# 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

*Eugene Devic was a French neurologist who summarized the features of the condition in 1894*

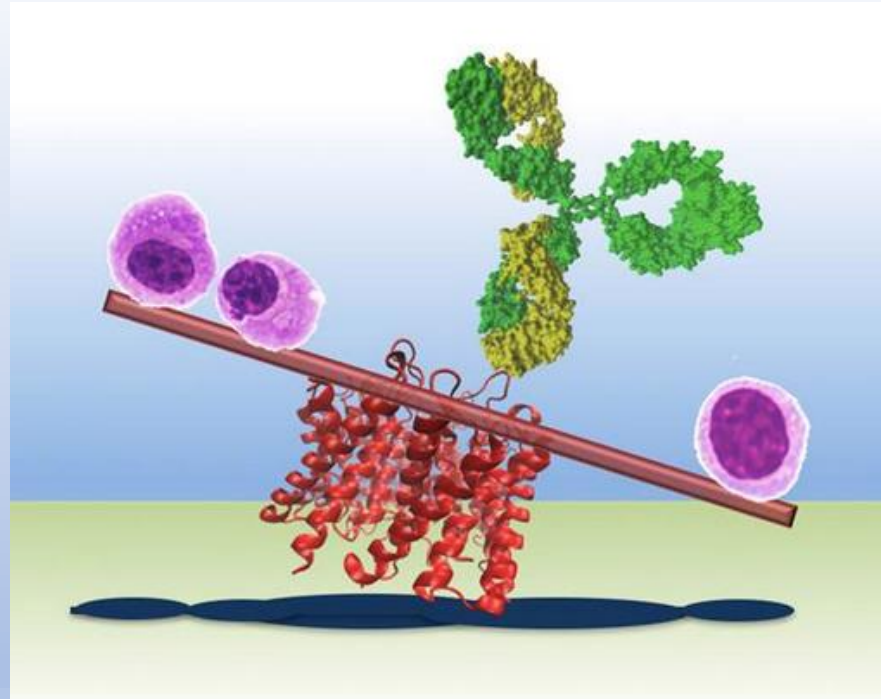
https://rarediseases.org/rare-diseases/neuromyelitis-optica/

# Definition NMO spectrum disorders

- Pathophysiological entities: presence or absence of AQP4-Ab
- In ~60-90% of cases, AQP4-Ab are present

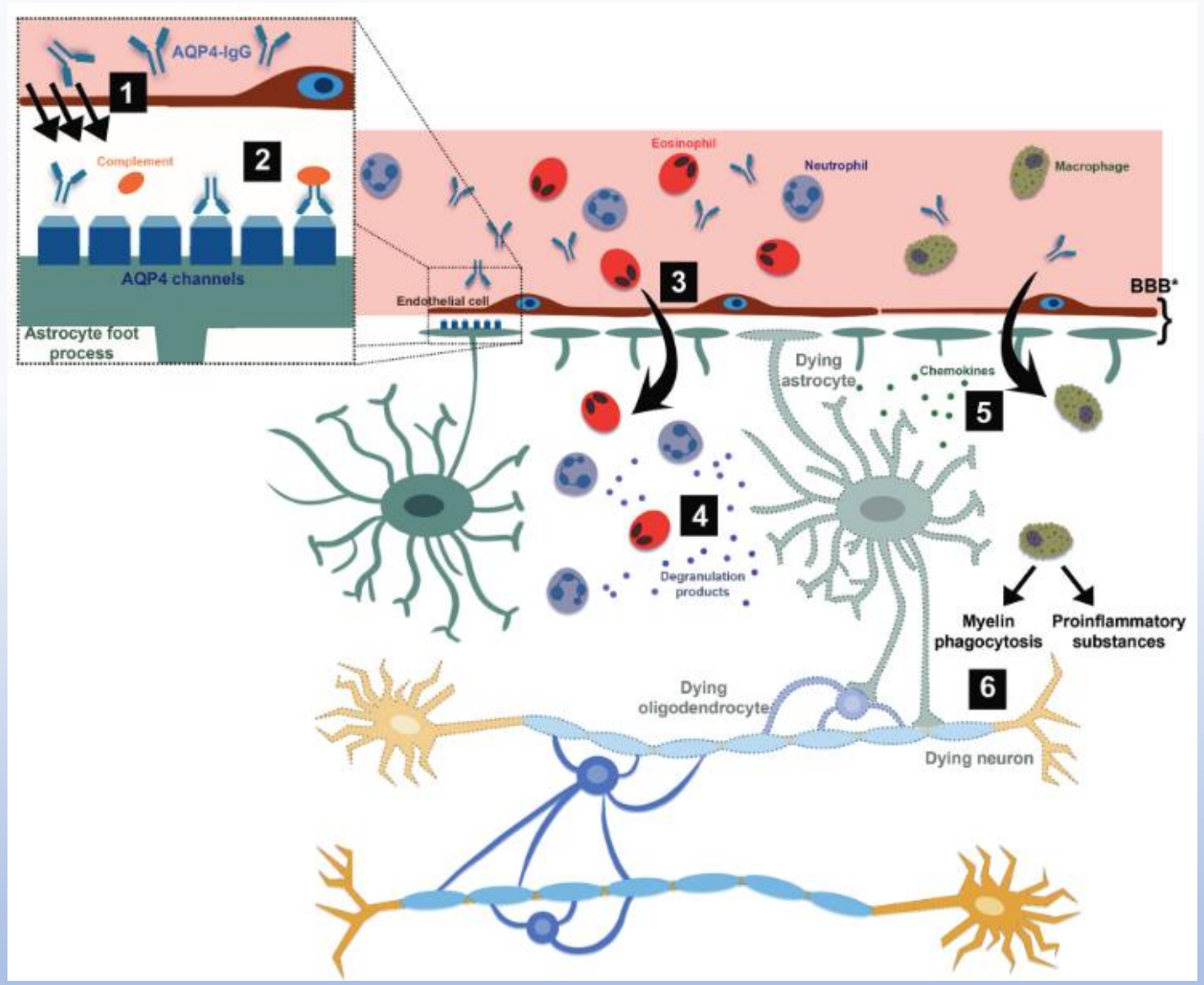
  => primarily astrocytopathic disease
- In ~25-40% of AQP4-Ab *negative* NMOSD patients autoantibodies against MOG-Ab present

