Myelin Oligodendrocyte Glycoprotein (MOG) Associated Neurological Spectrum Disorders

NEHA SHARMA MD
What is NMOSD?
What is NMOSD?

- Neuromyelitis Optica Spectrum Disorder (NMOSD)

- Aquaporin-4 channels
  - Located in astrocytic processes of the BBB

- Neuro-inflammatory diseases that affects the CNS (especially optic nerve and spinal cord)
  - Aquaporin-4 IgG Antibody
  - Secondary demyelination
AQP4-IgG positive = 1 core clinical characteristic required, exclusion of alternate diagnosis

AQP4-IgG negative = 2 core clinical characteristic required, exclusion of alternate diagnosis

Note: 1 of 2 core clinical characteristic must be Optic Neuritis, Transverse Myelitis* or Area Postrema syndrome

*must be LETM
NMOSD vs. MOG
How does MOGSD relate to NMOSD?

- Also a Neuro-inflammatory disease
  - Primary demyelination
  - Occurs in ~40% of NMOSD seronegative patients

- Affects the optic nerve

- Can affect brain and spinal cord
MOG
What is MOG?

- Myelin Oligodendrocyte Glycoprotein (MOG)
  - A protein found on the outer surface of the myelin sheath in the CNS

- Neuro-inflammatory disease of the CNS
  - Anti-MOG Antibody
  - Especially the optic nerve
Pathogenesis
Pathogenesis of Anti-MOG Antibody

- Anti-MOG Antibody found in periphery, enter CNS via BBB breakdown secondary to infection (50% of patients)

- Complement mediated cytotoxicity leading to demyelination
MOG-Targeted Autoimmunity

**MOG-Specific**
- B
- MOG-Specific
- Tfh
- MOG-Specific
- Teff
- Peripherals
  - Anti-MOG-Ab
- **Blood-Brain Barrier**
  - MOG
  - Olig. & Myelin Damage
  - Complement
  - MBP
  - CNS
  - N

AQP4-Targeted Autoimmunity

**AQP4-Specific**
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[Source: https://nn.neurology.org/content/2/1/e62]
Epidemiology
Epidemiology of Anti-MOG Antibody Syndrome

- Earlier age of onset (compared to NMOSD)
  - 6-70 years (median 31 years)

- Incidence of 0.2-1.4 per 100,000 cases

- Female:Male
  - 1-2:1
Clinical Presentation
Clinical Presentation of Anti-MOG Antibody Syndromes

- Monophasic and Relapsing course
  - 93% if disease present ≥ 8 years

- Children
  - ADEM most common
  - Bilateral > unilateral optic neuritis

- Adult
  - Bilateral > unilateral optic neuritis
    - Optic nerve head edema

- Other presentations seen during relapse
  - Brainstem encephalitis
  - Isolated myelitis
  - Cerebral symptoms
  - Cerebellar symptoms
Diagnosis
3.7. Diagnosis

Recently, an international panel of experts [133] formulated the diagnostic criteria for MOG-related disorders in adults. Accordingly, MOG-related disorders should be diagnosed in patients who meet all of the following criteria:

1. Monophasic or relapsing acute ON, myelitis, brainstem encephalitis, or any combination of these symptoms
2. MRI or electrophysiological (visual evoked potentials in patients with isolated ON) findings compatible with CNS demyelination

Clinical, laboratory and imaging features that favor the diagnosis of conditions other than MOG-related disorders (“red-flags”) include:

a. Chronic progressive course (progressive MS, sarcoidosis and tumors) or acute onset (ischemia);

b. Clinical and paraclinical findings suggesting other conditions such as:

   i. Tuberculosis, borreliosis, syphilis, Behçet’s disease, subacute combined degeneration of the spinal cord, Leber’s hereditary optic neuropathy, lymphoma, and paraneoplastic disorders;
   ii. Peripheral demyelination

c. Brain MRI abnormalities such as:

   i. Lesion adjacent to lateral ventricle associated with inferior temporal lobe lesion, or Dawson’s finger-type lesion;
   ii. Increasing number of lesions between relapses.

d. Serum MOG-IgG at low titers.

