Neuromyelitis Optica 2014:
Clinical Spectrum and Diagnosis

Brian G. Weinshenker, MD, FRCP(C)

Disclosures

• Royalties related to patent for discovery of NMO-IgG
  • licensed to RSR, Ltd.

• Consulting contracts related to NMO clinical research:
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  • GlaxoSmithKline Pharmaceuticals
  • Chord Pharmaceuticals
  • Chugai Pharmaceuticals

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

• Member Attack Adjudication Committee for MedImmune (Chair)
Outline

• NMO: Historical context
• The new face of NMO
• Helpful diagnostic clues in distinguishing NMO from MS
• Brain lesions in NMO
• NMO and systemic autoimmune disease
• Formulating new diagnostic criteria

1894: Single case: Bilateral optic neuritis and myelitis

1900 – 1990: Monophasic illness with bilateral optic neuritis and myelitis

2000-2007: Monophasic or relapsing illness dominated by optic neuritis or myelitis associated with NMO-IgG

2007 – present: Spectrum of conditions, usually but not always relapsing, including or sometimes confined to intractable vomiting/hiccup, symptomatic narcolepsy, tumefactive lesions of the brain; commonly associated with systemic autoimmunity
Current 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

The “New Face” of NMO
64 y woman

2010:
- Neck pain; dx: “spinal stenosis”; cervical fusion

Mid-2011:
- Dysphagia, hoarseness, jaw pain; “shingles?”
- Vibrating sensation; Lhermitte’s?
- Movement related tonic spasms; responsive to carbamazepine

PI: Myasthenia gravis, in remission

Exam: Reduced DTR’s UE; equivocal plantar responses
64 y woman

- CSF: normal; IgG index 0.47; neg OCB; neg MBP
- AchR binding and modulating antibodies positive
- NMO-IgG
  - ELISA negative
  - CBA: positive X2
- Diagnosis NMOSD
- Treated with rituximab: no new events at 2 years f/u

64 y woman: The new face of NMO

- Did not have:
  - either optic neuritis or myelitis
  - major disabilities or death
  - NMO-IgG on standard testing (ELISA)
- Clues that led to diagnosis
  - late age of onset
  - systemic autoimmunity (myasthenia gravis)
  - brainstem lesion
  - paroxysmal tonic spasms
  - no OCB
  - otherwise normal MRI of brain
  - positive serology for NMOSD
Why are current diagnostic criteria inadequate in 2013?

- 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?

What it might be:
Neuromyelitis Optica Spectrum Disorders: What are the limits?
**What it might be:**
Neuromyelitis Optica Spectrum Disorders: What are the limits?
MS Diagnostic Criteria Don’t Distinguish NMO from MS: AQP4 Antibodies “Trump” Clinical Diagnosis in Thai Patients

All AQP4+ patients had NMO typical symptoms (e.g. vomiting) or NMO typical brain lesions

N=37

N=16

Key Points in Differential Between MS vs NMO

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Findings in NMO</th>
<th>Relative Diagnostic Utility</th>
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<tbody>
<tr>
<td>Race/ethnicity</td>
<td>Non-white ancestry</td>
<td>++</td>
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<tr>
<td>Gender</td>
<td>Predilection for women (80% in NMO versus 65% of MS)</td>
<td>+</td>
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<tr>
<td>Attack severity</td>
<td>More severe than MS</td>
<td>++</td>
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<tr>
<td>Attack residua</td>
<td>Greater residual impairment than MS attacks</td>
<td>++</td>
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<tr>
<td>Brain MRI</td>
<td>Normal or nonspecific</td>
<td>++</td>
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<tr>
<td>Hypothalamic lesions</td>
<td></td>
<td>****</td>
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<tr>
<td>Spinal cord MRI</td>
<td>T2-weighted lesion &gt;3 vertebral segments</td>
<td>****</td>
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<tr>
<td>CSF cell count and differential</td>
<td>&gt;50x10^6 WBC/L; neutrophil predominance</td>
<td>+++</td>
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<tr>
<td>CSF immunoglobulin</td>
<td>IgG index nl; absent oligoclonal bands</td>
<td>+</td>
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<tr>
<td>NMO-IgG</td>
<td>Seropositive</td>
<td>****</td>
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</table>
Evaluation of brain lesions

- Almost no brain lesion excludes NMO
- Some lesions are more suggestive than others:
  - brainstem lesions
  - longitudinally extensive corticospinal tract lesions
Evaluation of brain lesions

