MAYO CLINIC

Diagnostic Criteria for Neuromyelitis Optica 2014

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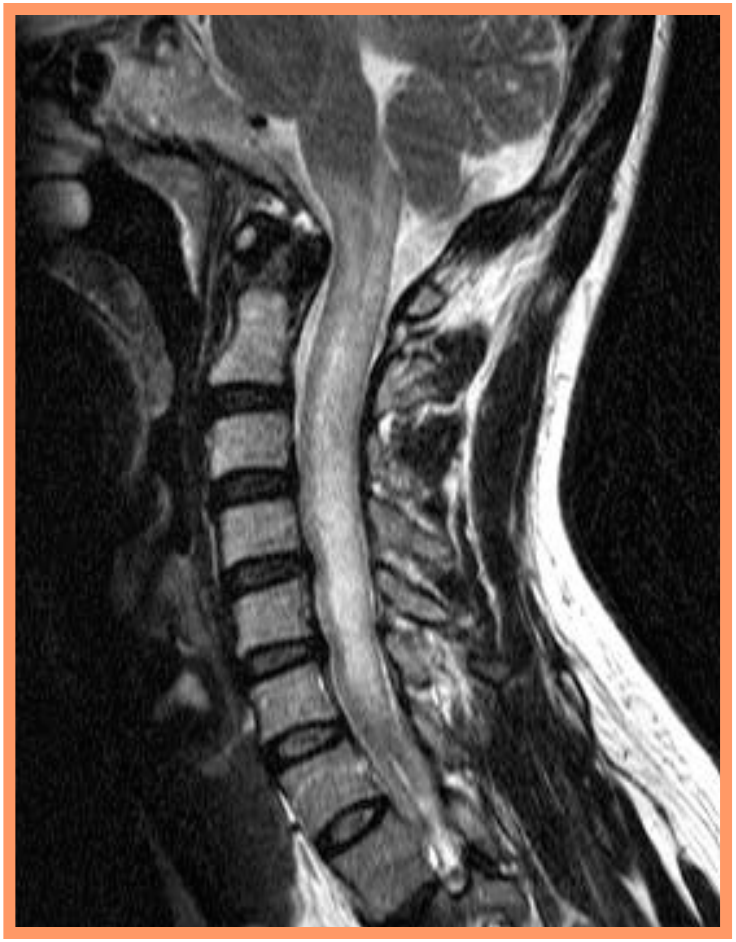
Disclosures

- Royalties related to patent for discovery of NMO-IgG
  - licensed to RSR Ltd; Oxford University
- Consulting contracts related to NMO clinical research (within past 5 years):
  - GlaxoSmithKline Pharmaceuticals
  - Elan Pharmaceuticals
  - Chord Pharmaceuticals
  - Chugai Pharmaceuticals
  - Novartis Pharmaceuticals
  - Alexion Pharmaceuticals
- Member DSMB
  - Biogen Idec (Chair)
  - Novartis
  - Mitsubishi (Chair)
- Member Attack Adjudication Committee:
  - MedImmune (Chair)

NMO Criteria (2006)

- Transverse myelitis and optic neuritis
- At least two of the following features:
  - 1) MRI brain negative/nondiagnostic for MS
  - 2) MRI spinal cord lesion extending over ≥3 vertebral segments (LETM)
  - 3) NMO-IgG seropositivity



Wingerchuk et al, Neurology, 2006

Why are current diagnostic criteria inadequate in 2014?

- Discovery of NMO-IgG
  - NMO can be recognized reliably at an earlier point
- Limited versions of NMO
  - recurrent myelitis or recurrent optic neuritis
- Brain lesions may occur
  - may be the presenting manifestations
  - may be highly suggestive or diagnostic
- Co-association of other autoimmune conditions:
  - Do they exclude NMO?

International Panel for NMO Diagnosis (IPND)

- Convened October, 2011
- Co-chairs:
  - Dean Wingerchuk
  - Brian Weinshenker
- Overall objective:
  - To revise NMO diagnostic criteria to reflect advances in:
    - Clinical and radiological spectrum
    - Serological testing

