UT Southwestern
O'Donnell Brain Institute

Assessing Condition-Specific Knowledge in Patients with Rare Neuroimmune Disorders

Background

Rare Neuroimmune Disorders (RNDs): AFM, TM, ON, ADEM, MOGAD, NMOSD

Advancements in Diagnosis: Antibody testing (MOG, AQP4) has revolutionized diagnostic approaches

Challenges: Overlapping symptoms make diagnosis complex

Seronegative cases add to the difficulty

Diagnosis: Having an accurate diagnosis is critical for effective management and treatment

Background

Confusion around diagnosis: Misdiagnosis (Guillain-Barre, MS). Revision of diagnosis.

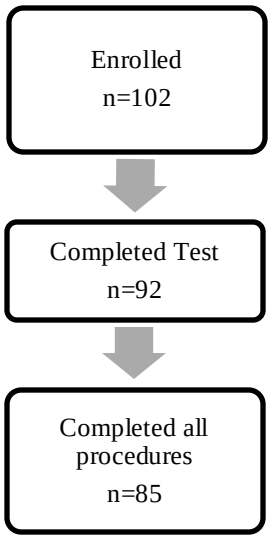
Health Literacy and Education: These have been shown to be predictors of patient outcomes and disease management

Study Aim: To assess condition-specific knowledge in RND patients

Methods

- A questionnaire to assess condition-specific knowledge in patients with rare neuroimmune conditions was developed with the following sections-
- **Demographics: Age, gender, educational attainment**
- **Test of Knowledge:**
  - **Domains covered: localization, etiology, symptoms, relapse.**
- **Medical Term Recognition Test (METER)**
- **Patient-Determined Disease Step Test (PDDST)**
- Patients with RNDs such as AFM, TM, ADEM, MOGAD, and NMOSD, were able to take the test virtually in the clinic or at home using a Redcap survey

