NMO spectrum disorder versus Multiple Sclerosis: clinical and diagnostic aspects

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Disclosure

• On site PI Pharnext (CMT)
• Co-investigator FORCE trial (postpolio syndrome)
• Member Data Safety Monitoring Board Novartis (SMA)
• Chair International Data Monitoring Committee Dynacure (centronuclear myopathy)
Learning objectives

At the end of this lecture the learner is able to

- Outline strategies for early and accurate diagnosis of neuromyelitis optica spectrum disorder (NMOSD)
- Distinguish NMOSD from MS
NMO spectrum disorder

- Rare demyelinating CNS disease (0.037-0.7/100,000 in Australia and New Zealand to 0.73–10/100,000 persons in Afro-Caribbean region) (Papp et al. Neurology 2021)
- Inflammatory disorders of CNS
  - Severe immune-mediated demyelination and axonal damage
  - Damage optic nerve and spinal cord
- Risk factors:
  - Female: male ratio (10:1)
  - Commonly 32-45 years of age, pediatric (>18) and elderly patients (>50) reported
  - African descent
  - One third of attacks preceded by fever or vaccination
- Familial NMO 3%
Synonyms
Neuromyelitis Optica Spectrum disorder

- (Asian, Japanese) opticospinal MS
- Devic disease
- Devic syndrome
- Optic neuromyelitis
- Opticomyelitis
- NMOSD

https://rarediseases.org/rare-diseases/neuromyelitis-optica/
Definition NMO spectrum disorders

• Pathophysiological entities: presence or absence of AQP4-Ab
• In ~60-90% of cases, AQP4-Ab are present
  => primarily astrocytopathic disease
• In ~25-40% of AQP4-Ab negative NMOSD patients autoantibodies against MOG-Ab present
  ⇒ primarily oligodendrocytopathic.
• Double-negative NMOSD (? yet unknown autoantibodies) ~ 16%

Hamid et al. JNNP 2017
Pathogenesis

Garbugio Dutra et al.
RadioGraphics 2018
Case 1 – misdiagnosed as MS

• 34-year-old woman presented with diplopia, visual disturbance, and gait impairment.
• Diagnosed with MS – no details about therapy
• 12 yrs after onset: left-sided pain, numbness and paralysis
• MRI brain: signal changes in the right portion of the splenium, hyperintensity surrounding lateral ventricle on FLAIR image
• CSF was negative for oligoclonal bands
• Steroid pulse therapy and therapy with interferon beta-1a started
• Lesion disappeared after 1 yr of follow-up
• Diagnosed with Sjögren’s syndrome 12 yrs after onset

Matsusue et al. Acta Radiol Open 2016
• 13 yrs after onset T2-weighted images showed lower cervical and upper thoracic cord lesions spanning > five vertebral segments
• Serum sample (13 yrs after onset) positive for anti-AQP4 antibody => NMO
• Maintenance therapy: predonine (15 mg/day) and AZA (75 mg/day).
Clinical features

- Acute attacks (days or weeks)
  - Bilateral or rapidly sequential optic neuritis
  - => severe visual loss OR
  - Longitudinally extensive transverse myelitis (> 3 vertebral segments)
    => disabling paraplegia
  - Typically relapsing course
  - Most often first attack monosymptomatic
  - Concomitant appearance of ON and TM in 15-40%
- Repeated attacks separated by periods of remission (interval weeks, months or years).
Non-opticospinal syndromes

• Brainstem syndrome
  • Involvement of area postrema => nausea, vomiting, hiccups
  • Oculomotor dysfunction, deafness, facial palsy, vertigo, trigeminal neuralgia
  • Acute neurogenic respiratory failure and death

• Other sites of CNS involvement:
  • Diencephalic (narcolepsy, anorexia, inappropriate diuresis, hypothermia, and hypersomnia)
  • Cerebral lesions

More common in seropositive patients
Non-opticospinal initial symptoms

Li et al. BMC Neurology 2021
Non-neurological manifestations

• 30-40% have co-existing auto-immune disorder (Sjögren’s syndrome, SLE, thyroiditis, myasthenia gravis, auto-immune encephalitis)

Wingerchuk et al. Neurology 2015
Revised diagnostic criteria for NMOSD with AQP4-IGG

(International Panel for NMOSD Diagnosis)

<table>
<thead>
<tr>
<th>Requirements</th>
<th>Core Clinical Characteristics</th>
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</thead>
<tbody>
<tr>
<td>1. At least 1 core clinical characteristic</td>
<td>1. Optic neuritis</td>
</tr>
<tr>
<td>2. Positive test for AQP4-IgG using best available detection method</td>
<td>2. Acute myelitis</td>
</tr>
<tr>
<td>(cell-based assay strongly recommended)</td>
<td>3. Area postrema syndrome: episode of otherwise otherwise</td>
</tr>
<tr>
<td>3. Exclusion of alternative diagnoses</td>
<td>unexplained hiccups or nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td>4. Acute brainstem syndrome</td>
</tr>
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<td></td>
<td>5. Symptomatic narcolepsy or acute diencephalic clinical syndrome</td>
</tr>
<tr>
<td></td>
<td>with NMOSD-typical diencephalic MRI lesions</td>
</tr>
<tr>
<td></td>
<td>6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions</td>
</tr>
</tbody>
</table>