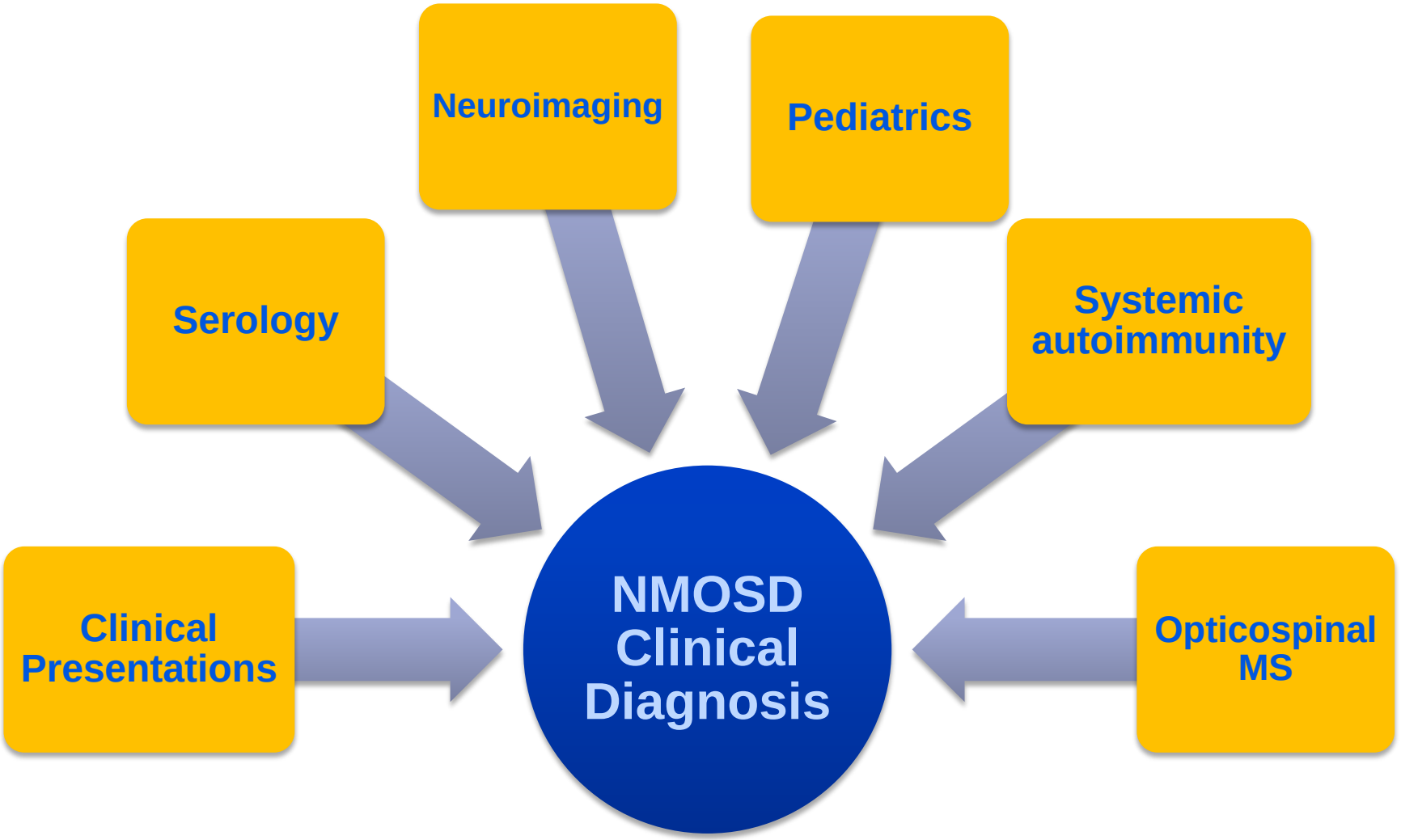
Initial IPND Consensus Principles

- Clinical diagnosis
  - AQP4 antibodies
    - *Not sufficient*
      - False positives
      - Population-based study of MS-like illness: clinical NMO 0.2%; CBA+ 0.3%; ELISA+ 0.7% (*Pittock et al. 2014 JAMA Neurol.doi:10.1001/jamaneurol.2014.1581*)
    - *Not required*
      - Differences between seronegative and seropositive poorly defined
- Use best available evidence and panel consensus

Methods

- 18 members from 9 countries
- 6 Working Groups
  - Specific charges relevant to NMO diagnosis

IPND Methods



IPND Methods

- Systematic literature review by each WG
  - Expert librarian assistance (K Wellik, Mayo Clinic)
  - Medline, EMBASE
  - 1950-2012
  - Quarterly updates to January, 2014

IPND Methods

- Stage 1
  - Roster of clinical/MRI syndromes diagnosed as NMO, NMOSD, or associated with AQP4-IgG
  - Evaluate re: inclusion and specificity
- Stage 2
  - Electronic surveys
    - Case vignettes
    - Clinical, MRI, lab, AQP4-IgG data
    - Diagnosis: definite, possible, or not NMOSD
- Stage 3
  - Data integration and refinement of draft criteria

Results:
Nomenclature

- NMOSD: unified term
- Stratified by serostatus
  - NMOSD with AQP4-IgG
  - NMOSD without AQP4-IgG (or testing unavailable)
  - Allows for future revisions
    - e.g. discovery and validation of other antibodies associated with NMOSD clinical phenotype

Revised Diagnostic Criteria:
NMOSD with AQP4-IgG

Requirements

- At least 1 core clinical characteristic
- Positive test for AQP4-IgG
- No better explanation
  - Clinical and MRI red flags