  ⇒ primarily oligodendrocytopathic.
- Double-negative NMOSD (? yet unknown autoantibodies) ~ 16%



Hamid et al. JNNP 2017

# Pathogenesis



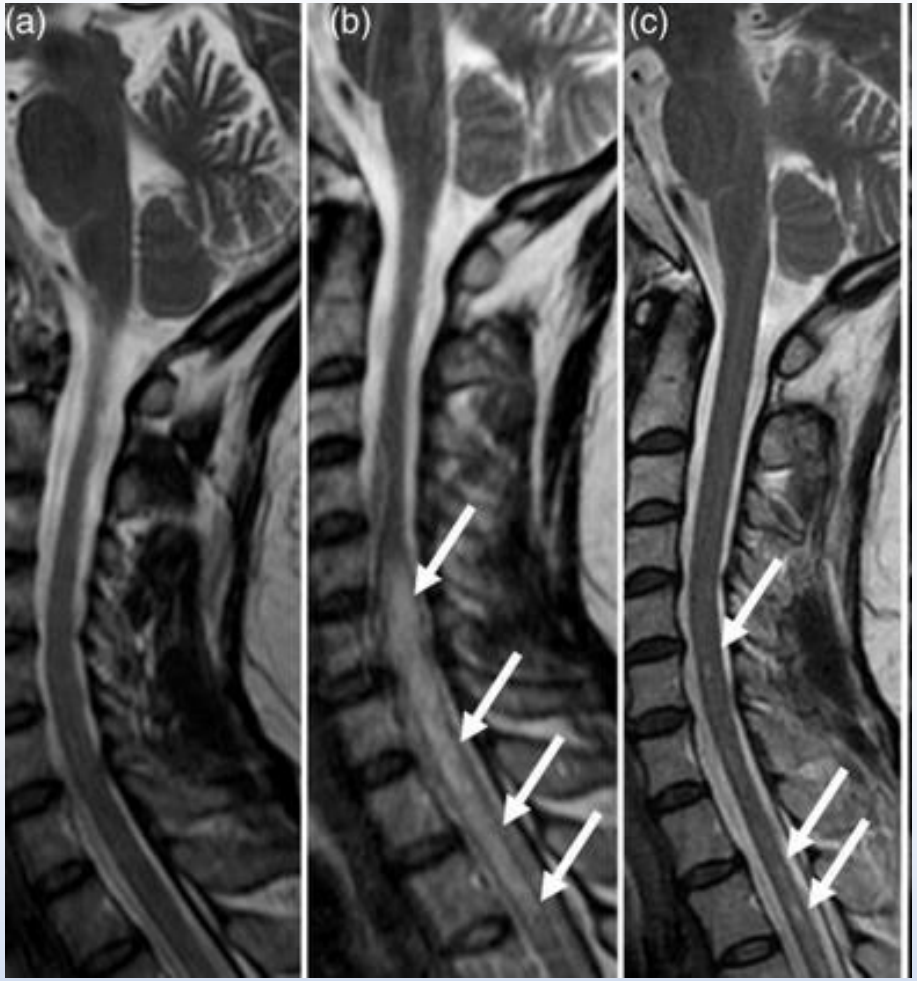

Garbugio Dutra et al.
RadioGraphics 2018

# 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

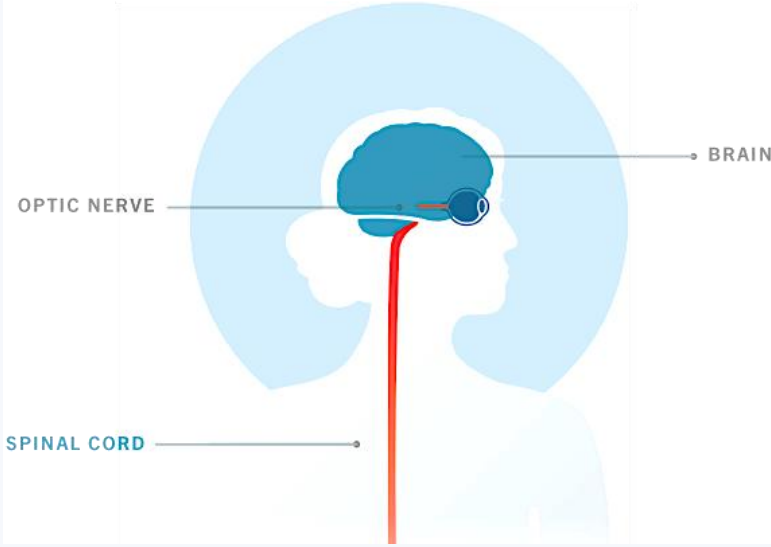
Matsusue et al. Acta Radiol Open 2016

# Case 1 cont’d



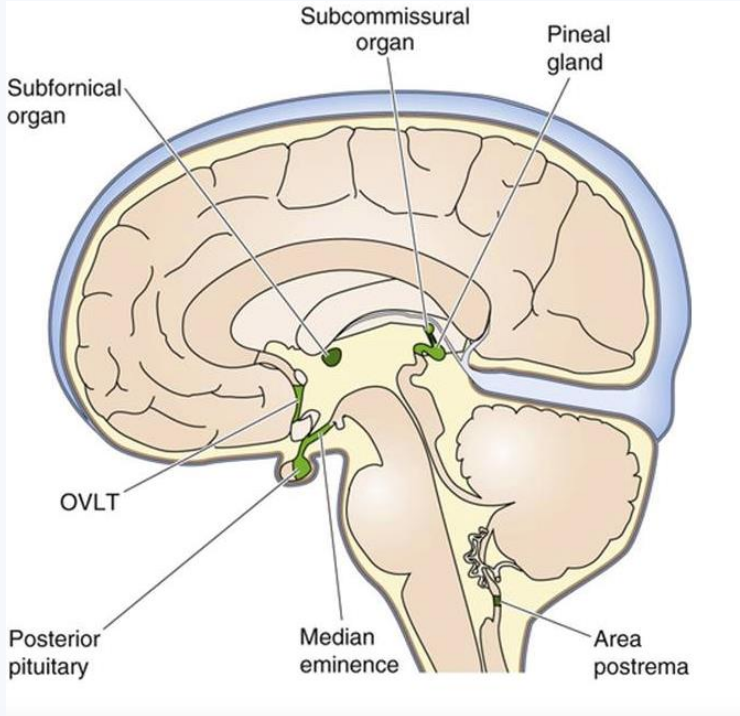

- 13 yrs after onset T2-weighted images showed lower cervical and upper thoracic cord lesions spanning > five vertebral segments
- Serum sample (13 yrs after onset) positive for anti-AQP4 antibody => NMO