It is recommended that patients who test positive for MOG-IgG but in whom a “red flag” is suspected undergo retesting, preferably employing a different CBA [133].
Diagnosis of Anti-MOG Antibody Syndromes

- **Serum**
  - Check for Anti-MOG Ab (IgG)

- **CSF**
  - Pleocytosis
    - WBC ≥ 100 cells/microliter
  - Monocytes and Neutrophils
  - Intrathecal IgG
    - Restricted oligoclonal bands
Diagnosis of Anti-MOG Antibody Syndromes

- **MRI Brain**
  - Bilateral optic nerves
    - Anterior optic pathways extending to retrobulbar and orbital segments
  - Fluffy, poorly demarcated lesions
    - Pons and/or adjacent to fourth ventricle
    - Less than 3 lesions
  - Children
    - Bilateral large brainstem and deep grey matter lesions

- **MRI Spine**
  - Longitudinally extensive T2 abnormalities
    - More than 3 vertebral segments
    - Ventral Thoracolumbar region
  - MRI can be normal in MOG-IgG + patients
Figure 3. Examples of MRI abnormalities in anti-MOG syndrome. (a). Axial T1-weighted MRI reveals longitudinal extensive gadolinium enhancement of both optic nerves. (b). Coronal T2-weighted MRI shows hyperintense thickening of perioptic nerve sheath. (c). Sagittal T2/FLAIR-weighted image shows large fluffy lesion in the medulla.
Patients in relapse:

25-32% of patients fulfilled 2015 NMOSD criteria

Table 1  NMOSD diagnostic criteria for adult patients

<table>
<thead>
<tr>
<th>Diagnostic criteria for NMOSD with AQP4-IgG</th>
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<tbody>
<tr>
<td>1. At least 1 core clinical characteristic</td>
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<tr>
<td>2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)</td>
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<tr>
<td>3. Exclusion of alternative diagnoses*</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status</th>
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</thead>
<tbody>
<tr>
<td>1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:</td>
</tr>
<tr>
<td>a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome</td>
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<tr>
<td>b. Dissemination in space (2 or more different core clinical characteristics)</td>
</tr>
<tr>
<td>c. Fulfillment of additional MRI requirements, as applicable</td>
</tr>
<tr>
<td>2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable</td>
</tr>
<tr>
<td>3. Exclusion of alternative diagnoses*</td>
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<table>
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<tr>
<th>Core clinical characteristics</th>
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<tbody>
<tr>
<td>1. Optic neuritis</td>
</tr>
<tr>
<td>2. Acute myelitis</td>
</tr>
<tr>
<td>3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting</td>
</tr>
<tr>
<td>4. Acute brainstem syndrome</td>
</tr>
<tr>
<td>5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions (figure 3)</td>
</tr>
<tr>
<td>6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions (figure 3)</td>
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<th>Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status</th>
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<tr>
<td>1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over ~1/2 optic nerve length or involving optic chiasm (figure 1)</td>
</tr>
<tr>
<td>2. Acute myelitis: requires associated intramedullary MRI lesion extending over 3 contiguous segments (LETM) OR 3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis (figure 1)</td>
</tr>
<tr>
<td>3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions (figure 2)</td>
</tr>
<tr>
<td>4. Acute brainstem syndrome: requires associated periapendymal brainstem lesions (figure 2)</td>
</tr>
</tbody>
</table>
Patients in relapse:

15-33% fulfilled revised McDonald MS criteria

**Table 1. McDonald Criteria for Diagnosis of Multiple Sclerosis**

<table>
<thead>
<tr>
<th>Typical attack or clinically isolated syndrome at onset</th>
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<tbody>
<tr>
<td>≥2 attacks and objective clinical evidence of ≥2 lesions</td>
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<tr>
<td>≥2 attacks and objective clinical evidence of 1 lesion AND history of prior attack</td>
</tr>
<tr>
<td>≥2 attacks and objective clinical evidence of 1 lesion</td>
</tr>
<tr>
<td>AND history of prior attack implicating different lesion site</td>
</tr>
<tr>
<td>OR ≥1 MS-typical T2-enhancing lesion that is periventricular, juxtacortical, infratentorial, or in spinal cord</td>
</tr>
<tr>
<td>1 attack and objective clinical evidence of ≥2 lesions</td>
</tr>
<tr>
<td>AND history of prior attack implicating different lesion site</td>
</tr>
<tr>
<td>OR simultaneous presence of both enhancing and nonenhancing MS-typical lesions (symptomatic or asymptomatic)</td>
</tr>
<tr>
<td>OR new T2 or enhancing MS-typical lesion compared to previous MRI findings</td>
</tr>
<tr>
<td>OR presence of oligoclonal bands in CSF (not serum)</td>
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<tr>
<td>Progression of disability from onset</td>
</tr>
<tr>
<td>1 attack and objective clinical evidence of 1 lesion</td>
</tr>
<tr>
<td>AND history of prior attack implicating different lesion site</td>
</tr>
<tr>
<td>OR ≥1 MS-typical T2-enhancing lesion in ≥2 periventricular, juxtacortical, infratentorial, or spinal cord sites</td>
</tr>
<tr>
<td>AND history of prior attack implicating different lesion site</td>
</tr>
<tr>
<td>OR simultaneous presence of both enhancing and nonenhancing MS-typical lesions (symptomatic or asymptomatic)</td>
</tr>
<tr>
<td>OR new T2 or enhancing MS-typical lesion compared to previous MRI findings</td>
</tr>
<tr>
<td>OR presence of oligoclonal bands in CSF (not serum)</td>
</tr>
<tr>
<td>1 year of disability progression</td>
</tr>
<tr>
<td>AND 2 of the following:</td>
</tr>
<tr>
<td>OR ≥1 MS-typical T2-enhancing lesion in ≥2 periventricular, juxtacortical, infratentorial, or spinal cord sites</td>
</tr>
<tr>
<td>OR ≥2 T2 spinal cord lesions</td>
</tr>
<tr>
<td>OR presence of oligoclonal bands in CSF (not serum)</td>
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Treatment
Treatment of Anti-MOG Antibody Syndromes