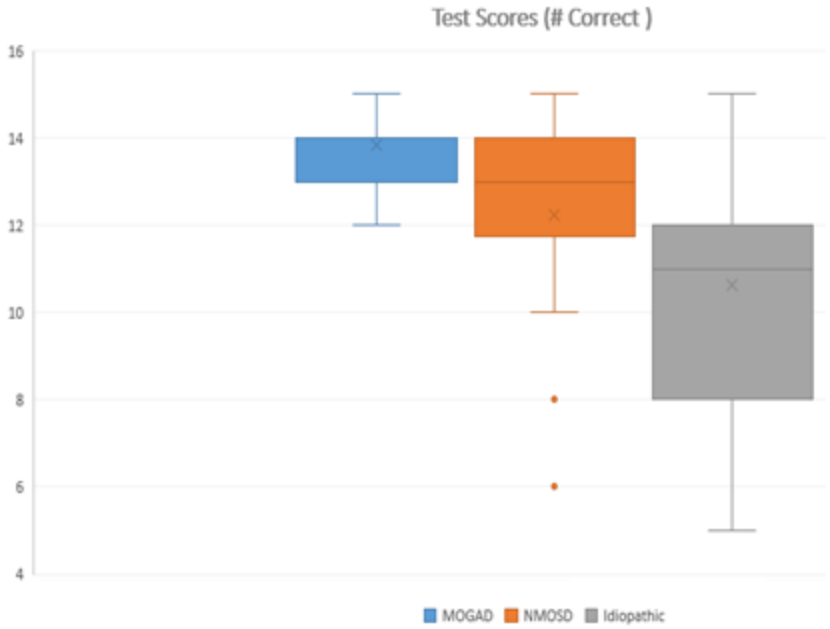
Results

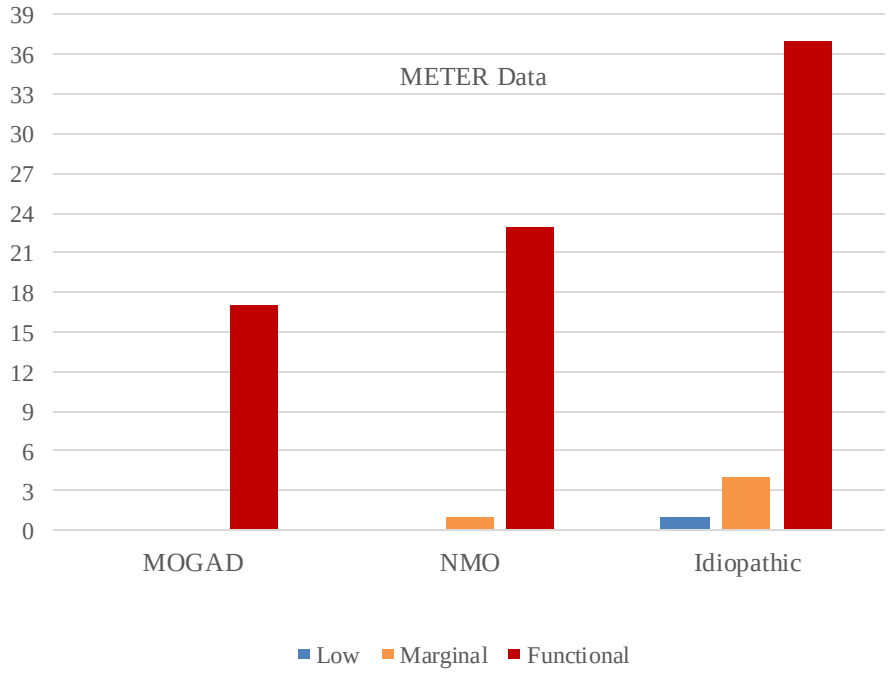


Demographics	
Age, years (median, range)	56 (20-80)
Sex (% Female)	65 (73)
Race/Ethnicity (%)	
Asian	1. (1.1)
Black/African American	14 (15.7)
Hispanic/Latin (%)	14 (15.7)
White	61 (68.5)
English as Primary Language (%)	85 (95.5)
Educational Attainment	
Less than 16 years (%)	24 (27)
16+ years (%)	61 (68.5)

Reported Diagnosis	
NMOSD	26 (29.2)
MOGAD	19 (21.3)
ADEM	2 (2.2)
AFM	2 (2.2)
TM	51 (57.3)
ON	6 (6.7)
More than One	12 (13.5)

Results





- Analysis for correlation of test scores with age, duration since diagnosis, health literacy, and self-reported disability are ongoing

Conclusion

- Individuals with idiopathic conditions (TM+ ADEM) scored lower on the test when compared to better characterized conditions like NMOSD and MOGAD

- Our population had a proportion of individuals with higher educational attainment and functional health literacy which may confound the generalizability of our findings in standard clinical practice

- Patients with vision loss may available additional barriers to study completion.

- Individuals with idiopathic conditions may benefit from targeted education about their diagnosis and relapse risk.

- Future analysis will assess the current relation of health literacy, education, disability scores with test performance

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Diagnostic Criteria and Rare Neuroimmune Disorders

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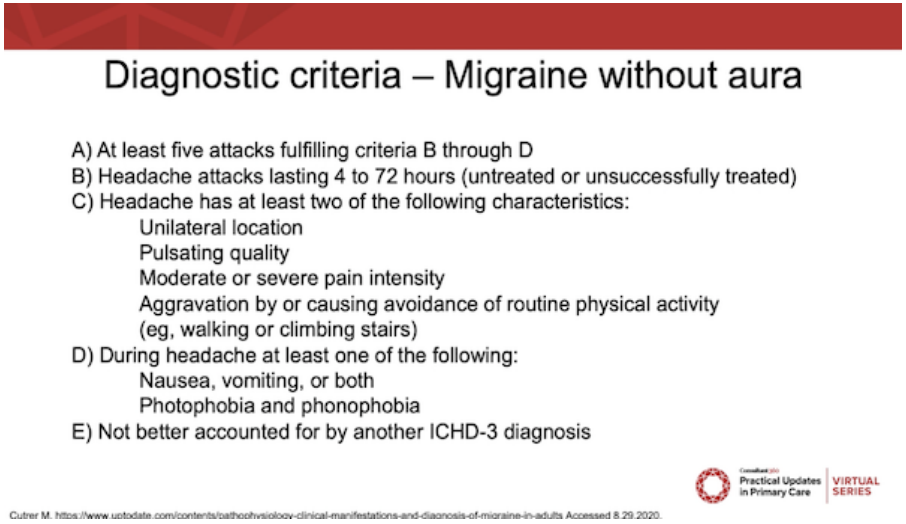
Diagnostic Criteria

- A set of signs, symptoms, and diagnostic tests used to facilitate accurate diagnosis of a condition.
- Often developed by a group of experts by consensus, and multiple revisions.
- Frequently updated to reflect advances in the field, often with a goal of more accurate and earlier diagnosis.