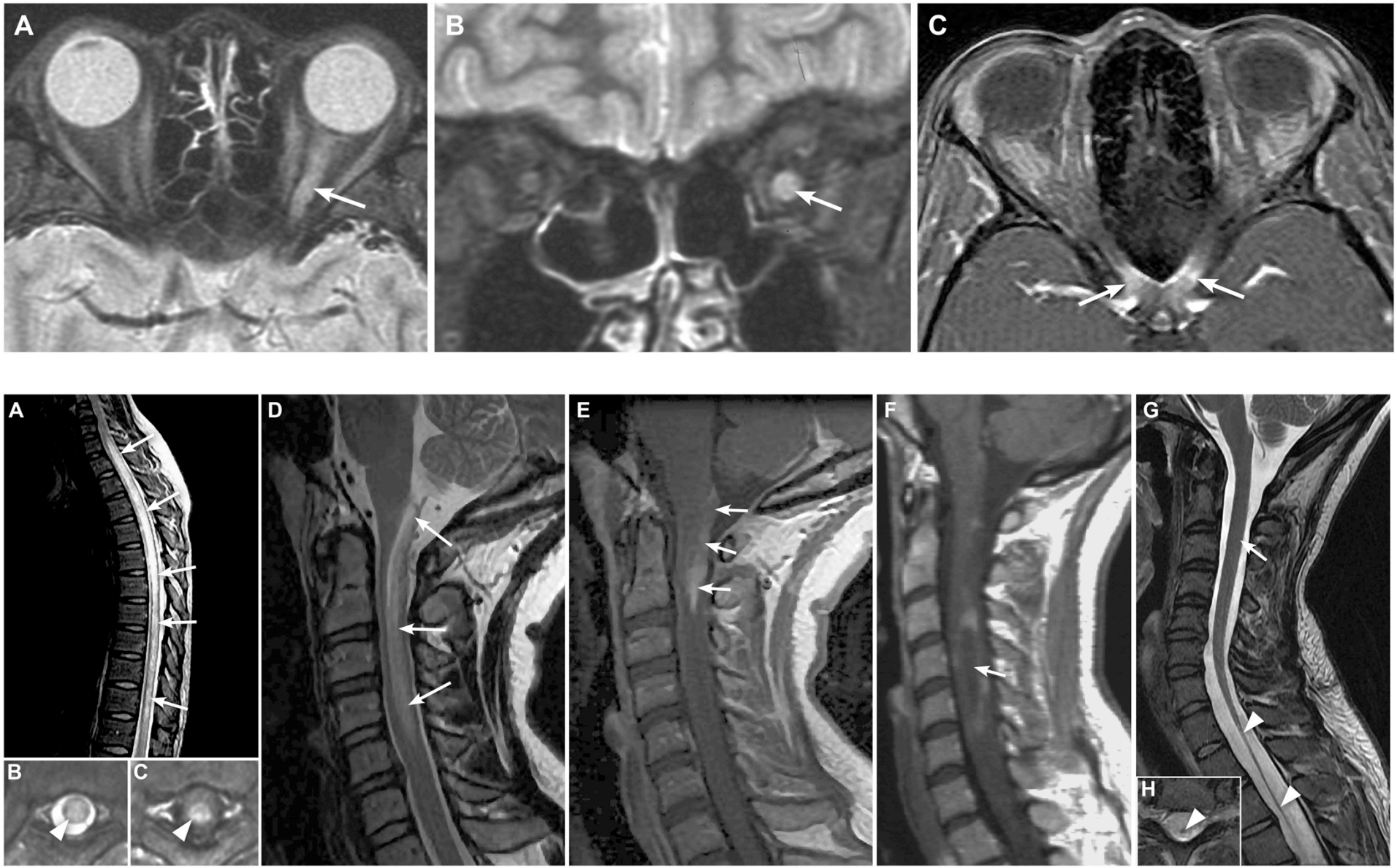
Core Clinical Characteristics

- Optic neuritis
- Acute myelitis
- Area postrema syndrome:
  - nausea/vomiting/hiccups
- Other brain stem syndrome
- Symptomatic narcolepsy or acute diencephalic syndrome with MRI lesion(s)
- Symptomatic cerebral syndrome with MRI lesion(s)