- Maintenance therapy: predonine (15 mg/day) and AZA (75 mg/day).

# 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).

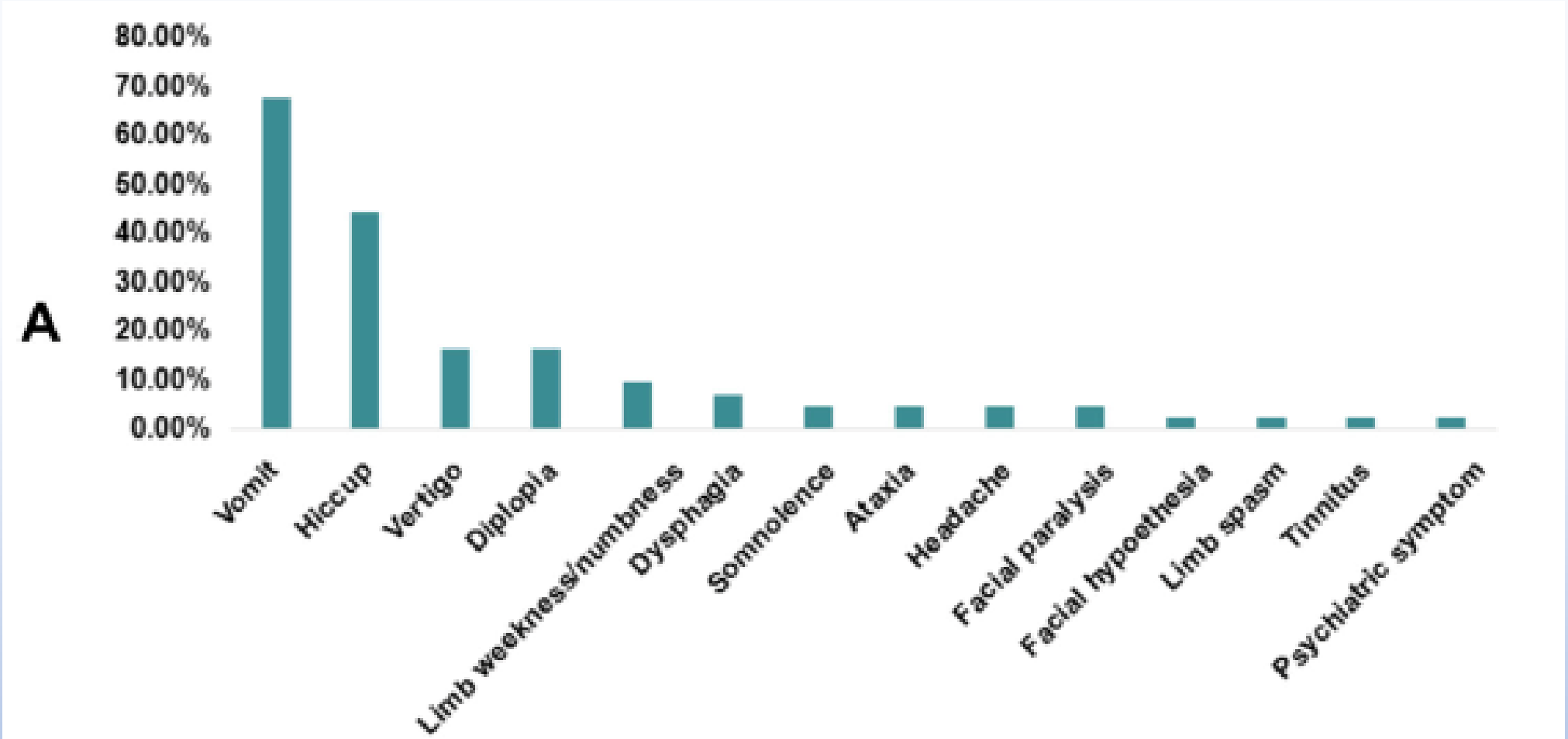
# Non-opticospinal syndromes




- 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

## REVISED DIAGNOSTIC CRITERIA FOR NMOSD WITH AQP4-IGG (International Panel for NMOSD Diagnosis)

### Requirements

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

### 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
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

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.