MS Criteria evolution over time

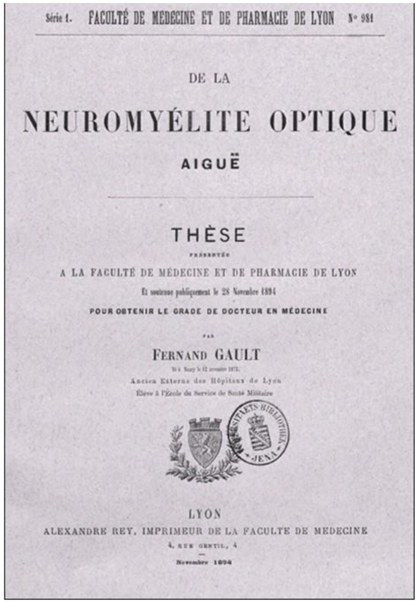
McDonald 2001 [6]	McDonald 2005 [15]	McDonald 2010 [7]	McDonald 2017 [9]
Three of the four following conditions: (1) At least one Gd-enhancing lesion or at least nine T2 hyperintense lesions (2) At least one infratentorial lesion must be present (3) At least one subcortical lesion must be present (4) At least three periventricular lesions must be present *Spinal cord lesion can substitute for a brain lesion	2001 definitions *plus* A spinal cord lesion can be considered equivalent to a brain infratentorial lesion A Gd-enhancing spinal cord lesion is considered to be equivalent to an enhancing brain lesion, and individual spinal cord lesions can contribute together with individual brain lesions to reach the required number of T2 lesions	≥1 T2 lesion in at least two of four areas: periventricular, juxtacortical, infratentorial, or spinal cord *A Gd-enhancing lesion not required for DIS *If subject has a brainstem or spinal cord lesion that is the symptomatic lesion, it is excluded	2010 criteria *plus* Cortical lesions can be used in fulfilling MRI criteria for dissemination in space No distinction between symptomatic and asymptomatic MRI lesions is required

Continued revisions to the MS criteria have allowed patients to fulfill 'dissemination in space and time' earlier in the disease, allowing for earlier diagnosis.

Evolution of NMOSD criteria

- Devic and Gault: Seminal paper in 1894 describing an individual's clinical course and pathology, previously reported cases.

- In 20th century, the definition of NMO remained controversial:
    - Distinction from MS.
    - Relapsing or monophasic disease
    - Myelitis + Optic neuritis, without brain or brainstem involvement.
    - Bilateral vs. Unilateral optic neuritis.



Série 1. FACULTÉ DE MEDECINE ET DE PHARMACIE DE LYON N° 981

DE LA

NEUROMYÉLITE OPTIQUE

AIGUË

THÈSE

PRÉSENTÉE

A LA FACULTÉ DE MÉDECINE ET DE PHARMACIE DE LYON

Et soutenue publiquement le 28 Novembre 1894

POUR OBTENIR LE GRADE DE DOCTEUR EN MÉDECINE

PAR

FERNAND GAULT

Ancien Externe des Hôpitaux de Lyon

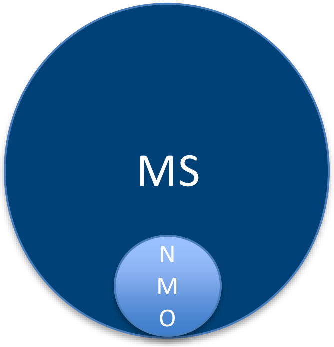
Élève à l'École du Service de Santé Militaire