- Almost no brain lesion excludes NMO
- Some lesions are more suggestive than others:
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  - longitudinally extensive corticospinal tract lesions
- Multiple periventricular lesions, especially adjacent to the temporal horns, is a “red flag”
Distinction of seropositive NMO spectrum disorder and MS brain lesion distribution

Lucy Matthews, MRCP
Rita Marasco, MD
Mark Jenkinson, DPhil
Wilhelm Küker, PhD
Sebastian Luppe, MD
Maria Isabel Leite, DPhil
Antonio Giorgio, MD, PhD
Nicola De Stefano, MD, PhD
Neil Robertson, DM
Heidi Johansen-Berg, DPhil
Nikos Evangelou, DPhil
Jacqueline Palace, DM

Neurology® 2013:801-8
Evaluation of brain lesions

- Almost no brain lesion excludes NMO
- Some lesions are more suggestive than others:
  - brainstem lesions
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- Multiple periventricular lesions, especially adjacent to the temporal horns, is a “red flag”
- Distinguish corpus callosum lesions of NMO from those of MS

Distinction of NMO from MS

Corpus Callosum Lesions in MS and NMO
Significance of Systemic Autoimmunity: Does it rule out diagnosis of NMO?

What it might be:
Co-associated autoimmune syndromes; NMO-IgG specific for NMO symptoms

NMO
(NMO-IgG +)

Lupus/Sjogren’s
(ANA/ENA +)

NMO-IgG+
NMO-IgG-
Neuromyelitis Optica Spectrum Disorders 2013

- Limited syndromes
  - Longitudinally extensive transverse myelitis
  - Optic neuritis

- Brain syndromes
  - Circumventricular
    - Nausea, vomiting
    - Narcolepsy
  - Encephalopathy
    - Variety of lesions: hypothalamic, tumefactive cerebral lesions, extensive corpus callosum lesions, PRES
  - Chronic encephalopathy/dementia
    - Impaired long term memory, executive function, accompanied by focal WM atrophy (Blanc F et al Arch Neurol 2008; 65: 84-88; Blanc F et al Plos One 2012; 7: e33878)

Neuromyelitis Optica Spectrum Disorders 2013

- Associated with comorbid conditions
  - Systemic autoimmune disease

- Other brainstem syndromes
  - Oculomotor
    - Hearing loss (Jarius S et al, J Neurol 2013 260:663–664)

- Spinal cord
  - Progressive myelopathy
  - Lumbosacral myeloradiculitis (Takai Y et al, Neurology 2012: 79)
Neuromyelitis Optica Spectrum Disorders 2013

- Endocrine/metabolic/systemic
  - SIADH with attacks
  - Anorexia
  - HyperCKemia during attacks
- Association with systemic disease
  - Autoimmune disease
  - Cancer
- Presymptomatic NMO-IgG seropositivity

Formulating Diagnostic Criteria

- Distinguish what is/are:
  - Pathognomonic
  - Highly suggestive (in the presence of positive serology, diagnostic)
  - Suggestive but requires dissemination of time and space
  - Allowable, but unhelpful diagnostically
  - Allowable, but “red flag”
  - Inconsistent/exclusionary
Items for consideration

• Clinical presentation
• MRI findings: spine and brain
• CSF findings
  • Pleocytosis >50/uL; PMN’s >5/uL
  • Presence of OCB
• NMO-IgG
• Pathology: biopsy

Pathognomonic

• NMO-IgG?
• Biopsy?
Aquaporin-4 antibody–positive cases beyond current diagnostic criteria for NMO spectrum disorders

- Routine testing of patients with NMO, NMOSD, MS at Tohoku University, Sendai
- 298 consecutive patients
  - 72 seropositive
    - 33 (45.8%) NMO
    - 26 (36.1%) accepted NMOSD
    - 13 (18.1%) other
      - 7 monophasic ON
      - 2 brainstem
      - 4 myelitis, not >3VS

NMO:
Does pathology help?

Courtesy C. Lucchinetti
- 37 years old female
- Numerous relapses during the last years
- Despite treatment with: Interferon-ß, Mitoxantrone or natalizumab

*C9neo deposits: Pattern II lesion?*

*Lee et al., Neuropathol. Appl. Neurobiol., 2010*
Pattern III lesion?