touch NEUROLOGY

# 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

touch NEUROLOGY

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

Mangioni et al. BMC Pharmacology and Toxicology 2014

# 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

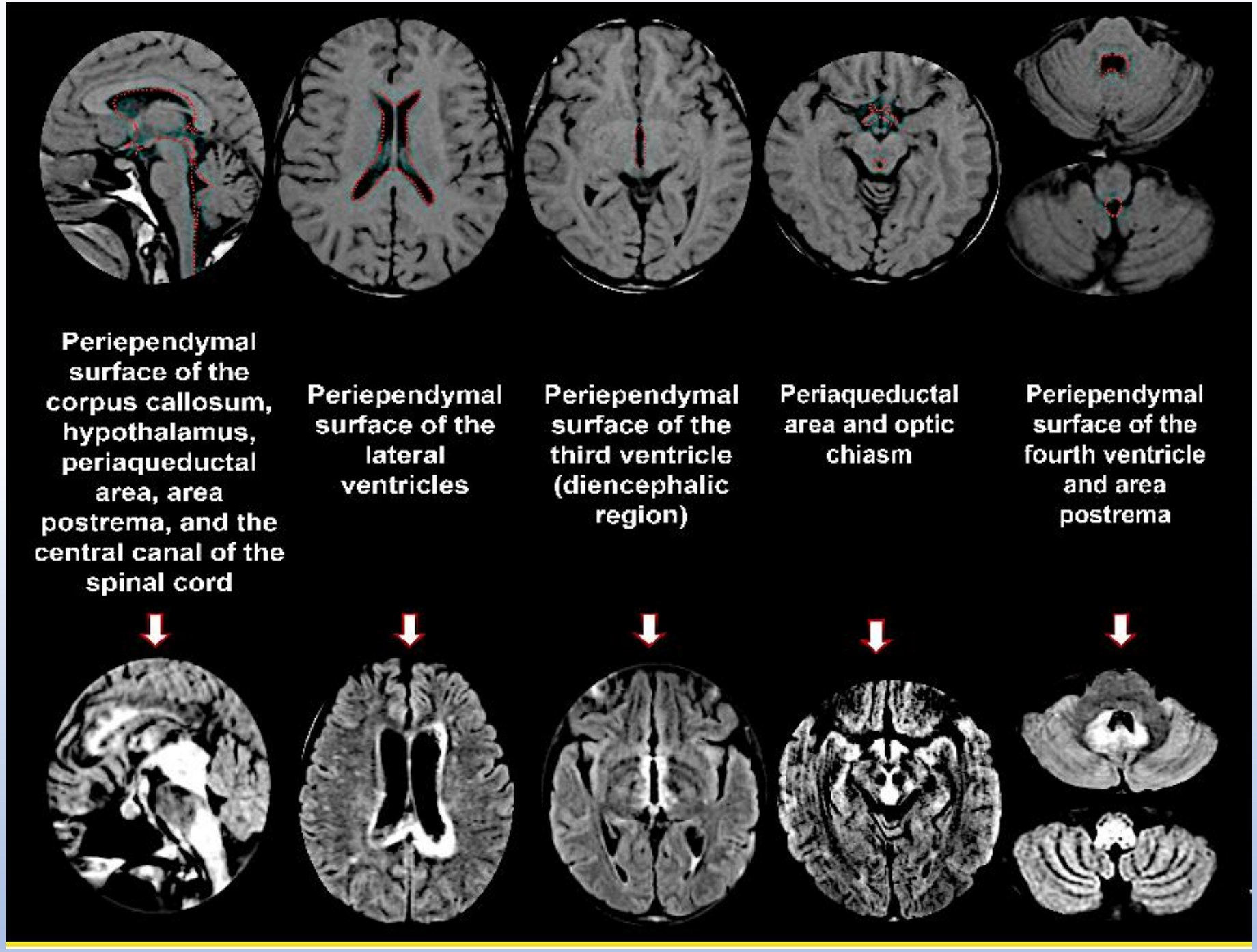
# Distinction between NMOSD with MOG or AQP4 antibodies, or double-negative NMOSD

**Table 2** Comparison of clinical features between patients with NMOSD with MOG antibodies, AQP4 antibodies, and seronegative patients

| Characteristics | MOG Abs+ (n = 16) | AQP4 Abs+ (n = 139) | Seronegative (n = 60) | *p* Value |
|---|---|---|---|---|
| Phenotype, n (%) | | | | |
| NMO | 1/16 (6.3) | 85/139 (61.1) | 15/60 (25.0) | |
| NMOSD-LETM | 5/16 (31.2) | 43/139 (30.9) | 30/60 (50.0) | <0.0001 |
| NMOSD-ON | 10/16 (62.5) | 11/139 (8.0) | 15/60 (25.0) | |
| Female, n (%) | 6/16 (37.5) | 122/139 (87.8) | 40/60 (66.7) | <0.0001 |
| Patients with a single attack, n (%) | 8 (50.0) | 23 (16.6) | 18 (30.0) | 0.0031 |
| Simultaneous ON + myelitis attacks (any time), n (%) | 1 (6.25) | 32 (23.0) | 6 (10.0) | 0.0406 |
| No. of attacks, median (range) | 1.5 (1-3) | 4 (1-33) | 2.5 (1-18) | <0.0001 |
| EDSS, median (range) | 1.5 (0-8) | 5.8 (1-8.5) | 4 (0-7) | <0.0001 |