*Neurology 2015;85:177–189*
Diagnosing NMOSD

Core clinical characteristics
- Optic neuritis
- Acute myelitis
- Area postrema syndrome
- Acute brainstem syndrome
- Narcolepsy/acute diencephalic clinical syndrome
- Symptomatic cerebral syndrome

Cell-based aquaporin 4 (AQP4)-IgG test
High specificity (91-110%) and varying sensitivity (83-91%)

NMOSD with AQP4-IgG
- 1 core characteristic
- Positive APQ4-IgG test

NMOSD without AQP4-IgG/AQP4-IgG status unknown
- ≥2 different, separated, core characteristics
- Optic neuritis, acute myelitis with LETM, or APS (area postrema syndrome)
- Negative/unavailable AQP4-IgG test
- Additional MRI requirements: LETM >3 VS, etc.
Red flags: Atypical findings in NMSOD

**Clinical/laboratory findings**
- Progressive overall clinical course
- <4 hours or >4 weeks to nadir of attack
- Partial transverse myelitis
- CSF oligoclonal bands

**Imaging characteristics**

**Brain lesions**
- Perpendicular to lateral ventricular surface
- Adjacent to lateral ventricle in inferior temporal lobe
- Juxtacortical with subcortical U-fibres
- Cortical lesions
- Persistent gadolinium enhancement

**Spinal cord lesions**
- <3 complete vertebral segments
- Predominantly in peripheral cord
- Indistinct signal change on T2 sequences

Windchuk et al. Neurology 2015
Case 2 – classical case

- 32-year-old man with chronic hepatitis C was administered anti-viral therapy with pegylated-interferon-α2a plus ribavirin
- After 12 weeks of therapy, rapid and progressive worsening of vision in his left eye => retrobulbar optic neuritis
- Symptoms spontaneously resolved.
- Two weeks later acute lower limb weakness and constipation and urinary retention. Ex/: bilateral lower limb hyposthenia.
- CSF: Normal
- Dx/: Viral encephalitis - R/ high-dose corticosteroids and acyclovir
Case 2 cont’d

- A few days later, clinical deterioration: flaccid paraplegia, constipation, hypoesthesia below Th10
- MRI: longitudinally extensive transverse myelitis
- Anti-aquaporin4 antibodies (AQP4-Ab) in serum were positive => NMOSD
- Lack of response to the high-dose steroid therapy
- Plasmapheresis, followed by intravenous immunoglobulin.
- After 4 months of physiotherapy and steroid treatment, full recovery of sphincter control and walking with assistance
- ? Peg-IFNα a trigger
Distinction between NMOSD with MOG or AQP4 antibodies, or double-negative NMOSD

<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>Phenotype, n (%)</td>
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<tr>
<td>NMO</td>
<td>1/16 (6.3)</td>
<td>85/139 (61.1)</td>
<td>15/60 (25.0)</td>
<td></td>
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<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>3/16 (37.5)</td>
<td>122/139 (87.8)</td>
<td>40/60 (66.7)</td>
<td>&lt;0.0001</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>

Sato et al. Neurology 2014
Imaging

Periependymal surface of the corpus callosum, hypothalamus, periaqueductal area, area postrema, and the central canal of the spinal cord

Periependymal surface of the lateral ventricles

Periependymal surface of the third ventricle (diencephalic region)

Periaqueductal area and optic chiasm

Periependymal surface of the fourth ventricle and area postrema

Garbugio Dutra et al. RadioGraphics 2018
Imaging optic nerve

Axial and sagittal gadolinium-enhanced fat-saturated T1-weighted images

Garbugio Dutra et al. RadioGraphics 2018
Imaging spinal cord

Typical spinal cord involvement

Sagittal T2-weighted image shows LETM extending into the area postrema (arrowhead)

Garbugio Dutra et al.
RadioGraphics 2018
Distinctive imaging features of ON, TM and brain lesions in AQP4-IgG–positive vs MOG-IgG–positive NMOSD & MS

<table>
<thead>
<tr>
<th></th>
<th>NMOSD-AQP4-IgG+</th>
<th>MOG-IgG+</th>
<th>Multiple Sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) Optic nerve</td>
<td><img src="image" alt="Optic nerve" /></td>
<td><img src="image" alt="Optic nerve" /></td>
<td><img src="image" alt="Optic nerve" /></td>
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<tr>
<td>B) Spinal cord</td>
<td><img src="image" alt="Spinal cord" /></td>
<td><img src="image" alt="Spinal cord" /></td>
<td><img src="image" alt="Spinal cord" /></td>
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<tr>
<td>C) Brain</td>
<td><img src="image" alt="Brain" /></td>
<td><img src="image" alt="Brain" /></td>
<td><img src="image" alt="Brain" /></td>
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</tbody>
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Garbugio Ditra RadioGraphics 2018
Disease pattern