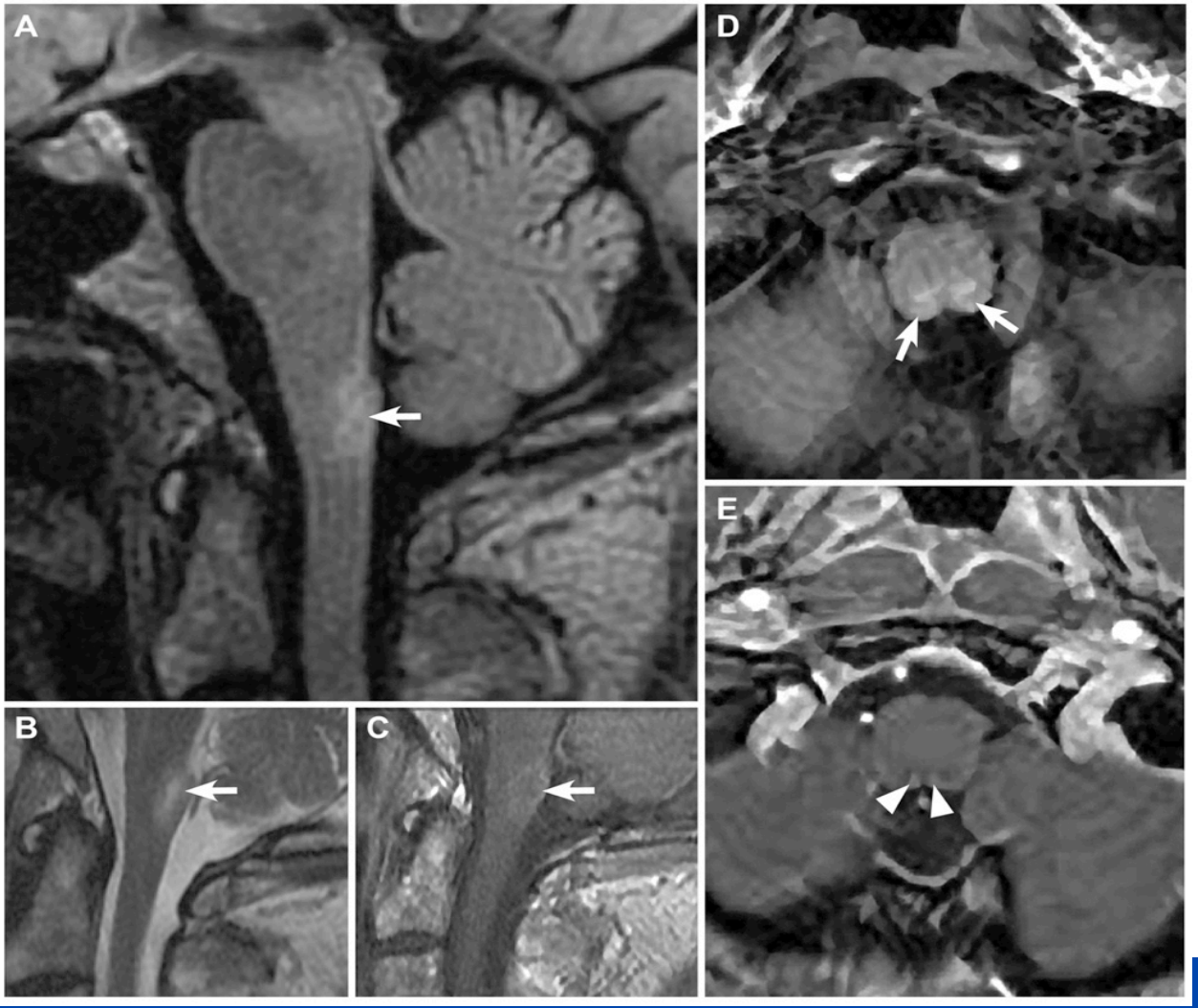
Revised Diagnostic Criteria:
NMOSD without AQP4-Ig (or unavailable)

- At least 2 core clinical characteristics all satisfying:
  - 1 of ON, myelitis, or area postrema syndrome
  - Dissemination in space
    - Isolated recurrent ON or recurrent TM do not qualify
  - Additional MRI requirements
    - AP syndrome: dorsal medulla lesion
    - Myelitis: LETM
    - ON: normal brain MRI ***OR*** >1/2 ON ***OR*** chiasm lesion
  - Negative test(s) for AQP4-IgG using best available assay, or testing unavailable
- No better explanation for the clinical syndrome