- Includes use of Prednisone
  - Can titrate down
    - Increases chances of relapse
    - Long-term use of Prednisone recommended

- Severe or refractory to steroids
  - Use Plasmapheresis or IVIG

- No consensus on use of other biologic immunosuppressants
Differential Diagnosis & Summary
Differential Diagnosis

- Neuromyelitis Optica Spectrum Disorders
  - Primarily – Optic Neuritis or Transverse Myelitis (LETM)

- Multiple Sclerosis

- Brainstem Encephalitis

- Acute Disseminated Encephalomyelitis
<table>
<thead>
<tr>
<th>MOG-IgG associated disorder</th>
<th>Neuromyelitis optica spectrum disorder</th>
</tr>
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<tbody>
<tr>
<td><strong>Clinical syndrome</strong></td>
<td><strong>Clinical syndrome</strong></td>
</tr>
<tr>
<td>ADEM, ON, TM, autoimmune encephalitis</td>
<td>ON, TM, BS</td>
</tr>
<tr>
<td>MRI</td>
<td>MRI</td>
</tr>
<tr>
<td>Atypical</td>
<td>Atypical</td>
</tr>
<tr>
<td><strong>CSF</strong></td>
<td><strong>CSF</strong></td>
</tr>
<tr>
<td>OCB 10%</td>
<td>OCB 10%</td>
</tr>
<tr>
<td><strong>Antibodies</strong></td>
<td><strong>Antibodies</strong></td>
</tr>
<tr>
<td>MOG-IgG positive</td>
<td>AQP4-IgG positive</td>
</tr>
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<tr>
<th>Other acquired demyelinating syndrome</th>
<th>Multiple Sclerosis</th>
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<tr>
<td><strong>Clinical syndrome</strong></td>
<td><strong>Clinical syndrome</strong></td>
</tr>
<tr>
<td>ON, TM, (multi)focal demyelinating</td>
<td>ON, TM, BS</td>
</tr>
<tr>
<td>MRI</td>
<td>MRI</td>
</tr>
<tr>
<td>Atypical</td>
<td>Typical</td>
</tr>
<tr>
<td><strong>CSF</strong></td>
<td><strong>CSF</strong></td>
</tr>
<tr>
<td>OCB mostly negative</td>
<td>OCB 90%</td>
</tr>
<tr>
<td><strong>Antibodies</strong></td>
<td><strong>Antibodies</strong></td>
</tr>
<tr>
<td>MOG-IgG and AQP4-IgG negative</td>
<td>MOG-IgG and AQP4-IgG negative</td>
</tr>
</tbody>
</table>

**Figure 2.** Spectrum of demyelinating diseases of the central nervous system.
Thank You!

Questions?
Abbreviations

- MOG – Myelin Oligodendrocyte Glycoprotein
- NMOSD – Neuromyelitis Optica spectrum disorder
- CNS – central nervous system
- BBB – blood brain barrier
- IgG – immunoglobulin G
- AQP4 – aquaporin-4
- LETM – longitudinal extensive transverse myelitis
- Tfh – T follicular helper cell
- Teff – T effector cell
- Ab – antibody

- N – neuron
- A – astrocyte
- Olig. – oligodendrocyte
- Neutro. – neutrophil
- Eosin. – eosinophil
- GFAP – glial fibrillary acidic protein
- ADEM – Acute disseminated encephalomyelitis
- MRI – magnetic resonance imaging
- ON – optic neuritis
- CBA – cell based assay
Abbreviations

- CSF – cerebrospinal fluid
- MS – multiple sclerosis
- IVIG – intravenous immunoglobulin
- IV – intravenous
- E.g. – example
- MMF – mycophenolate mofetil
- AZA – azathioprine
- MTX – methotrexate
- WBC – white blood cell
- TM – transverse myelitis
- BS – brain stem
- OCB – oligoclonal bands
References