Within 5 years:
- 50% of people require a wheelchair
- 62% are functionally blind (or no useful vision)

Relapse rates:
- 60% relapse within 1 year
- 90% relapse within 3 years
Comparison with MS

• Previously believed that NMO and MS represented one disease entity with variable phenotypes and expression.
• NMO is distinct from RRMS with respect to pathogenesis, neuropathology and response to treatment and imaging features.
• Rapidly sequential ON or bilateral simultaneous ON highly suggestive of NMO.
• Severe visual impairment highly suggestive of NMO.
• CSF: moderate pleocytosis more prominent than MS.
• Oligoclonal bands positive in ~30%.
• ‘MS’ medication may worsen NMOSD (Papadopoulos et al. 2014).
Case 3 – very late-onset NOMSD

• 82-year-old woman presented with acute gait disturbance, hypoesthesia and bladder and rectal disturbance over 3 days.
• Ex/ asymmetric paraparesis with extensor plantar responses. Sensory disturbances below Th10.
• CSF: elevated myelin basic protein level, immunoglobulin G and albumin ratios, and positive oligoclonal bands.

Furijawa et al. Case Rep Neurol 2020
Case 3 cont’d

- Spinal MRI (T2WI): two high signals extending from Th1 to Th2 and Th7 to Th9
- Autoimmune myelitis was suspected => R/high-dose methylprednisolone
- 17 days after onset serum positive for anti-AQP4 (cell-based assay).
- Diagnosis: NMOSD => Treatment: immunoadsorption plasmapheresis and daily prednisolone
- Outcome: able to walk using a walker.
Patients’ experience and Quality of life

Most patients had an initial diagnosis other than NMOSD

Strong negative impact on physical health
- Pain
- Bowel/bladder dysfunction

Relatively unimpaired emotional wellbeing
Biggest negative factors were
- Inability to work
- Reduced QoL and sexual function
- Increased pain

QoL assessment in 193 patients with NMOSD

Beekman et al. Neurology 2019
11 NMOSD patients – all had had CNS infections
91% (10/11) were female, with an average age of 30 years at presentation (range 15–51 years).
Longitudinally extensive transverse myelitis and Optic neuritis – all bilateral simultaneous or sequential – commonest first presentations in 45% (5/11) and 36% (4/11) of cases
27% (3/11) presented with acute brainstem syndrome and only one patient had area postrema syndrome as a second symptom after LETM

Sokhi et al. eNeurologicalSci 2021
Cases of NMOSD from the East Africa region, challenges in diagnostics and healthcare access

• AQP4-IgG testing (immunofluorescence not cell-based): 64% (7/11) positive result
• One case could not afford testing for AQP4-IgG, and the remaining 3 patients were included because they fulfilled clinical and radiological criteria
• Significant impact of early involvement of a neurologist
  • timeline to diagnosis (average of 2.3 months from first presentation if seen by a neurologist first)
  • number of relapses before diagnosis (1.3 vs 2.4 average relapses),
  • outcome as measured by EDSS (3.6 vs 5.4)
Treatment

• Acute relapses require immediate treatment.
• Early high-dose steroids and plasmapheresis/immunoadsorption associated with better long-term outcomes.
• RCTs support the use of
  • B-cell depletion (rituximab, inebilizumab),
  • interleukin-6 signaling blockade (tocilizumab, satralizumab),
  • complement inhibition (eculizumab)
  to decrease relapse rates in NMOSD
• Mortality 3–7% as compared to natural history studies (22%–30%)

Wallach et al. Neurol Clin 2021
Drug Treatment of Neuromyelitis Optica Spectrum Disorders: Out with the Old, in with the New?
Conclusions

• NMOSD is a spectrum of diseases
• NMO-specific anti-aquaporin-4 (AQP4) antibody distinctive role
• Within the seronegative group a MOG-positive subset can be distinguished
• ON and TM most common (‘core’) clinical features
• Other CNS manifestations (e.g. brainstem, diencephalic, cerebral)
• Differences AQP4-IgG–seropositive and seronegative patients
• Differences MS and NMO/DS
• MR imaging important tool for diagnosis of NMOSD
Similarities between NMOSD and MS

MS
- Th1
- SAA ↑ → ↓

NMOSD
- Demyelination
  - Spinal cord ring enhancement
  - Short transverse myelitis
  - Th17
  - SAA ↑

- Astrocytopathy
  - LETM
  - Th17
  - SAA ↑

Yokote and Misuzawa
Neural Regen Res 2016