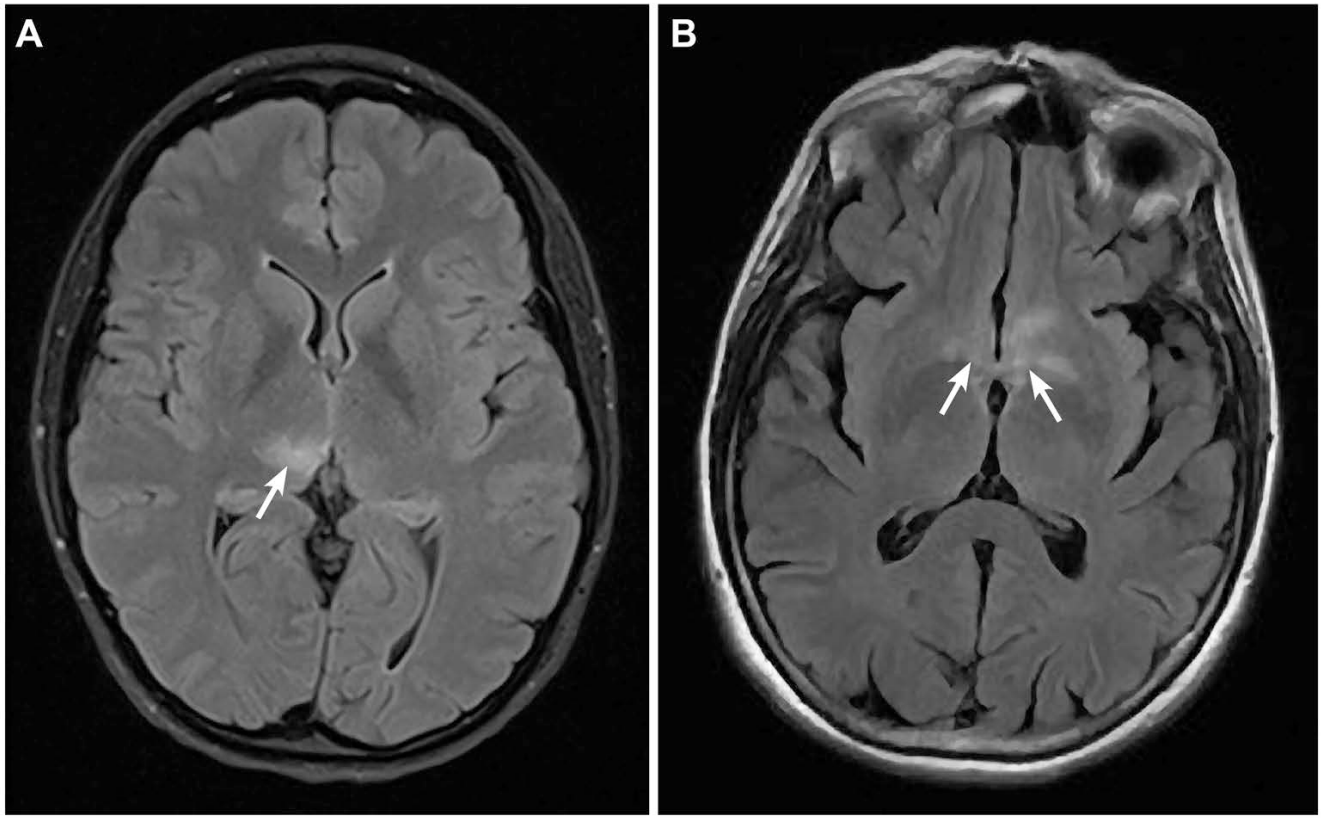
ON and Spinal Cord MRI Lesions



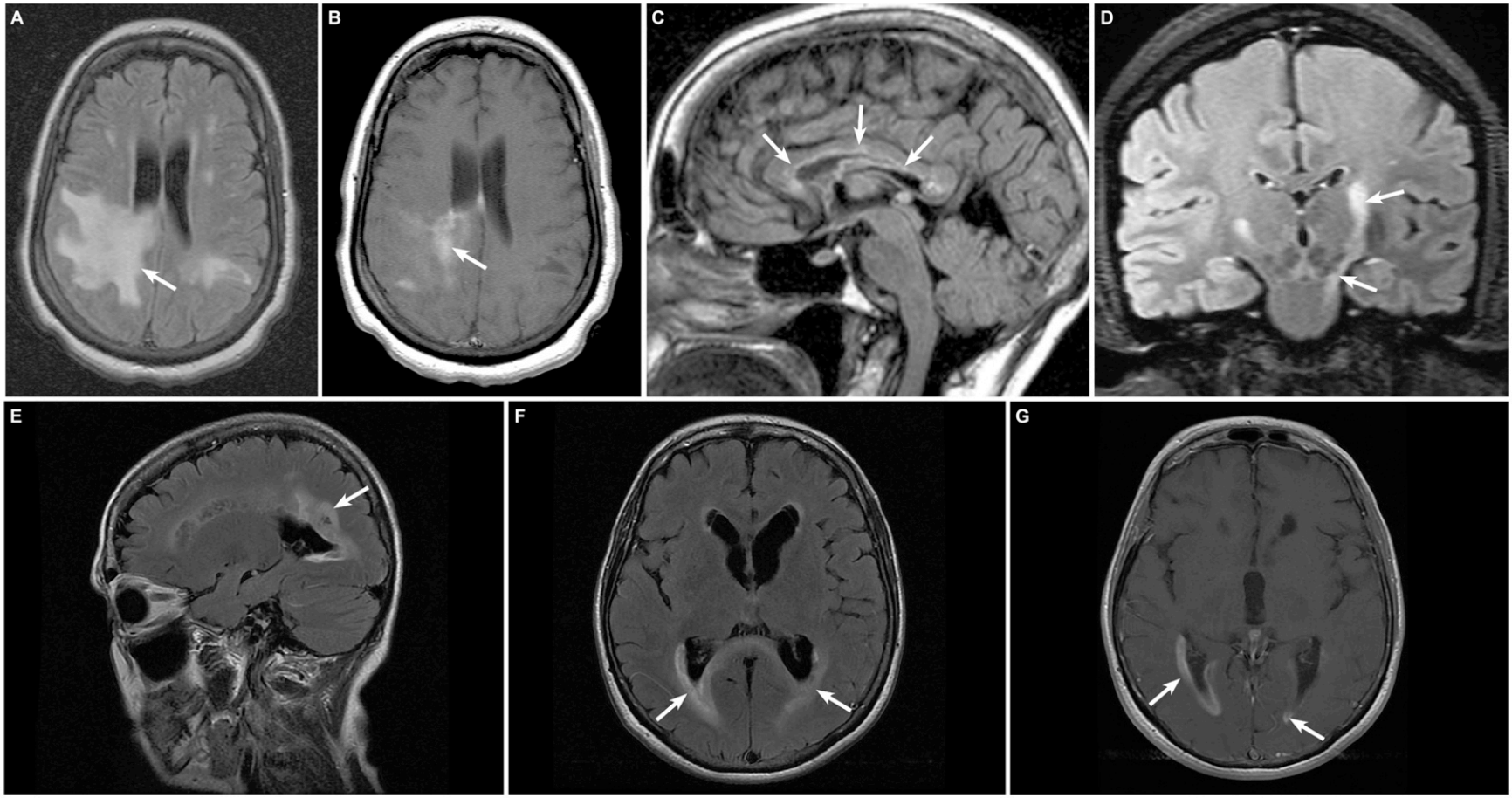
Area Postrema/Dorsal Medulla MRI Lesions



