 87% enhancing
  - Amphiphysin (9/30)
  - CRMP-5 (9/30)
  - ANNA-1 (2/30)
- Caution: 6/20 responded to steroids

LETM beyond NMO

- Dural AVF
  - LETM extending into conus
  - Exertion-related worsening of weakness
  - Middle-aged or elderly men
  - Flow voids on T2 MRI
LETM beyond NMO
Rheumatologic diseases

- Autoimmune disease
  - Sjogren’s (Ssa, SSb)
  - Antiphospholipid syndrome
  - SLE (ANA, dsDNA)

- NMO IgG helps to determine if coexistent with NMO

Typical brain lesions → Multiple sclerosis

- Recent vaccination
- Recent or current febrile illness
- Serum or CSF serology/PCR
- Known diagnosis
- Clinical features of disease activity
- Serological markers
  ▸ Autoimmune related myelitis

- Diffusion restriction and ADC reduction
  ▸ Cord ischemia
- NMO IgG positive
- Optic neuritis
- No or NMO-specific brain lesions
- Prominent flow voids
  ▸ Spinal vascular malformation
- Malignancy
  ▸ Clinical syndrome
  ▸ Specific autoantibodies
  ▸ Paraneoplastic

- B12 deficiency
  ▸ Copper deficiency
- Malignancy
  ▸ Clinical syndrome
  ▸ Specific autoantibodies
  ▸ Paraneoplastic

- Human T-cell Lymphotropic virus 1
  ▸ Vacuolar myelopathy (AIDS)
- Malignancy
  ▸ Clinical syndrome
  ▸ Specific autoantibodies
  ▸ Paraneoplastic

LETM – Risk of recurrence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk ratio</th>
<th>p Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any recurrent TM (NMO, rheumatologic, recurrent TM)</td>
<td></td>
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<td></td>
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<tr>
<td>CSF WBC &gt;5 cells/μL</td>
<td>1.67</td>
<td>0.003</td>
<td>1.14-2.45</td>
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<tr>
<td>CSF protein &gt;60 mg/dL</td>
<td>1.27</td>
<td>0.152</td>
<td>0.922-1.74</td>
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<tr>
<td>IgG index &gt;0.7</td>
<td>2.14</td>
<td>&lt;0.001</td>
<td>1.44-3.17</td>
</tr>
<tr>
<td>Oligoclonal bands</td>
<td>1.45</td>
<td>0.033</td>
<td>1.05-1.99</td>
</tr>
<tr>
<td>Vitamin D &lt;30 ng/mL</td>
<td>4.00</td>
<td>&lt;0.001</td>
<td>1.60-9.99</td>
</tr>
<tr>
<td>Vitamin D &lt;20 ng/mL</td>
<td>2.38</td>
<td>0.001</td>
<td>1.54-3.69</td>
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<tr>
<td>Vitamin B₁₂ &lt;200 pg/mL</td>
<td>0.54</td>
<td>0.229</td>
<td>0.157-1.86</td>
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<tr>
<td>ANA ≥1:160</td>
<td>1.69</td>
<td>0.006</td>
<td>1.23-2.32</td>
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<tr>
<td>Double-stranded DNA Ab</td>
<td>1.03</td>
<td>0.664</td>
<td>0.484-2.17</td>
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<tr>
<td>SS-A Ab</td>
<td>1.89</td>
<td>0.003</td>
<td>1.44-2.48</td>
</tr>
<tr>
<td>SS-B Ab</td>
<td>1.97</td>
<td>0.073</td>
<td>1.61-2.43</td>
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</table>
NMOSD
New diagnostic criteria (2014)

- Core clinical characteristics
  - Optic neuritis (ON)
  - Transverse myelitis (TM)
  - Area postrema syndrome (AP)
  - Other brainstem syndrome
  - Acute diencephalic syndrome (DI, narcolepsy, SIADH)
  - Symptomatic cerebral syndrome (PRES, ADEM)
NMOSD

- **NMOSD with AQP4 antibody**
  - 1 of 6 core clinical characteristics
  - NMO IgG positive

- **NMOSD without AQP4 antibody**
  - 2 of 6 core clinical characteristics
    - 1 of these has to be ON, TM, or AP syndrome
    - Disseminated in space (e.g. ON x 2 does not count)
  - Corresponding MRI features
NMO MRI features (AP)
NMO MRI features: (diencephalic syndrome)
NMO MRI features: Cerebral
NMO IgG tests

- RSR ELISA (now licensed to Athena diagnostics) (~$470)
- Mayo CBA/FACS (~$450)
  - M1 isoform
- Oxford CBA/FACS (~$100+ shipping)
  - M23 isoform
M1 vs M23
Membrane assembly and diffusional mobility of M1 and M23 isoforms of AQP4.