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

AQP4-IgG+
Diagnosis NMO

Lee et al., Neuropathol. Appl. Neurobiol., 2010
NMO: Does pathology help diagnose atypical cases?

Neuromyelitis Optica Lesions May Inform Multiple Sclerosis Heterogeneity Debate

Wolfgang Brück, MD,1 Bogdan Popescu, MD,2 Claudia F. Lucchinetti, MD,3 Silva Markovic-Plese, MD, PhD,4 Ralf Gold, MD,5 Dietmar Rudolf Thal, MD,6 and Imke Metz, MD1

ANN NEUROL 2012;72:385–394

NMO: Does pathology help?

| Table 3: Histochemical Comparison of Active Demyelinating NMO and MS Lesions |
|---|---|---|---|---|
| **NMO Chondrocytes** | **NMO Lesions with Predominantly Oligodendroglial Location** | **Cerebral/Supratentorial NMO Lesions with Features Resembleating Patients II and III: MS** | **Inflammatory Demyelinating Lesions Reported by Bennett and Prineas in 2006** |
| Antigens | Loss | Loss (25%); loss of intermediate filaments (15%) | Primed | Primed |
| Aquaporin-4 immunoreactivity | Loss | Loss (57%); loss of intermediate filaments (15%) | NS | NS |
| Fixed proteins | Present | Present (77%) | NS | NS |
| Neuronophagy/neurophil | Pos. | Pos. (17%) | Pos. | Pos. |
| Perivascular complement deposits | Pos. | Pos. (17%) | Neg. | Neg. |
| NMO pattern II characteristics | | | | |
| Complement deposition within macroagglutin | Neg. | Neg. (17%) | Neg. | Neg. |
| MS pattern III characteristics | | | | |
| Oligodendrocyte apoptosis | Not present | Not present (97%) | Present | Present |
| Myelin basic protein | Pos. | MAB > others (97%) | Not present | Not present |
| Chemos | | | | |
| Oligodendrocytes | Loss | Loss (63%); reduction (17%) | Varying | Varying |
| Myelin vacuolation | Primed | Primed (17%) | NS | NS |

*Histochemical characteristics are described in original studies.12,13,14,15,16,17

1Complement deposition within macroagglutin as reported by Bennett and Prineas in 2006.
2MAB = myelin basic protein; MS = multiple sclerosis; Pos. = positive; Neg. = negative; NMO = neuromyelitis optica; NS = not assessed; NS = not assessed.
Highly suggestive

• Myelitis with LETM
• Optic neuritis with severe visual impairment
• Intractable vomiting/hiccup

In this context, in an AQP4 seropositive individual, likely sufficient for diagnosis of NMO after first event

Red flag although consistent

• Progressive cognitive decline
• Lumbosacral myeloradiculitis
NMO: Heterogeneous?

• Seropositive versus seronegative: More likely to be/have:
  • Woman
  • Systemic autoimmune disease
  • Unilateral ON
  • ON OR myelitis
  • Relapses

Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype
by Joanna Kitley, Mark Woodhall, Patrick Waters, M. Isabel Leite, Emma Devenney, John Craig, Jacqueline Palace, and Angela Vincent

<table>
<thead>
<tr>
<th>Table</th>
<th>Summary of investigations in MOG-antibody-positive NMO/NNMO patients</th>
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<tbody>
<tr>
<td>No. 1</td>
<td>Patient 12/12 years old, female</td>
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<tr>
<td></td>
<td>Incomplete presentation of neuromyelitis</td>
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<td></td>
<td>Acute inflammation</td>
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<td>Acute inflammatory cell infiltrate</td>
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<td>MRI: T2 hyperintense lesion in the optic nerve</td>
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<td>CSF: normal</td>
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<td></td>
<td>Other findings: normal</td>
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Algorithms: "F" = follow-up, MOG = myelin-oligodendrocyte glycoprotein, NMO = neuromyelitis optica, NNMO = neuromyelitis optica spectrum disorder, OCR = optic neuritis, MNP = multifocal motor neuropathy, VEP = visual evoked potential, WBC = white blood cell count

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September 18, 2012
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

• No features are entirely sensitive or specific for NMO
• NMO-IgG enabling recognition of a broader spectrum of NMO pathology
• Convincing NMOSD include (in the presence of NMO-IgG):
  • Any ON or LETM associated
  • Selected brain syndromes: intractable vomiting, narcolepsy
  • Connective tissue disease-associated myelitis/ON
• Pathology may be revealing in selected patients