LYON

ALEXANDRE REY, IMPRIMEUR DE LA FACULTE DE MEDECINE

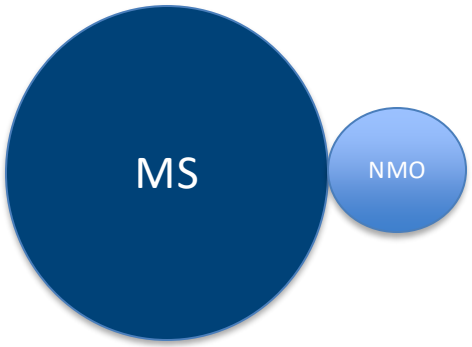
4, RUE GENTIL, 4

Novembre 1894



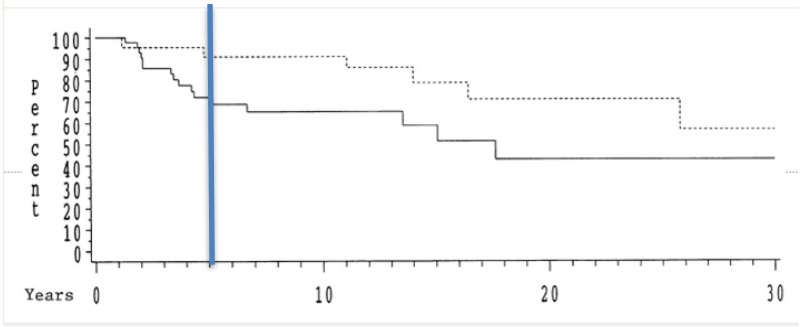
1999 NMO Criteria.

- Based on a review of cases evaluated at Mayo Clinic.
- Defined the disorder clinically.
  - Required both optic neuritis and acute myelitis.
  - Absence of brain abnormalities.



Diagnosis requires all absolute criteria *and* one major supportive criterion *or* two minor supportive criteria
Absolute criteria
1. Optic neuritis
2. Acute myelitis
3. No evidence of clinical disease outside of the optic nerve or spinal cord
Supportive criteria
Major
1. Negative brain MRI at onset (does not meet criteria of Paty et al.[10]) (25/28 patients)
2. Spinal cord MRI with signal abnormality extending over ≥3 vertebral segments (21/23 patients)
3. CSF pleocytosis of >50 WBC/mm^3 *OR* >5 neutrophils/ mm^3 (20/54 patients)
Minor
1. Bilateral optic neuritis (59/71 patients)
2. Severe optic neuritis with fixed visual acuity worse than 20/200 in at least one eye (31/69 patients)
3. Severe, fixed, attack-related weakness (MRC grade ≤2) in one or more limbs (32/71 patients)

Figure 3. Survival analysis of patients with a monophasic (dashed line) and relapsing (solid line) course.



Wingerchuk et al. Neurology 1999.

Discovery of Aquaporin-4 antibody led to revisions in NMO criteria

- Broadening of the phenotype: brain and brainstem lesions!
- AQP4+ patients may be diagnosed earlier in their course (after a single episode of optic neuritis or myelitis).

Table 1 NMOSD diagnostic criteria for adult patients

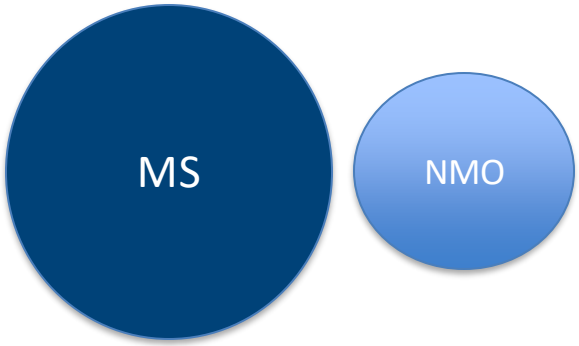
Diagnostic criteria for NMOSD with AQP4-IgG
1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses[a]

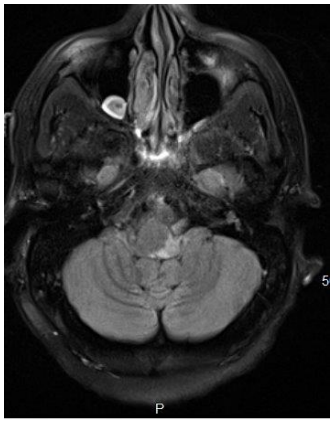
Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status
1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
   a. At least 1 core clinical characteristic must be optic neuritis, acute 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[a]