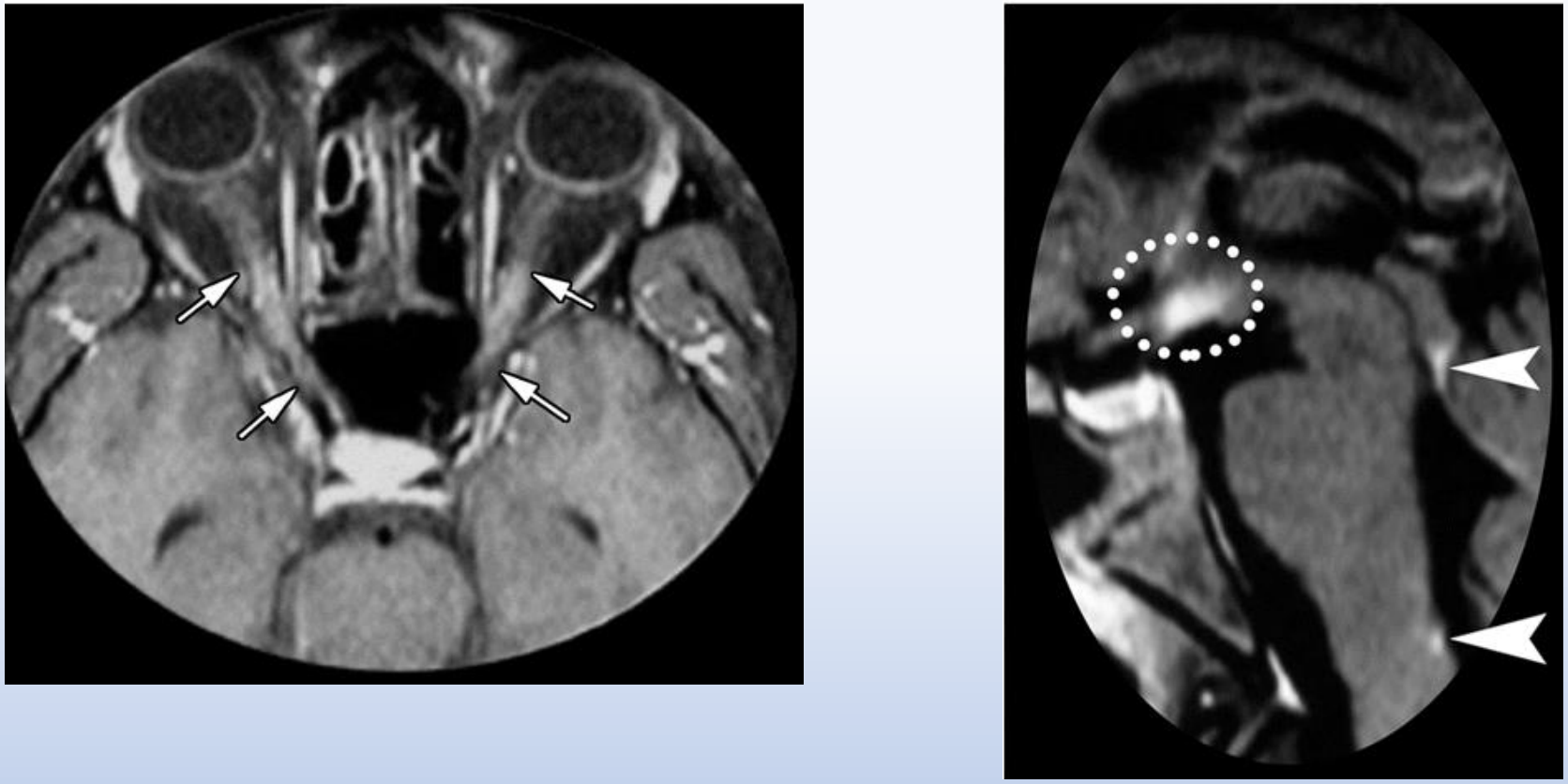
Sato et al.
Neurology 2014

# Imaging




Garbugio Dutra et al.
RadioGraphics 2018

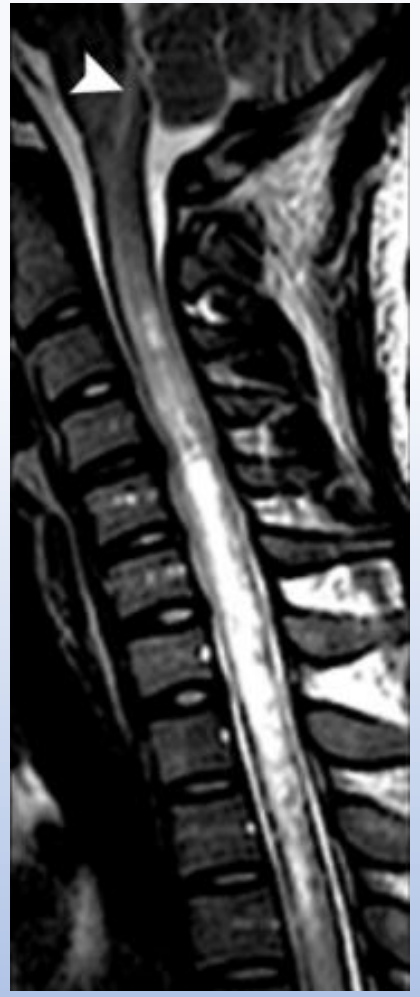
# Imaging optic nerve



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

Garbugio Dutra et al.
