Distinguishing MS from Neuromyelitis Optica (NMO)

Dr. Tony Traboulsee,  
MS Clinic Director  
University of British Columbia  
Vancouver, BC Canada

Dr. Jack Simon,  
Neuroradiologist,  
Portland VA Medical Center  
and Oregon Health and Sciences University
Disclosures - Simon

- Research support: Biogen Idec
Disclosures - Traboulsee

• Non Pharma:
  – Canadian Asian MS research supported by Canadian Institute for Health Research
  – NMO research supported by Vancouver Hospital Foundation

• Pharma:
  – Research Grants: Bayer, Biogen, Merck Serono, Teva
  – Speakers bureau: Bayer, Merck Serono, Teva
  – Consultant: Bayer, Merck Serono, Teva, Biogen, Sanofi-Aventis
  – DSMB or Steering committee: Merck Serono, Roche
Disclosures - Traboulsee

• Off label treatment warning:
  – There are no approved therapies for neuromyelitis optica
  – Any discussion of treatments is based on anecdotal personal experience, published case series and/or the opinions of US and international colleagues who also treat NMO.
Objectives

• To be aware of clinical and MRI features that distinguish NMO from MS
• To understand that NMO is an astrocytopathy and MS is a demyelinating disorder.
• The treatment strategies are different for NMO than for MS.
Case discussion

• AL is a 21 year old Chinese Canadian woman living in Toronto starting her career as a flight attendant.
• During the summer she had three attacks of optic neuritis, severe, with poor recovery after steroids.
• In the fall, she developed a 4th attack of ON and became paraplegic over 72 hours.
• Her brain MRI was normal
Longitudinally Extensive Spinal Cord Lesion
NMO: Classic spinal cord findings

Longitudinally Extensive Spinal Cord Lesion (LESCL or LETM)
≥ 3 spinal segments, swollen, central
Axial location of spinal cord lesions may help distinguish NMO from MS

MS Proton Density

NMO T2 weighted

Slide adapted from K Fujihara

Ref: Nakamura J Neurol 2008
Short cord lesions can occur in both MS and NMO

Classic MS: short lesion

NMO Short lesion

MS Lesion on Sagittal T2

Small NMO lesion on PD
Long cord lesions: differential diagnosis
Differential Diagnosis - LESCL

• Autoimmune
  – NMO
  – Lupus (SLE)
  – Sjogren’s syndrome
  – Antiphospholipid syndrome

• Inflammatory
  – MS
  – Acute Disseminated Encephalomyelitis (ADEM)
  – Neuro-Behcet’s
  – Neurosarcoidosis

• Infectious
  – Parainfectious: EB, CMV, H.simplex, Varicella zoster, mycoplasma
  – Syphilis, TB
  – Schistosomiasis, Toxocara, Ascaris

The Differential Diagnosis of Longitudinally Extensive Transverse Myelitis
Kitley, Leite, George, Palace  MS 2012
Differential Diagnosis- LESCL

• Neoplastic
  – Paraneoplastic-autoantibody, lung, breast
  – Intramedullary tumor- astrocytoma, ependymoma

• Metabolic
  – B12, Copper

• Vascular
  – Cord infarction, fistula

• Radiotherapy

• Post-vaccination
Diffuse subtle long cord lesions seen in conventional MS should not be confused with LESCL of NMO

Progressive MS T2 weighted

Progressive MS Proton Density
SLE

44 yo presents with acute transverse myelopathy

Clinical clues for SLE:
Neuropsychiatric symptoms, rash, ulcers, arthralgia
Astrocytoma

Clue---Disease Course
Slowly Progressive Myelopathy
MR Imaging in a Case of Postvaccination Myelitis

Lisa M. Tartaglino, Terry Heiman-Patterson, David P. Friedman, and Adam E. Flanders
Mimics - cord stroke

T2 weighted

axial T2
Mimics: Syphilis

T2 weighted

T1 post contrast
T2 weighted

Mimics - Syphilis

axial T2
Mimics - Syphilis

PRE Treatment
T2 weighted

POST Treatment
T2 weighted
MS – Not a LESCL
NMO
Long cord lesions: natural history

Sagittal T2 Acute Lesion
60% of LESCL patients are positive for aquaporin 4 antibodies
40% of LESCL decrease in size and 28% completely resolve

Acute Long Cord Lesion
LESCL/LETM

LESCL completely resolved

Severe atrophy post LESCL
LESCL – Split into 3 non-LESCL
LESCL is a characteristic lesion of NMO. Best seen during acute attack. Centrally located. Rare mimics to consider. NMO cord lesions can be short.
19th Century: Recognition of MS and NMO

Pathologic description of MS by Robert Carswell

Jean Martin Charcot (1825-93) comprehensive review of MS cases.