Diencephalic MRI Lesions



Cerebral MRI Lesions



Red Flags:
Clinical and Laboratory

- Clinical course/lab more typical of MS or other pathology
  - Progressive course
  - Rapid nadir (infarction)
  - Continual worsening more than 4 weeks from onset
  - Partial TM without LETM
  - CSF oligoclonal bands

- Comorbidity, established or suspected, that mimics NMOSD
  - Sarcoidosis
  - Cancer (lymphoma or CRMP-5 associated ON/myelopathy)
  - Infection with potential neurologic involvement (e.g., HIV, syphilis)

Red Flags:
Radiology

Brain

- "MS-typical" lesions
  - "Dawson's fingers"
  - adjacent to lateral ventricle temporal lobe
  - Juxtacortical lesion(s)
  - Cortical lesion(s)
- Suspicious of other pathology
  - Lesion(s) with persistent (>3 months) gadolinium enhancement

Spinal Cord

- MS-typical
  - Short cord lesion(s)
  - Predominantly (>70%) peripheral cord on axial T2
  - Asymptomatic cord lesion(s)
  - Diffuse, indistinct T2 signal change (longstanding or progressive MS)
- Suspicious of other pathology
  - Persistent (>3 months) gadolinium enhancement
  - "Tractopathy" (e.g., paraneoplastic disorder)

Pediatric NMOSD

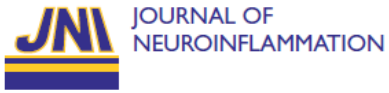
- Same criteria as adult NMOSD
- Cautions:
  - LETM in pediatric MS
- Greater incidence of cerebral presentations

Opticospinal MS

- Historically important
- Confusing terminology
  - a form of MS versus NMO versus something unique?
- Similarly defined in Asia, patients have the same disease
- “Superseded” terminology

NMO:
Heterogeneous?

Jarius *et al. Journal of Neuroinflammation* 2012, **9**:14
http://www.jneuroinflammation.com/content/9/1/14



RESEARCH Open Access

Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: A multicentre study of 175 patients

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Seropositive versus seronegative: More likely to be/have:

- ***Woman***
- ***Systemic autoimmune disease***
- ***Unilateral ON***
- ***ON OR myelitis***
- ***Relapses***

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OPEN

Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders

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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
Age, y, median (range)				
At first attack	37.5 (3-70)	37 (4-78)	32.5 (10-69)	0.0915
At sampling	42 (6-70)	49 (15-82)	38 (12-69)	0.0004
Follow-up, y, median (range)	2 (1-19)	7 (0-45)	3 (0-32)	0.0002
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

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NMO:
Beginnings of Classification of Heterogeneity?

- Seropositive NMO
- Seronegative NMO
  - False negative serologic assay
  - MS mimicking NMO
  - Other disorders that mimic NMO:
    - Sarcoidosis
    - Paraneoplastic
  - “True seronegative NMO”
    - Younger patients
    - Monophasic course
    - Less severe clinical manifestations
    - MOG antibodies?

Summary

- NMOSD is the unified term for NMO/NMOSD
- AQP4-IgG Seropositive:
  - Requires at least 1 of the 6 core clinical characteristics
- AQP4-IgG Seronegative or Unavailable:
  - At least 2 core clinical characteristics
    - 1 must be ON, acute myelitis or area postrema syndrome
    - MRI support
    - Dissemination in space

Implications to Clinical Trials

- “New disease”?
  - Estimate 2X number of cases
    - facilitates enrolment and enhances study feasibility
  - Historical data on prognosis/outcome:
    - unreliable?
- Heterogeneity in prognosis, behavior between
  - seropositive and seronegative