RadioGraphics 2018

# Imaging spinal cord



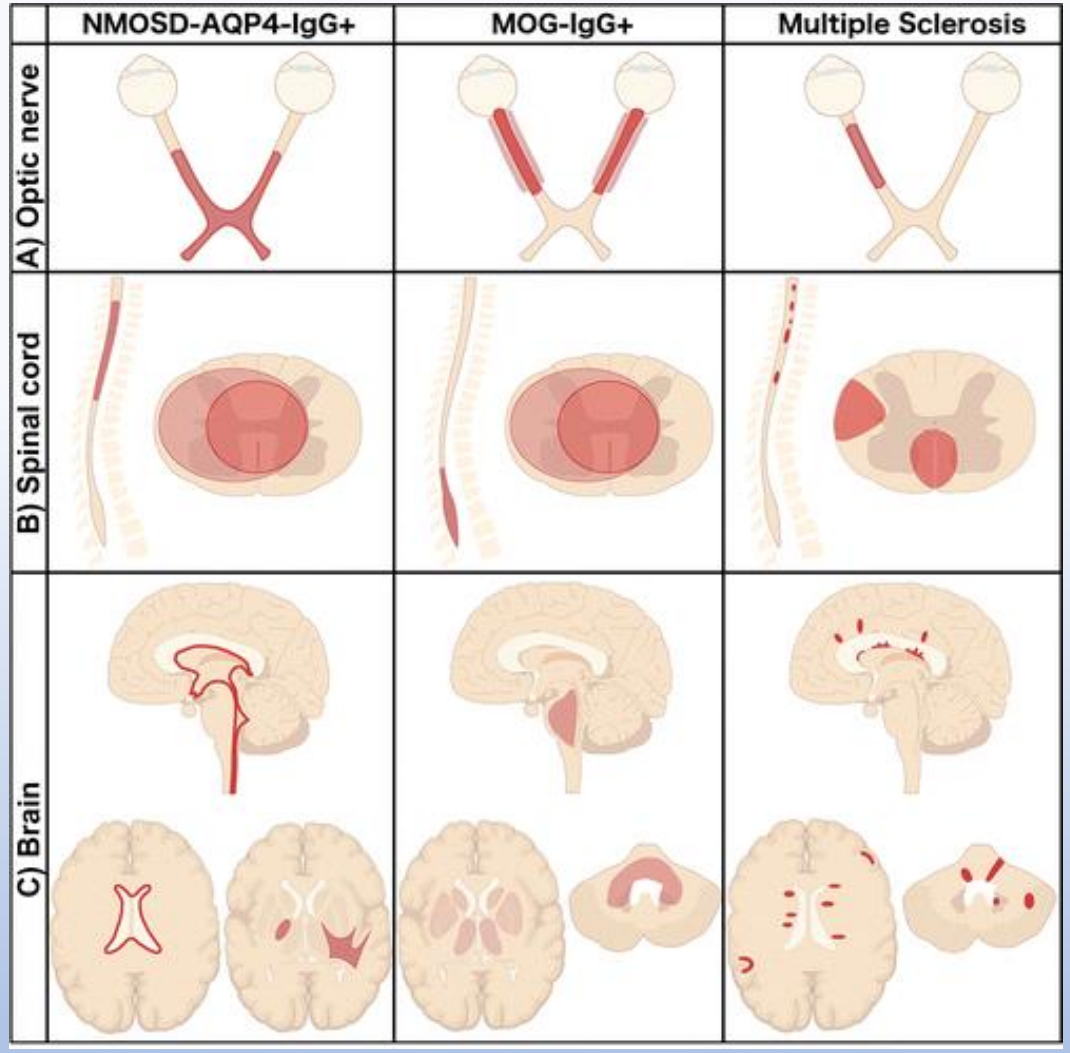
Typical spinal cord involvement

Sagittal T2-weighted image shows LETM

extending into the area postrema (arrowhead)

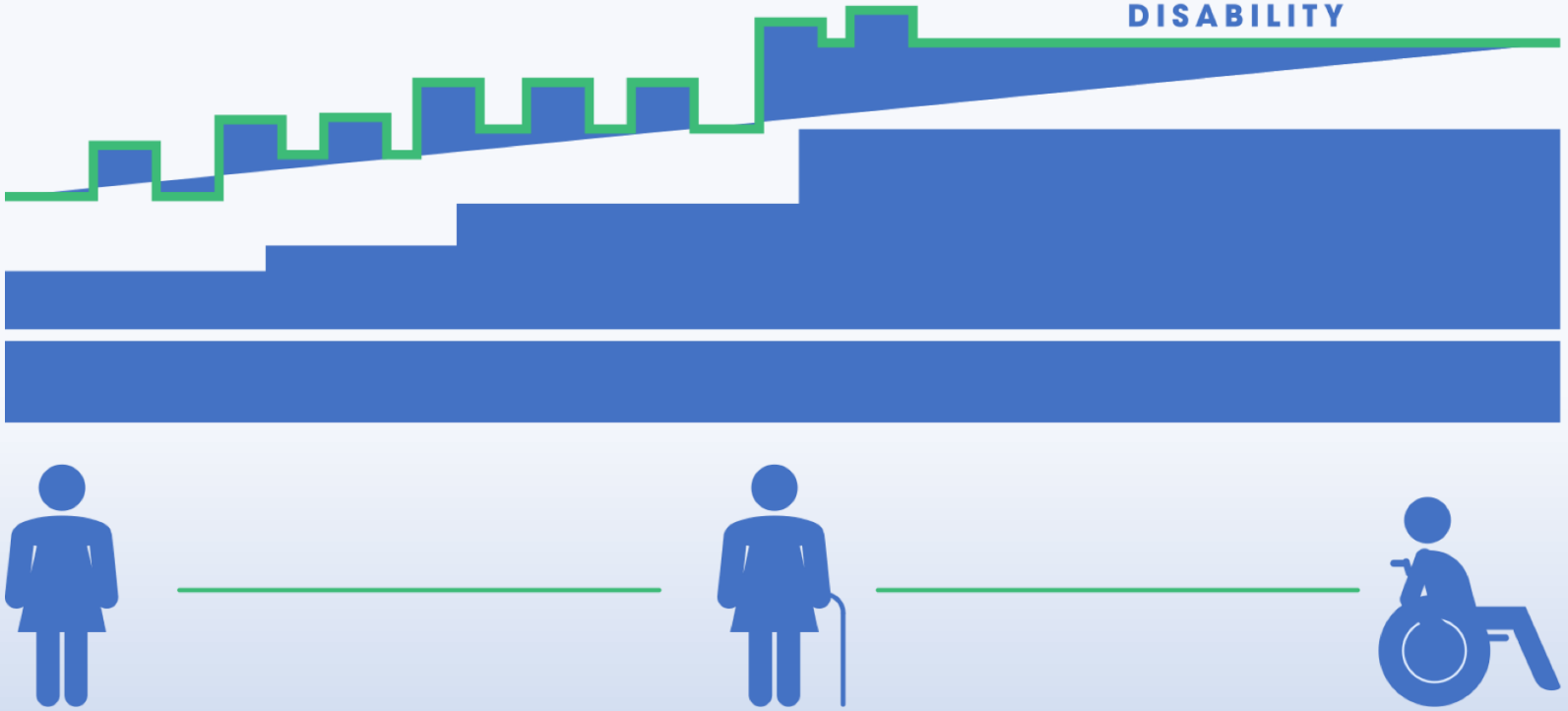
Garbugio Dutra et al.
RadioGraphics 2018

