NMO and MOG
Optic Neuritis

Groningen
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Disclosures

NIHR UK
Zeiss (OCTA, ANGI)
UCSF (RECOVER trial)
Stichting MS Research NL
Heidelberg Academy (speaker)
Amsterdam UMC (RESTORE trial*)
Novartis (SC OCTiMS, QC PASSOS)
The Moorfields Biomedical Research Centre

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Overview

- Background: from MS to MOG & NMO
- International view
- Differential diagnoses
- Diagnosis and treatment of NMO-ON & MOG-ON
- Conclusion
When do we need a syndromic definition of a disease?
- In absence of a diagnostic test
- Multiple Sclerosis diagnosis:
  - DIS & DIT
- New diagnostic tests
  - AQP4 antibodies
  - MOG antibodies
## Syndromic definition of MS

<table>
<thead>
<tr>
<th>Number of lesions with objective clinical evidence</th>
<th>Additional data needed for a diagnosis of multiple sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 clinical attacks</td>
<td>None*</td>
</tr>
<tr>
<td>≥2 clinical attacks</td>
<td>None*</td>
</tr>
<tr>
<td>1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location†)</td>
<td>Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡</td>
</tr>
<tr>
<td>1 clinical attack</td>
<td>Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶</td>
</tr>
<tr>
<td>1 clinical attack</td>
<td>Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ AND Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶</td>
</tr>
</tbody>
</table>

The small print: * No additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered. In addition, spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting multiple sclerosis, with a presentation other than a typical clinically isolated syndrome, or with atypical features. If imaging or other tests (eg, CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of multiple sclerosis, and alternative diagnoses should be considered.
AQP4

V. Lennon et al. 2004

D. Wingerchuk et al. 2007
# NMOSD

## Table 1 NMOSD diagnostic criteria for adult patients

### Diagnostic criteria for NMOSD with AQP4-IgG
1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses

### Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status
1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
   a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
   b. Dissemination in space (2 or more different core clinical characteristics)
   c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses

### Core clinical characteristics
1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions (figure 3)
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions (figure 3)

### Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status
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)
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)
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions (figure 2)
4. Acute brainstem syndrome: requires associated periependymal brainstem lesions (figure 2)

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D. Wingerchuk et al. 2015
MOG

Peripheral immune system

A Trigger?

B MOG-specific B cell → Differentiation → MOG-specific plasma cell

C CNS

D Blood-brain barrier

BAFF APRIL CXCL13 CCL19 IL-6 IL-17 G-CSF TNFα

MOG-specific plasma cell → MOG-specific cell

MOG protein → Injury

Macrophages

MOG-1901

Myelin sheath
### Diagnosis of MOGAD (requires fulfilment of A, B, and C)

| (A) Core clinical demyelinating event | Optic neuritis*  
|                                         | Myelitis†  
|                                         | ADEM‡  
|                                         | Cerebral monofocal or polyfocal deficits§  
|                                         | Brainstem or cerebellar deficits¶  
|                                         | Cerebral cortical encephalitis often with seizures|| |
| (B) Positive MOG-IgG test | Cell-based assay: serum¶¶  
| Clear positive** | No additional supporting features required  
| Low positive† † | • AQP4-IgG seronegative AND  
| Positive without reported titre | • ≥1 supporting clinical or MRI feature  
| Negative but CSF positive§§ |  
| Supporting clinical or MRI features | Optic neuritis  
| | • Bilateral simultaneous clinical involvement  
| | • Longitudinal optic nerve involvement (> 50% length of the optic nerve)  
| | • Perineural optic sheath enhancement  
| | • Optic disc oedema  
| Myelitis | • Longitudinally extensive myelitis  
| | • Central cord lesion or H-sign  
| | • Conus lesion  
| Brain, brainstem, or cerebral syndrome | • Multiple ill-defined T2 hyperintense lesions in supratentorial and often infratentorial white matter  
| | • Deep grey matter involvement  
| | • Ill-defined T2-hyperintensity involving pons, middle cerebellar peduncle, or medulla  
| | • Cortical lesion with or without lesional and overlying meningeal enhancement  
| (C) Exclusion of better diagnoses including multiple sclerosis¶¶¶ |
A clinical observation: CRION

- Individuals with optic neuritis
- Corticosteroid responsive
- Relapse on corticosteroid reduction

D. Kidd et al. 2003
A. Petzold & G.T. Plant 2014
Summary background

- 1860: Description of Optic Neuritis
- 1868: Description of Multiple Sclerosis
- 2003: Discovery of NMO-IgG
- 2004: Discovery of NMO-IgG
- 2007: NMO-ON
- 2013: Re-discovery of MOG-IgG
- 2019: MOG-ON
- 2019: MOG-ON in 25-100% of CRION
- Future new auto-antibody discoveries?
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Classification of optic neuritis

Level 1 dichotomisation to guide general management

Optic neuritis

- Autoimmune (usually relapsing)
- Infectious or systemic (usually monophasic)

Level 2 consensus opinion

- AQP4-ON
- CRMP5-ON
- MOG-ON
- MS-ON
- SION
- RION
- CRION

- Infectious optic neuritis
- Post-infectious optic neuritis
- Post-vaccination optic neuritis (panel 4)

- Systemic disorders (panel 4)
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Differential Diagnoses

Panel 4: Infections and systemic disorders associated with optic neuritis

Causes of infectious and post-infectious optic neuritis

Systemic disorders causing optic neuritis
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Diagnosis of optic neuritis

Diagnosis based on clinical assessment and paraclinical tests (panel 1)

(a) Subacute monocular loss of vision, dyschromatopsia, pain worsening on eye movements, RAPD + 1 paraclinical test
(b) Like (a) without pain + 2 paraclinical tests
(c) Like (a) or (b) but binocular (RAPD unreliable) + MRI and another paraclinical test

Definite optic neuritis

(d) Clinically seen in acute phase, with features of (a), (b), or (c), with fundus examination consistent with optic neuritis classical disease course and no available paraclinical tests
(e) Retrospective typical history + paraclinical test(s)

Possible optic neuritis

(f) Loss of vision with features from panel 3 being present that suggest alternative pathology and paraclinical tests showing alternative pathology

Not optic neuritis
Time is vision

Case for a new corticosteroid treatment trial in optic neuritis: review of updated evidence

Axel Petzold, 1,2 Tasanee Braithwaite, 3 Bob W van Oosten, 4 Lisanne Balk, 5 Elena H Martinez-Lapiscina, 5, 6 Russell Wheeler, 7 Nils Wiegerinck, 8 Christiaan Waters, 9 Gordon T Plant 10

MOG-ON
NMO-ON
MS-ON
RION
CRION

E. Osinga et al 2017

J. Rode et al 2023
Treatment & relapse

$R = 0.81, p < 0.0001, n = 863$
Long term immune suppression
Treatments for MOG & NMO-ON

MOG-ON
NMO-ON

Trial
- Phenytion
- Statins

Approved
- Satralizumab
- Inebilizumab

Phase 3/4
- ACTH
- Eculizumab
- Corticosteroids

Phase 2
- ACTH
- Amiloride
- Vit. D
- Clemastine
- Early IVMP

Phase 0/1
- Fingolimod
- Minocycline
- EPO

Steroid saving:
- AZT
- MTX
- MMF
- IVIG
- PLEX
Conclusion

- Optic Neuritis: from clinic to tests
- Antibodies are essential for diagnosis
- Novel diagnostic criteria
- Guidance on differential diagnoses
- Update on treatment
Thank you