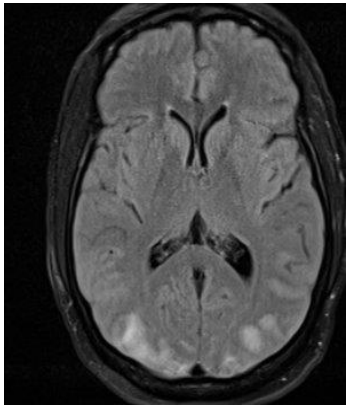
Core clinical characteristics
1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions (figure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

Abbreviations: AQP4 = aquaporin-4; IgG = immunoglobulin G; LETM = longitudinally extensive transverse myelitis lesions; NMOSD = neuromyelitis optica spectrum disorders.
[a] See table 2 and text discussion on serologic considerations for recommendations regarding interpretation of clinical and serologic testing.







Wingerchuk et al. Neurology 2015.

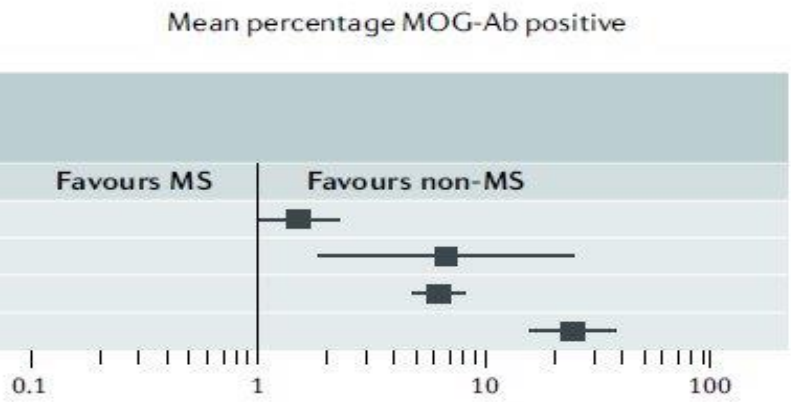
MOG Antibodies: Another Story

Early studies of MOG antibodies suggested they were found in high rates in patients with MS, but also in healthy individuals (not an ideal disease marker).

Improved testing (cell-based assays) revealed with MOG antibodies are present in high numbers in patients with non-MS demyelinating disorders.

b

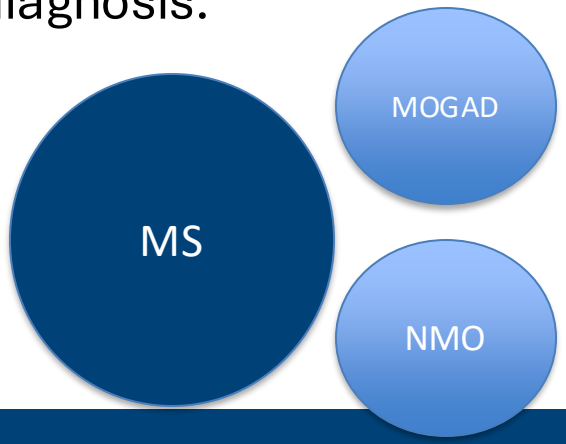
Assay	Studies	Patients with MOG-Ab positive non-MS	Patients with MOG-Ab positive MS
AQP4-Ab negative other demyelinating disease versus MS			
IB/ELISA	6	39/240 (16%)	77/677 (11%)
RIA	1	13/101 (13%)	3/140 (2%)
CBA-FACS	19	265/997 (27%)	75/1380 (5%)
CBA-IF	23	550/1918 (29%)	22/1353 (2%)



Reindl and Waters. Nat Rev Neurol, 2019.

2023 MOGAD criteria seek to define another new disorder.

- Define typical features of MOGAD.
- Recommend reviewing supportive features in patients with lower titers.
- Identify red flags that may suggest an alternate diagnosis.