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- Tony Traboulsee, MD
- Paddy Waters, PhD
- Brian Weinshenker, MD
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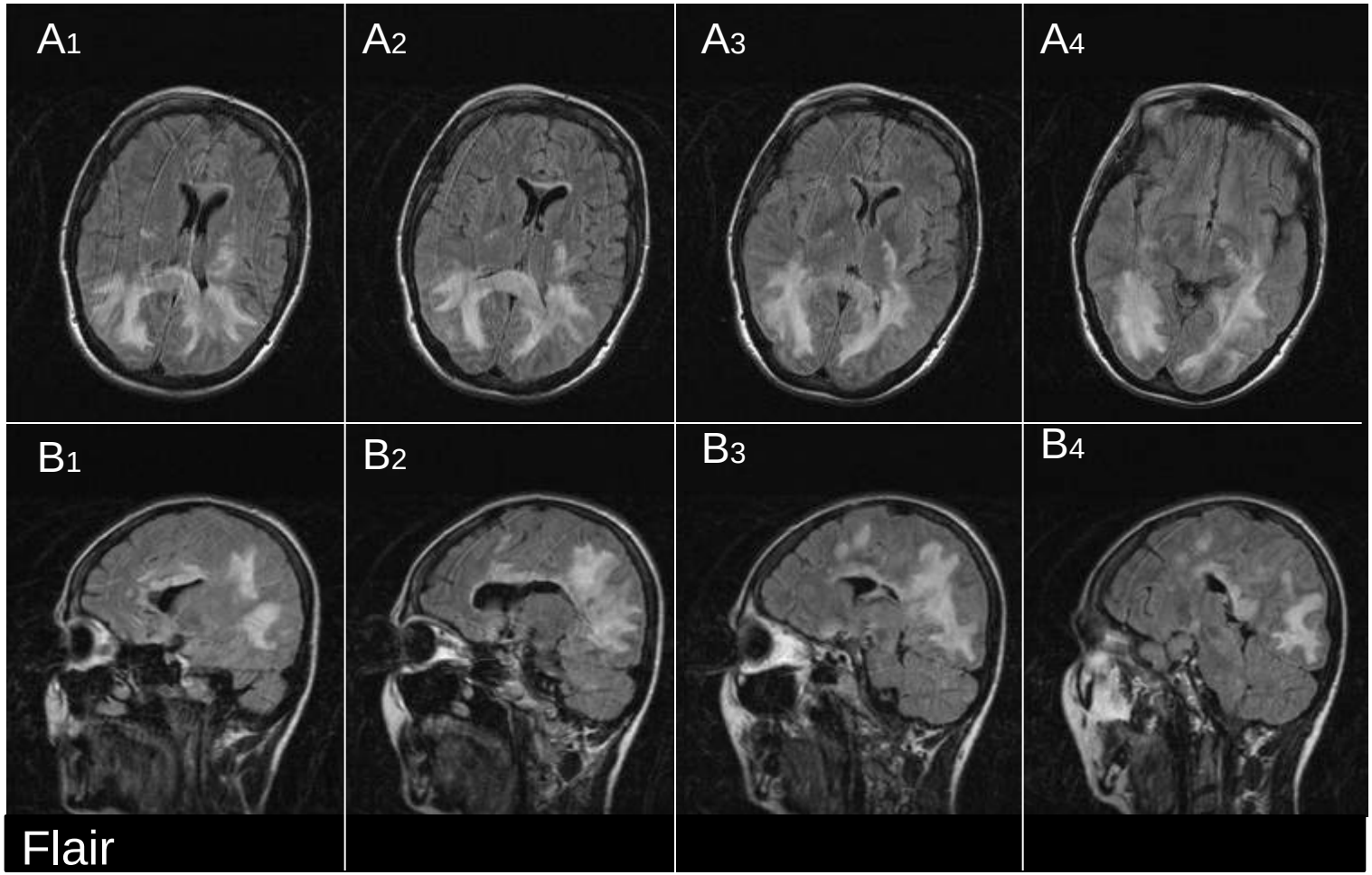
Systemic Autoimmune Disease

- NMO diagnosis allowable
- Concurrence with SLE, SS, MG increases likelihood of a diagnosis of NMO
- Association with systemic autoimmune disease more likely reflects concurrence than causation

Pathology for Diagnosis

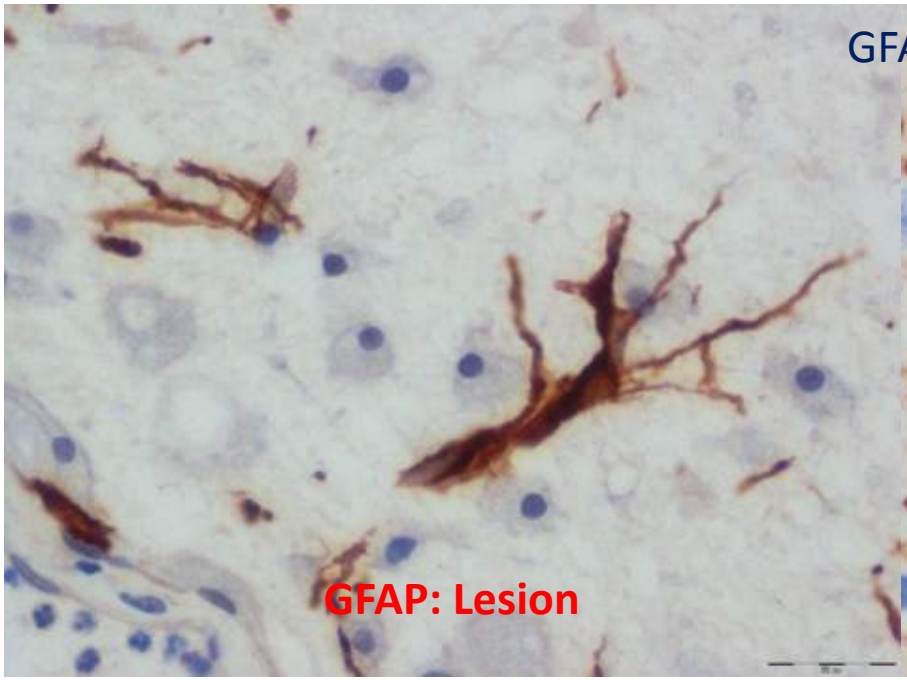
- Not routine
- AQP4-IgG obviates need for biopsy in most cases
- Atypical cases:
  - Astrocytopathy and selective AQP4 loss may
    - establish diagnosis
    - exclude other pathologies