1884 Devic and Gault reviewed 17 cases

45 year old woman with rapid bilateral optic neuritis and transverse myelitis. Died within 1 month of onset. Necrotic lesions in spinal cord and optic nerve.
Optic neuritis is a common presentation of both MS and NMO.
Optic neuritis is a common presentation of MS and NMO

Severe Optic Neuritis

Poor recovery favours NMO or compressive lesion

Good recovery favours MS but can occur in NMO
A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis

Lancet 2004; 364: 2106-12  Vanda A Lennon, Dean M Wingerchuk, Thomas J Kryzer, Sean J Pittock, Claudia F Lucchinetti, Kazuo Fujihara, Ichiro Nakashima, Brian G Weinshenker
MS attacks myelin

NMO attacks astrocytes
Loss of AQP4 & GFAP in NMO Lesions

NMO

Relatively preserved

Lost extensively

Astrocytic Damage

MBP

AQP4

GFAP

MS

Lost & well demarcated

Preserved

Demyelination & Gliosis

(Misu, 2006, 2007)
Figure. Relapsing neuromyelitis optica (NMO) survival: time from disease onset to death. Nonparametric survival curve for relapsing NMO survival. Median survival = 17.4 years. Bold line is probability estimate; lighter lines are 95% CIs.
Wingerchuck 2006
Optic Neuritis and Acute Myelitis and 2/3:
• LESCL >3 segments
• Brain MRI at onset not diagnostic of MS
• NMO-IgG seropositive
NMO Spectrum Disorders (NMOSD)

1. Classic NMO
2. Limited forms of NMO:
   - Longitudinally Extensive Spinal Cord Lesions (LESCL > 3 spinal segments)
   - Recurrent or simultaneous bilateral optic neuritis (ON)
3. ON or LESCL associated with another autoimmune disease (example Sjogren’s, Lupus myelitis)
4. ON or transverse myelitis with NMO like brain lesions.
### UBC Hospital NMO Clinic Experience

<table>
<thead>
<tr>
<th>Referrals</th>
<th>168</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NMOSD</strong></td>
<td>121</td>
</tr>
<tr>
<td><strong>Definite NMO</strong></td>
<td>34</td>
</tr>
<tr>
<td><strong>Asian ethnicity</strong></td>
<td>50 (41%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>36 (+/-13)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>68%</td>
</tr>
<tr>
<td><strong>Disability (EDSS)</strong></td>
<td>2.0</td>
</tr>
</tbody>
</table>
# UBC Hospital NMO Clinic Experience

## Aquaporin 4 antibodies

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite NMO</td>
<td>14/32 (41%)</td>
</tr>
<tr>
<td>NMOSD</td>
<td>23/106 (22%)</td>
</tr>
</tbody>
</table>

## Oligoclonal bands present in CSF

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite NMO</td>
<td>8/21 (38%)</td>
</tr>
<tr>
<td>NMOSD</td>
<td>17/63 (27%)</td>
</tr>
</tbody>
</table>
NMO Clinical Summary

Astrocytopathy
Antibodies helpful, but not always positive
30% Asian MS = NMO
Malignant disease course
Neuromyelitis Optica Diagnostic Criteria

Main Criteria (2/2)
1. Optic Neuritis
2. Transverse myelitis

Supportive criteria (2/3)
• Brain MRI not meeting MS diagnostic criteria
• Spinal cord > 3 contiguous segments
• NMO-IgG seropositive
Brain MRI abnormalities in NMO

What proportion of NMO patients have a normal brain MRI?

- 11%
- 30%
- 60%
- 75%
- 100%
Brain MRI abnormalities in NMO

• Normal Brain MRI: 11% to 75% from several case series
  – Decreases with disease duration
• Nonspecific finding: 15% to 55%
  – Increases with age

S Pittock
Arch Neurol. 2006; 63:390-396
Brain MRI abnormalities in NMO

What proportion of NMO patients have an brain MRI that meets Barkhof criteria for MS?

- 0%
- 10%
- 30%
- 60%
- 80%
2001 and 2005 MRI Criteria for MS Dissemination in Space
3 out of 4 Barkhof/Tintore criteria  (present in 30% of NMO)

1 Infra-tentorial  
OR  
1 Spinal Cord

3 Periventricular

9 T2  
or  
1 Gd+

1 Juxtacortical
MS appearing Brain abnormalities in NMO

- Meet $\geq 3/4$ Barkhof criteria
  - 5% to 33%
- Meet Paty criteria
  - 11% to 74%
- Rate increases with disease duration

S Pittock
Arch Neurol. 2006; 63:390-396
NMO patient developing MS like lesions.