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 • ≥1 supporting clinical or MRI feature
		Positive without reported titre	
		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¶¶			

***Panel 3*: Red flags against a diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease**

- Progressive neurological impairment in the absence of attacks
- Rapid worsening of clinical deficits from onset to nadir within minutes to hours
- No improvement following treatment with high-dose corticosteroids for an acute attack
- MRI findings of well circumscribed T2-hyperintense lesions in a pattern meeting dissemination in space criteria for multiple sclerosis, especially when accompanied by CSF oligoclonal bands and by the accrual over time of new silent T2-hyperintense focal lesions and retention of most previous T2-hyperintense lesions
- Lesion contrast enhancement that persists for 6 months or more.[41]

Banwell et al. Lancet Neurol 2023.

ADEM criteria (2013)

- Define ADEM clinically based on:
  - Presence of confusion, mental status changes (encephalopathy).
  - MRI with multiple lesions (may include brain or spine).
  - Stability after 3-month period.

- These may distinguish ADEM from multiple sclerosis, but do not necessarily exclude mimics of idiopathic ADEM (such as MOGAD).

Pediatric ADEM (all are required)

- A first polyfocal, clinical CNS event with presumed inflammatory demyelinating cause
- Encephalopathy that cannot be explained by fever
- No new clinical and MRI findings emerge three months or more after the onset
- Brain MRI is abnormal during the acute (three-month) phase.
- Typically on brain MRI:
  - Diffuse, poorly demarcated, large (>1–2 cm) lesions involving predominantly the cerebral white matter
  - T1 hypointense lesions in the white matter are rare
  - Deep grey matter lesions (e.g. thalamus or basal ganglia) can be present

- Krupp et al. MSJ 2013.

Idiopathic TM Criteria (2002)

Table 1 *Criteria for idiopathic acute transverse myelitis*

Inclusion criteria	Exclusion criteria
Development of sensory, motor, or autonomic dysfunction attributable to the spinal cord	History of previous radiation to the spine within the last 10 y
Bilateral signs and/or symptoms (though not necessarily symmetric)	Clear arterial distribution clinical deficit consistent with thrombosis of the anterior spinal artery
Clearly defined sensory level	Abnormal flow voids on the surface of the spinal cord c/w AVM
Exclusion of extra-axial compressive etiology by neuroimaging (MRI or myelography; CT of spine not adequate)	Serologic or clinical evidence of connective tissue disease (sarcoidosis, Behçet's disease, Sjögren's syndrome, SLE, mixed connective tissue disorder, etc.)*
Inflammation within the spinal cord demonstrated by CSF pleocytosis *or* elevated IgG index *or* gadolinium enhancement. If none of the inflammatory criteria is met at symptom onset, repeat MRI and lumbar puncture evaluation between 2 and 7 d following symptom onset meet criteria	CNS manifestations of syphilis, Lyme disease, HIV, HTLV-1, *Mycoplasma*, other viral infection (e.g. HSV-1, HSV-2, VZV, EBV, CMV, HHV-6, enteroviruses)*
Progression to nadir between 4 h and 21 d following the onset of symptoms (if patient awakens with symptoms, symptoms must become more pronounced from point of awakening)	Brain MRI abnormalities suggestive of MS*
	History of clinically apparent optic neuritis*

*Do not exclude disease-associated acute transverse myelitis.

AVM = arteriovenous malformation; SLE = systemic lupus erythematosus; HTLV-1 = human T-cell lymphotropic virus-1; HSV = herpes simplex virus; VZV = varicella zoster virus; EBV = Epstein–Barr virus; CMV = cytomegalovirus; HHV = human herpes virus.

Transverse Myelitis Consortium Working Group. Neurology 2002.

Acute Flaccid Myelitis Criteria

- AFM can present with involvement in a single limb and without a sensory level, which should inform new myelitis criteria.

***Table 1** Criteria for idiopathic acute transverse myelitis*

Inclusion criteria
Development of sensory, motor, or autonomic dysfunction attributable to the spinal cord
Bilateral signs and/or symptoms (though not necessarily symmetric)
Clearly defined sensory level
Exclusion of extra-axial compressive etiology by neuroimaging (MRI or myelography; CT of spine not adequate)
Inflammation within the spinal cord demonstrated by CSF pleocytosis *or* elevated IgG index *or* gadolinium enhancement. If none of the inflammatory criteria is met at symptom onset, repeat MRI and lumbar puncture evaluation between 2 and 7 d following symptom onset meet criteria
Progression to nadir between 4 h and 21 d following the onset of symptoms (if patient awakens with symptoms, symptoms must become more pronounced from point of awakening)

*Do not exclude disease-associated acute transverse myelitis.