# NMO IgG tests

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## Serologic diagnosis of NMO

A multicenter comparison of aquaporin-4-IgG assays

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### Table 1: Sensitivity and specificity of 6 aquaporin-4-IgG assays

<table>
<thead>
<tr>
<th></th>
<th>NMO (n = 35)</th>
<th>NMOSD (n = 25)</th>
<th>Total (n = 60)</th>
<th>Controls (n = 86)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>ROC-AUC</th>
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<tbody>
<tr>
<td>IIF</td>
<td>17</td>
<td>12</td>
<td>29</td>
<td>0</td>
<td>48.3</td>
<td>100.0</td>
<td>0.742</td>
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<tr>
<td>FACS</td>
<td>25</td>
<td>21</td>
<td>46</td>
<td>0</td>
<td>76.7</td>
<td>100.0</td>
<td>0.883</td>
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<tr>
<td>CBA-O</td>
<td>24</td>
<td>20</td>
<td>44</td>
<td>0</td>
<td>73.3</td>
<td>100.0</td>
<td>0.867</td>
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<tr>
<td>ELISA-R (5.0)</td>
<td>18</td>
<td>18</td>
<td>36</td>
<td>0</td>
<td>60.0</td>
<td>100.0</td>
<td>0.800</td>
</tr>
<tr>
<td>FIPA-O</td>
<td>16</td>
<td>16</td>
<td>32</td>
<td>0</td>
<td>53.3</td>
<td>100.0</td>
<td>0.767</td>
</tr>
<tr>
<td>FIPA-M</td>
<td>16</td>
<td>16</td>
<td>32</td>
<td>2</td>
<td>53.3</td>
<td>97.7</td>
<td>0.755</td>
</tr>
</tbody>
</table>

Abbreviations: AUC = area under the curve; CBA = cell-based assay; FACS = fluorescence-activated cell sorting; FIPA = fluorescence immunoprecipitation assay; IgG = immunoglobulin G; IIF = indirect immunofluorescence; M = Mayo; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; O = Oxford; R = RSR/Kronus; ROC = receiver operating characteristic curve.

* Results for blinded study of 146 samples on 6 assays with calculated sensitivities and specificities. The final column is a measure of assay accuracy.

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AQP4 autoantibody assay performance in clinical laboratory service

OPEN

ABSTRACT

Objective: To compare performance of contemporary aquaporin-4–immunoglobulin (Ig) G assays in clinical service.

Methods: Sera from neurologic patients (4 groups) and controls were tested initially by service ELISA (recombinant human aquaporin-4, M1 isoform) and then by cell-based fluorescence assays: fixed (CBA, M1-aquaporin-4, observer-scored) and live (fluorescence-activated cell sorting [FACS], M1 and M23 aquaporin-4 isoforms). Group 1: all Mayo Clinic patients tested from January to May 2012; group 2: consecutive aquaporin-4-IgG-positive patients from September 2011 (Mayo and non-Mayo); group 3: suspected ELISA false-negatives from 2011 to 2013 (physician-reported, high likelihood of neuromyelitis optica spectrum disorders [NMOSD] clinically); group 4: suspected ELISA false-positives (physician-reported, not NMOSD clinically).

Results: Group 1 (n = 398): M1-FACS assay performed optimally (areas under the curves: M1 = 0.64; M23 = 0.57 [p = 0.02]). Group 2 (n = 30): NMOSD clinical diagnosis was confirmed by: M23-FACS, 24; M1-FACS, 23; M1-CBA, 20; and M1-ELISA, 18. Six results were suspected false-positive: M23-FACS, 2; M1-ELISA, 2; and M23-FACS, M1-FACS, and M1-CBA, 2. Group 3 (n = 31, suspected M1-ELISA false-negatives); results were positive for 5 sera: M1-FACS, 5; M23-FACS, 3; and M1-CBA, 2. Group 4 (n = 41, suspected M1-ELISA false-positives); all negative except 1 (positive only by M1-CBA). M1/M23-cotransfected cells expressing smaller membrane arrays of aquaporin-4 yielded fewer false-positive FACS results than M23-transfected cells.

Conclusion: Aquaporin-4-transfected CBAs, particularly M1-FACS, perform optimally in aiding NMOSD serologic diagnosis. High-order arrays of M23-aquaporin-4 may yield false-positive results by binding IgG nonspecifically. Neurology Neuroimmunology Neuroinflammation 2014;1:e11; doi: 10.1212/NXI.0000000000000011
ANTI-MOG NMO

- Conus involvement
- Bilateral ON, or simultaneous ON+TM
- Better prognosis, ?relapse
- So far, no patient has tested positive for AQP-4 and MOG
What is the diagnosis?

Sarcoidosis – note leptomeningeal enhancement

What is the diagnosis?

Cervical spondylotic myelopathy – pancake enhancement

What is the diagnosis?
Cobalamin (B12) deficiency

- Vit B12 = 108 pg/ml (211-946)
- MMA = 19571 nmol/L (0-378)
- Serum copper nl
- No antiparietal ab, anti-IF ab, no recent surgeries or dental procedures
- NO₂