Diagnostic Criteria for Neuromyelitis Optica 2014

Brian G. Weinshenker, MD, FRCP(C)
Disclosures

• Royalties related to patent for discovery of NMO-IgG
  • licensed to RSR Ltd; Oxford University

• Consulting contracts related to NMO clinical research (within past 5 years):
  • GlaxoSmithKline Pharmaceuticals
  • Elan Pharmaceuticals
  • Chord Pharmaceuticals
  • Chugai Pharmaceuticals
  • Novartis Pharmaceuticals
  • Alexion Pharmaceuticals

• Member DSMB
  • Biogen Idec (Chair)
  • Novartis
  • Mitsubishi (Chair)

• Member Attack Adjudication Committee:
  • MedImmune (Chair)
NMO Criteria (2006)

- Transverse myelitis and optic neuritis
- At least two of the following features:
  - 1) MRI brain negative/nondiagnostic for MS
  - 2) MRI spinal cord lesion extending over ≥3 vertebral segments (LETM)
  - 3) NMO-IgG seropositivity

Wingerchuk et al, Neurology, 2006
Why are current diagnostic criteria inadequate in 2014?

• Discovery of NMO-IgG
  • NMO can be recognized reliably at an earlier point

• Limited versions of NMO
  • recurrent myelitis or recurrent optic neuritis

• Brain lesions may occur
  • may be the presenting manifestations
  • may be highly suggestive or diagnostic

• Co-association of other autoimmune conditions:
  • Do they exclude NMO?
International Panel for NMO Diagnosis (IPND)

• Convened October, 2011

• Co-chairs:
  • Dean Wingerchuk
  • Brian Weinshenker

• Overall objective:
  • To revise NMO diagnostic criteria to reflect advances in:
    • Clinical and radiological spectrum
    • Serological testing
Initial IPND Consensus Principles

• Clinical diagnosis
  • AQP4 antibodies
    • Not sufficient
      • False positives
      • Population-based study of MS-like illness: clinical NMO 0.2%; CBA+ 0.3%; ELISA+ 0.7% ([Pittock et al. 2014 JAMA Neurol. doi:10.1001/jamaneurol.2014.1581](http://dx.doi.org/10.1001/jamaneurol.2014.1581))
  • Not required
    • Differences between seronegative and seropositive poorly defined

• Use best available evidence and panel consensus
Methods

• 18 members from 9 countries
• 6 Working Groups
  • Specific charges relevant to NMO diagnosis
IPND Methods

- Neuroimaging
- Pediatrics
- Serology
- Systemic autoimmunity
- Clinical Presentations
- Opticospinal MS

NMOSD Clinical Diagnosis
IPND Methods

• Systematic literature review by each WG
  • Expert librarian assistance (K Wellik, Mayo Clinic)
  • Medline, EMBASE
  • 1950-2012
  • Quarterly updates to January, 2014
IPND Methods

• Stage 1
  • Roster of clinical/MRI syndromes diagnosed as NMO, NMOSD, or associated with AQP4-IgG
  • Evaluate re: inclusion and specificity

• Stage 2
  • Electronic surveys
    • Case vignettes
    • Clinical, MRI, lab, AQP4-IgG data
    • Diagnosis: definite, possible, or not NMOSD

• Stage 3
  • Data integration and refinement of draft criteria
Results: Nomenclature

• NMOSD: unified term

• Stratified by serostatus
  • NMOSD with AQP4-IgG
  • NMOSD without AQP4-IgG (or testing unavailable)

• Allows for future revisions
  • e.g. discovery and validation of other antibodies associated with NMOSD clinical phenotype
Revised Diagnostic Criteria: NMOSD with AQP4-IgG

Requirements

• At least 1 core clinical characteristic
• Positive test for AQP4-IgG
• No better explanation
  • Clinical and MRI red flags

Core Clinical Characteristics

• Optic neuritis
• Acute myelitis
• Area postrema syndrome:
  • nausea/vomiting/hiccups
• Other brain stem syndrome
• Symptomatic narcolepsy or acute diencephalic syndrome with MRI lesion(s)
• Symptomatic cerebral syndrome with MRI lesion(s)
Revised Diagnostic Criteria: NMOSD without AQP4-Ig (or unavailable)

• At least 2 core clinical characteristics all satisfying:
  • 1 of ON, myelitis, or area postrema syndrome
  • Dissemination in space
    • Isolated recurrent ON or recurrent TM do not qualify
• Additional MRI requirements
  • AP syndrome: dorsal medulla lesion
  • Myelitis: LETM
  • ON: normal brain MRI OR >1/2 ON OR chiasm lesion
• Negative test(s) for AQP4-IgG using best available assay, or testing unavailable

• No better explanation for the clinical syndrome
ON and Spinal Cord MRI Lesions
Area Postrema/Dorsal Medulla MRI Lesions
Diencephalic MRI Lesions
Cerebral MRI Lesions
Red Flags: Clinical and Laboratory

- Clinical course/lab more typical of MS or other pathology
  - Progressive course
  - Rapid nadir (infarction)
  - Continual worsening more than 4 weeks from onset
  - Partial TM without LETM
  - CSF oligoclonal bands

- Comorbidity, established or suspected, that mimics NMOSD
  - Sarcoidosis
  - Cancer (lymphoma or CRMP-5 associated ON/myelopathy)
  - Infection with potential neurologic involvement (e.g., HIV, syphilis)
Red Flags: Radiology