# Distinctive imaging features of ON, TM and brain lesions in AQP4-IgG–positive vs MOG-IgG–positive NMOSD & MS




Garbugio Ditra RadioGraphics 2018

# Disease pattern




**WITHIN 5 YEARS**

**50%**
of people require a wheelchair

**62%**
are functionally blind (or no useful vision)

**60%**
relapse within 1 year

**90%**
relapse within 3 year

# Comparison with MS

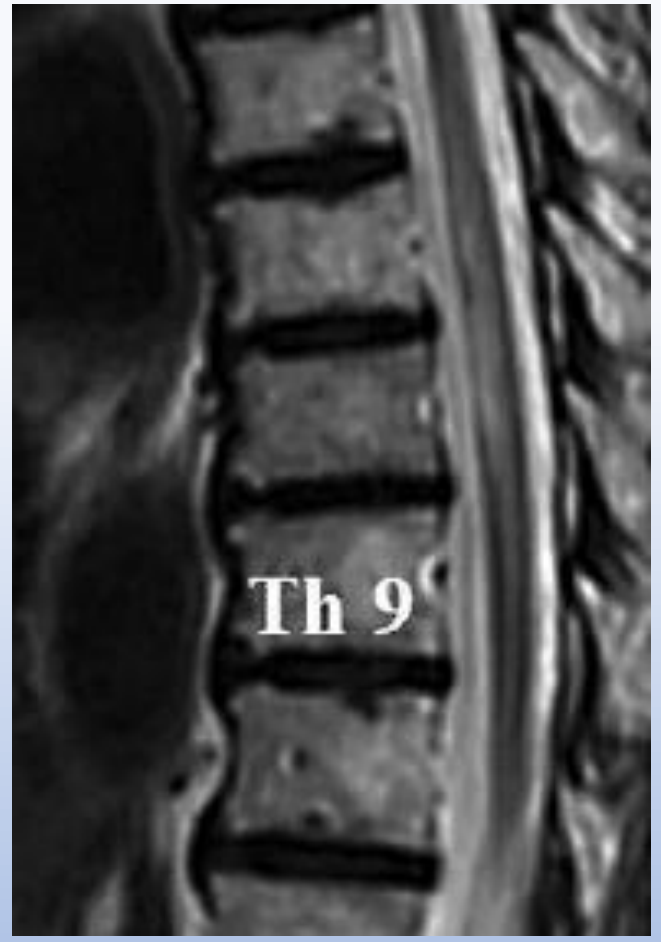
- Previously believed that NMO and MS represented one disease entity with variable phenotypes and expression,.
- NMO is distinct from RRMS with respect to pathogenesis, neuropathology and response to treatment and imaging feaures
- Rapidely sequential ON or bilateral simultaneous ON highly suggestive 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.