AVM = arteriovenous malformation; SLE = systemic lupus erythematosu
pes simplex virus; VZV = varicella zoster virus; EBV = Epstein–Barr vir

Diagnostic items	Definite	Probable	Possible	Uncertain
H1: Acute onset of limb(s) weakness (period from onset to nadir: hours to 10 days)	P	P	P*	P
H2: Prodromal fever or illness†	P/A	P/A	P/A	P
E1: Weakness involving one or more limbs, neck, face, or cranial nerves	P	P	P*	P
E2: Decreased muscle tone in at least one weak limb	P	P	P/A	P
E3: Decreased or absent deep tendon reflexes in at least one weak limb‡	P	P	P/A	P
MRI: Spinal cord lesion with predominant grey matter involvement, with or without nerve root enhancement§	P	P	P	ND
CSF: Pleocytosis (white cell count >5 cells/L)¶	P	A or ND	P/A or ND	P/A or ND

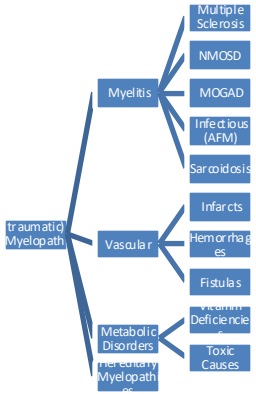
Factors that might suggest an alternative diagnosis

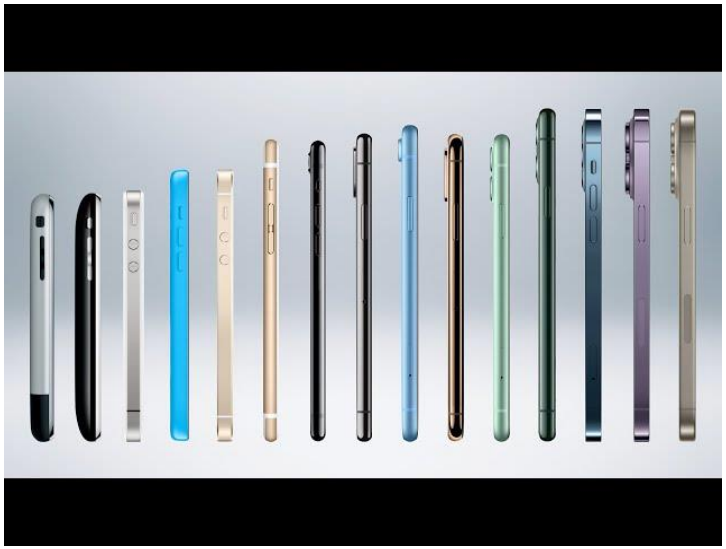
1. Encephalopathy that cannot be explained by fever, illness, respiratory distress, metabolic abnormalities, or medications
2. Presence of sensory deficits on examination||
3. Presence of lesions in supratentorial white matter or cortex, which should prompt consideration of ADEM, MOG-antibody associated disease, neuromyelitis optica spectrum disorder, encephalomyelitis, and others
4. Absence of CSF pleocytosis, which should prompt consideration of Guillain-Barré syndrome, botulism, ischaemic cord lesions, and others
5. Positive serum aquaporin-4 (AQP-4) antibody, which would exclude AFM
6. Positive serum MOG antibody, which would suggest MOG-antibody associated disease||

Murphy et al. Lancet 2021

Also, since 2002...

- AQP4 and MOG Antibody define new demyelinating disorders, which cause myelitis.
- Better recognition of sarcoidosis.
- Better classification of spinal cord infarcts, dural AV fistulas.
- Acute Flaccid Myelitis: motor predominant, asymmetric presentation in conflict with criteria.





New Criteria for Idiopathic Myelitis Must:

- Define clinical symptoms suggestive of myelitis
- Define the typical progression of myelitis (onset to nadir).
- Propose a diagnostic framework for determining etiology.
- Define 'red flags' for mimics of myelitis.
- Provide a definition for idiopathic myelitis.

Thank you!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