Brain MRI 3 years latter
2010 MRI Criteria for MS Dissemination in Space
>1 lesions in at least 2 of 4 regions (present in 60% of NMO)

1 Infra-tentorial or 1 Spinal Cord

3 1 Periventricular

1 Juxtacortical
Distinct Brain MRI abnormalities in NMO

- 8% to 69% prevalence
- Increases with disease duration
  - Extensive hemispheric brain lesions
  - Brainstem lesions contiguous with LESCL
  - Hypothalamic
  - Following cortical spinal tracks
  - Extensive corpus callosum lesions
  - Around 3rd and 4th ventricles
  - Patchy/cloudy enhancement
Brain MRI abnormalities in NMO

S. Pittock
Arch Neurol. 2006; 63:390-396
Unusual MRI lesions seen in NMO

Callosal Lesion
(Large, Edematous)
Brain Lesions in Anti-AQP4-positive Cases

Medullary Lesion

Hypothalamic Lesion

Callosal Lesion (Large, Edematous)

Intractable Hiccup & Nausea

Hypersomnia

(Misu, 2005; Nakashima, 2006; Takahashi, 2007; Shimizu, 2008; Nakamura, 2009)
Patchy Cloud like enhancement
S Ito
Tumor like lesions on MRI

Tumorfactive MS  Glioblastoma  Abscess
Some large NMO lesions may disappear
MS lesions rarely disappear

NMO Brain MRI Summary

Abnormal MRI common:
UBO’s
MS like lesions
NMO characteristic lesions
Treatment of NMO
Case discussion

• AL is a 21 year old Chinese Canadian woman
• 20/200 vision both eyes.
• Paraplegic
Time is brain, spinal cord and optic nerve
1. Methylprednisolone 1 gram IV for 3-5 days followed by oral steroid taper to prevent rebound.
Case discussion

• Jackie is 41 year old caucasian woman
• Acute transverse myelitis
• Paraplegic - wheel chair
• No response to steroids
• Sent to rehab facility
1. Methylprednisolone 1 gram IV for 3-5 days followed by oral steroid taper to prevent rebound.

Failure = no clinically meaningful response during treatment or within 3-5 days of treatment completion.

2. Plasmapheresis course of 5 treatments. Taper schedule if good response. Role for prednisone to prevent rebound.
Improvement in disability (EDSS) baseline, pre and post PLEX (N=52)
Responders: MS 37%, NMO 56%
Case discussion

• Jackie is 41 year old caucasian woman
• Acute transverse myelitis
• Paraplegic - wheel chair
• No response to steroids
• PLEX started at 3 months and continued for 3 months. EDSS 1.0
1. Methylprednisolone 1 gram IV for 3-5 days followed by oral steroid taper to prevent rebound. Failure = no clinically meaningful response during treatment or within 3-5 days of treatment completion.

2. Plasmapheresis course of 5 treatments. Taper schedule if good response. Role for prednisone.

3. The Mitoxantrone Rescue/Induction Protocol: 12mg/m2 IV monthly for three months.
Case discussion

- Sue is a 48 year old caucasian woman
- Acute transverse myelitis
- Quadriplegic - ICU
- No response to steroids
- No response to PLEX
1. Methylprednisolone 1 gram IV for 3-5 days followed by oral steroid taper to prevent rebound.

Failure = no clinically meaningful response during treatment or within 3-5 days of treatment completion.

2. Plasmapheresis course of 5 treatments. Taper schedule if good response. Role for prednisone.

3. The Mitoxantrone Rescue/Induction Protocol: 12mg/m2 IV monthly for three months.
Case discussion

• Sue
• Acute transverse myelitis
• Quadriplegic
• Mitoxantrone given at 4 months.
• Walks with a cane (EDSS 6.0)
UBC Mitoxantrone protocol for severe demyelination
Improvement at 6 months post Mitoxantrone
(18 cases of severe optic neuritis or transverse myelitis)
Prevention of NMO Relapses
anecdotal experience and/or case series

- Prednisone
- Azathioprine (target lymphocytes 0.5 to 1.0)
- Methotrexate
- Mycophenolate mofetil (cellcept)
- Rituximab
- Cyclophosphamide, Cyclosporine
- Mitoxantrone (induction only)
- Combination (e.g. Azathioprine plus prednisone)
NMO Treatment Summary

- NMO attacks are a neurological emergency.
- The treatment strategies are different for NMO than for MS.
- Prevention is key (chronic immune suppression)
Objectives

• To be aware of clinical and MRI features that distinguish NMO from MS
• To understand that NMO is an astrocytopathy and MS is a demyelinating disorder.
• The treatment strategies are different for NMO than for MS.
NMO Clinical Summary

Astrocytopathy
Antibodies helpful, but not always positive
30% Asian MS = NMO
Malignant disease course
Treat early
Treat aggressively
NMO and LESCL Summary

LESCL is a characteristic lesion of NMO
Best seen during acute attack
Centrally located
Rare mimics to consider
NMO cord lesions can be short
NMO Brain MRI Summary

Abnormal MRI common:
UBO’s
MS like lesions
NMO characteristic lesions
NMO Diagnostic Criteria

Wingerchuck 2006
Optic Neuritis and Acute Myelitis and 2/3:
• LESCL >3 segments
• Brain MRI at onset not diagnostic of MS
• NMO-IgG seropositive

Revisions to Diagnostic criteria will have to consider potential range of Brain MRI features and NMO spectrum disorder.