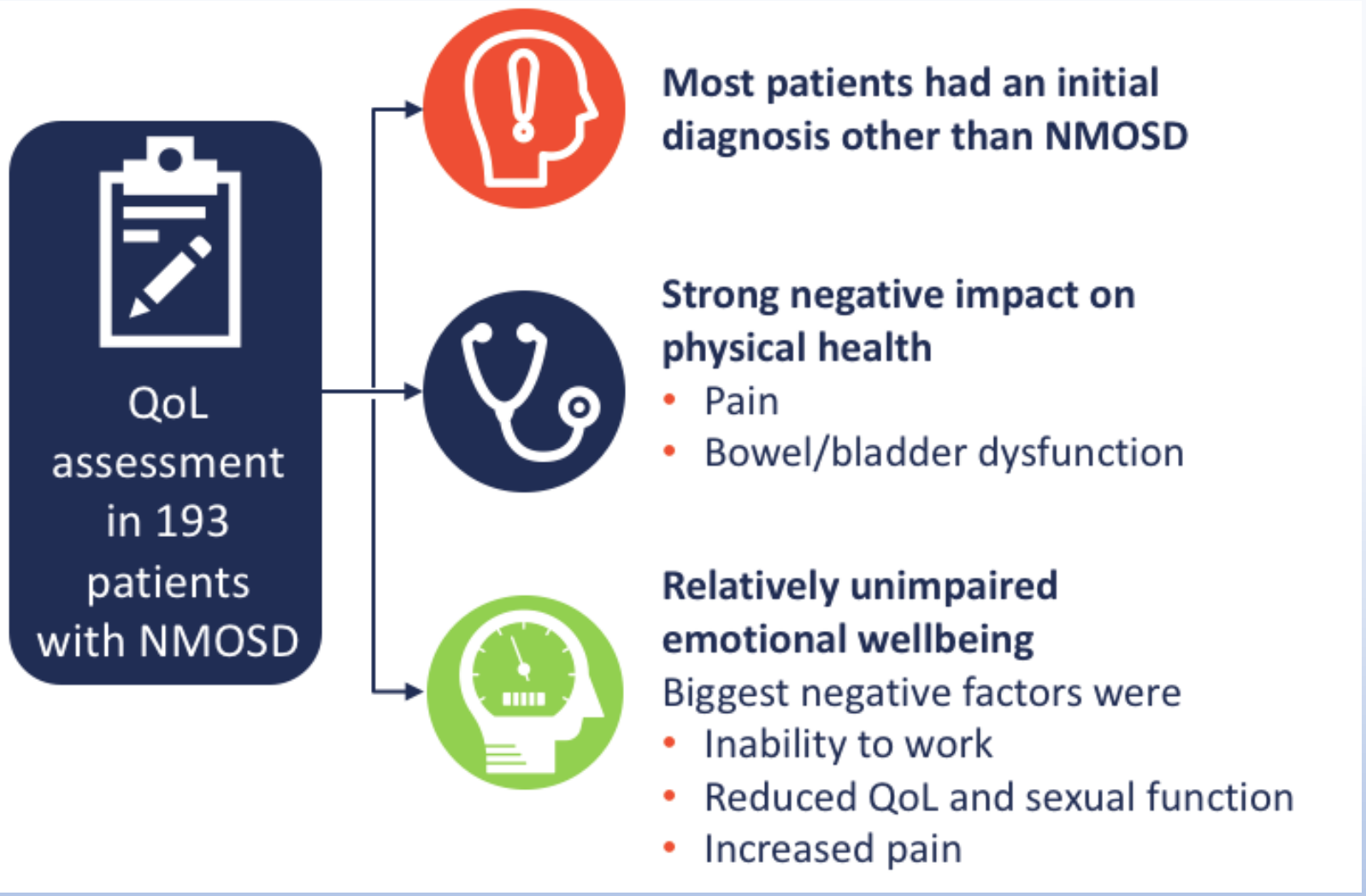
Furijawa et al. Case Rep Neurol 2020

# 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




Beekman et al. Neurology 2019

# Cases of NMOSD from the East Africa region, challenges in diagnostics and healthcare access

- 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 (immunofluorescene 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

ImmunoTargets and Therapy

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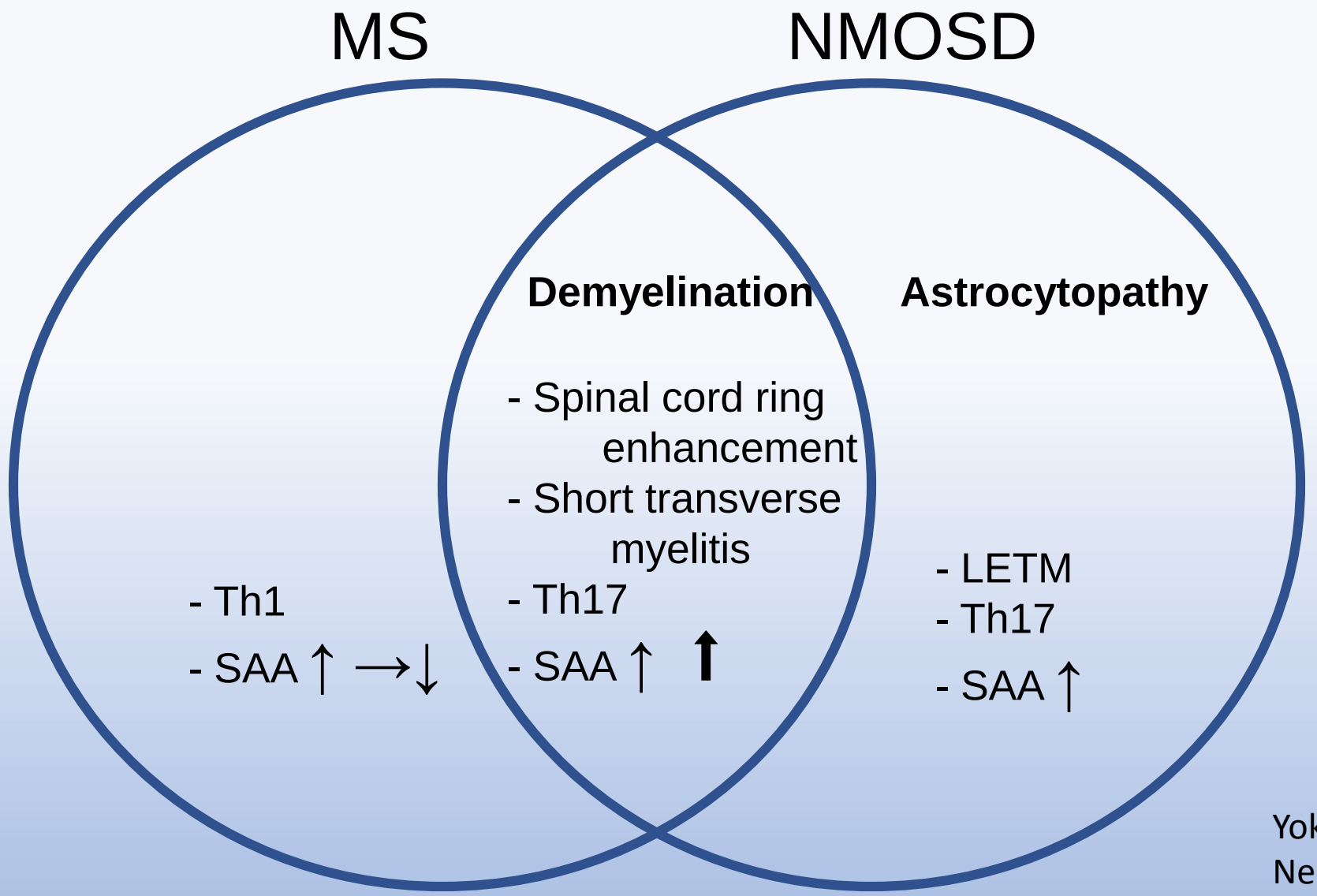
REVIEW

# 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 NMODS
- MR imaging important tool for diagnosis of NMOSD

# Similarities between NMOSD and MS




Yokote and Misuzawa
Neural Regen Res 2016