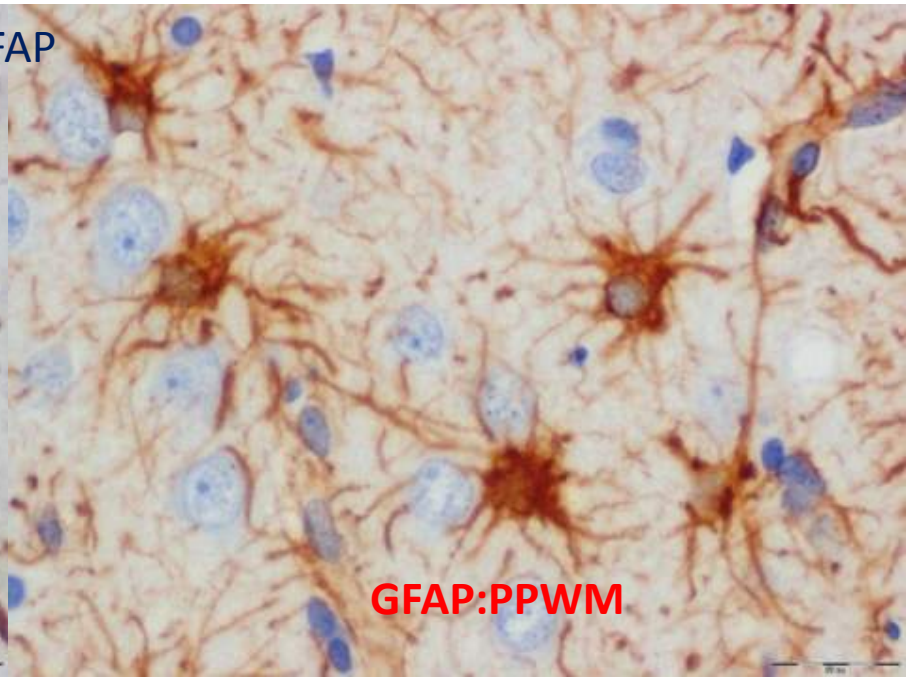


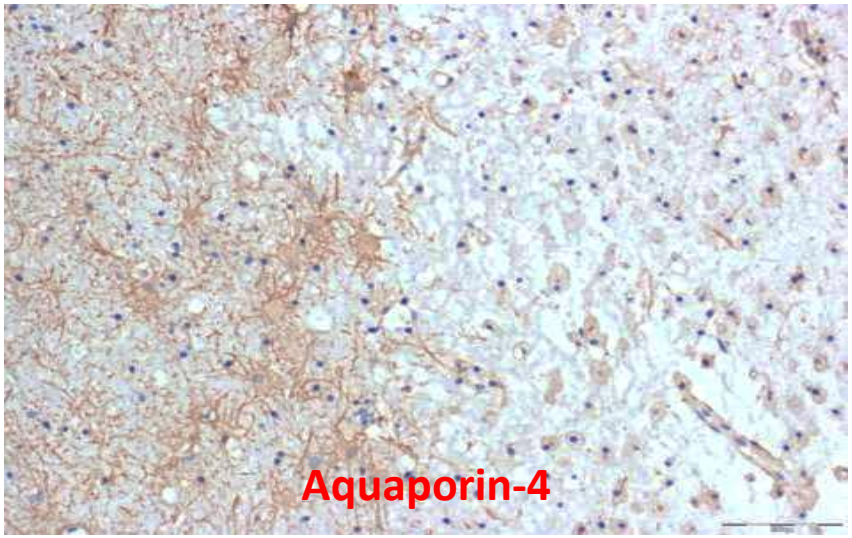
- 37 years old female
- Numerous relapses during the last years
- Despite treatment with:

  Interferon-ß, Mitoxantrone or natalizumab

Lee et al., Neuropathol. Appl. Neurobiol., 2010







AQP4-IgG+ Diagnosis NMO

Lee et al., Neuropathol. Appl. Neurobiol., 2010

EDITORIAL

The two faces of neuromyelitis optica

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- AQP4+, relapsing, older, female predominant, autoimmune
- MOG+, monophasic, younger, equal sex ratio, "ADEM-like"