**Brain**
- “MS-typical” lesions
  - “Dawson’s fingers”
  - adjacent to lateral ventricle temporal lobe
  - Juxtacortical lesion(s)
  - Cortical lesion(s)
- Suspicious of other pathology
  - Lesion(s) with persistent (>3 months) gadolinium enhancement

**Spinal Cord**
- MS-typical
  - Short cord lesion(s)
  - Predominantly (>70%) peripheral cord on axial T2
  - Asymptomatic cord lesion(s)
  - Diffuse, indistinct T2 signal change (longstanding or progressive MS)
- Suspicious of other pathology
  - Persistent (>3 months) gadolinium enhancement
  - “Tractopathy” (e.g., paraneoplastic disorder)
Pediatric NMOSD

• Same criteria as adult NMOSD

• Cautions:
  • LETM in pediatric MS

• Greater incidence of cerebral presentations
Opticospinal MS

• Historically important
• Confusing terminology
  • a form of MS versus NMO versus something unique?
• Similarly defined in Asia, patients have the same disease
• “Superseded” terminology
NMO: Heterogeneous?

Seropositive versus seronegative: More likely to be/have:

- Woman
- Systemic autoimmune disease
- Unilateral ON
- ON OR myelitis
- Relapses
# Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MOG Abs+ (n = 16)</th>
<th>AQP4 Abs+ (n = 139)</th>
<th>Seronegative (n = 60)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phenotype, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMO</td>
<td>1/16 (6.3)</td>
<td>85/139 (61.1)</td>
<td>15/60 (25.0)</td>
<td></td>
</tr>
<tr>
<td>NMOSD-LETM</td>
<td>5/16 (31.2)</td>
<td>43/139 (30.9)</td>
<td>30/60 (50.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NMOSD-ON</td>
<td>10/16 (62.5)</td>
<td>11/139 (8.0)</td>
<td>15/60 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>6/16 (37.5)</td>
<td>122/139 (87.8)</td>
<td>40/60 (66.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Age, y, median (range)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At first attack</td>
<td>37.5 (3-70)</td>
<td>37 (4-78)</td>
<td>32.5 (10-69)</td>
<td>0.0915</td>
</tr>
<tr>
<td>At sampling</td>
<td>42 (6-70)</td>
<td>49 (15-82)</td>
<td>38 (12-69)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Follow-up, y, median (range)</td>
<td>2 (1-19)</td>
<td>7 (0-45)</td>
<td>3 (0-32)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Patients with a single attack, n (%)</td>
<td>8 (50.0)</td>
<td>23 (16.6)</td>
<td>18 (30.0)</td>
<td>0.0031</td>
</tr>
<tr>
<td>Simultaneous ON + myelitis attacks (any time), n (%)</td>
<td>1 (6.25)</td>
<td>32 (23.0)</td>
<td>6 (10.0)</td>
<td>0.0406</td>
</tr>
<tr>
<td>No. of attacks, median (range)</td>
<td>1.5 (1-3)</td>
<td>4 (1-33)</td>
<td>2.5 (1-18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EDSS, median (range)</td>
<td>1.5 (0-8)</td>
<td>5.8 (1-8.5)</td>
<td>4 (0-7)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Table 2: Comparison of clinical features between patients with NMOSD with MOG antibodies, AQP4 antibodies, and seronegative patients.*

*Neurology® 2014;82:474-481*
NMO: Beginnings of Classification of Heterogeneity?

- Seropositive NMO
- Seronegative NMO
  - False negative serologic assay
  - MS mimicking NMO
  - Other disorders that mimic NMO:
    - Sarcoidosis
    - Paraneoplastic
  - “True seronegative NMO”
    - Younger patients
    - Monophasic course
    - Less severe clinical manifestations
    - MOG antibodies?
Summary

- **NMOSD** is the unified term for NMO/NMOSD

- **AQP4-IgG Seropositive:**
  - Requires at least 1 of the 6 core clinical characteristics

- **AQP4-IgG Seronegative or Unavailable:**
  - At least 2 core clinical characteristics
    - 1 must be ON, acute myelitis or area postrema syndrome
    - MRI support
    - Dissemination in space
Implications to Clinical Trials

• “New disease”?  
  • Estimate 2X number of cases  
    • facilitates enrolment and enhances study feasibility  
  • Historical data on prognosis/outcome:  
    • unreliable?  

• Heterogeneity in prognosis, behavior between  
  • seropositive and seronegative
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Systemic Autoimmune Disease

• NMO diagnosis allowable
• Concurrence with SLE, SS, MG increases likelihood of a diagnosis of NMO
• Association with systemic autoimmune disease more likely reflects concurrence than causation
Pathology for Diagnosis

• Not routine

• AQP4-IgG obviates need for biopsy in most cases

• Atypical cases:
  • Astrocytopathy and selective AQP4 loss may
    • establish diagnosis
    • exclude other pathologies
- 37 years old female
- Numerous relapses during the last years
- Despite treatment with: Interferon-β, Mitoxantrone or natalizumab

Lee et al., Neuropathol. Appl. Neurobiol., 2010
GFAP

GFAP: Lesion

GFAP:PPWM

AQP4-IgG+

Diagnosis NMO

Lee et al., Neuropathol. Appl. Neurobiol., 2010
The two faces of neuromyelitis optica

- AQP4+, relapsing, older, female predominant, autoimmune
- MOG+, monophasic, younger, equal sex ratio, “ADEM-like”