Neuro Talk

Updates in MOGAD

Insights in Mechanism and Diagnosis

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Scope of Talk

- Importance of MOGAD
- Structure and function of MOG
- Pathogenesis of MOGAD
- Clinical features
- Diagnosis
- Treatment

Introduction

Importance of MOGAD

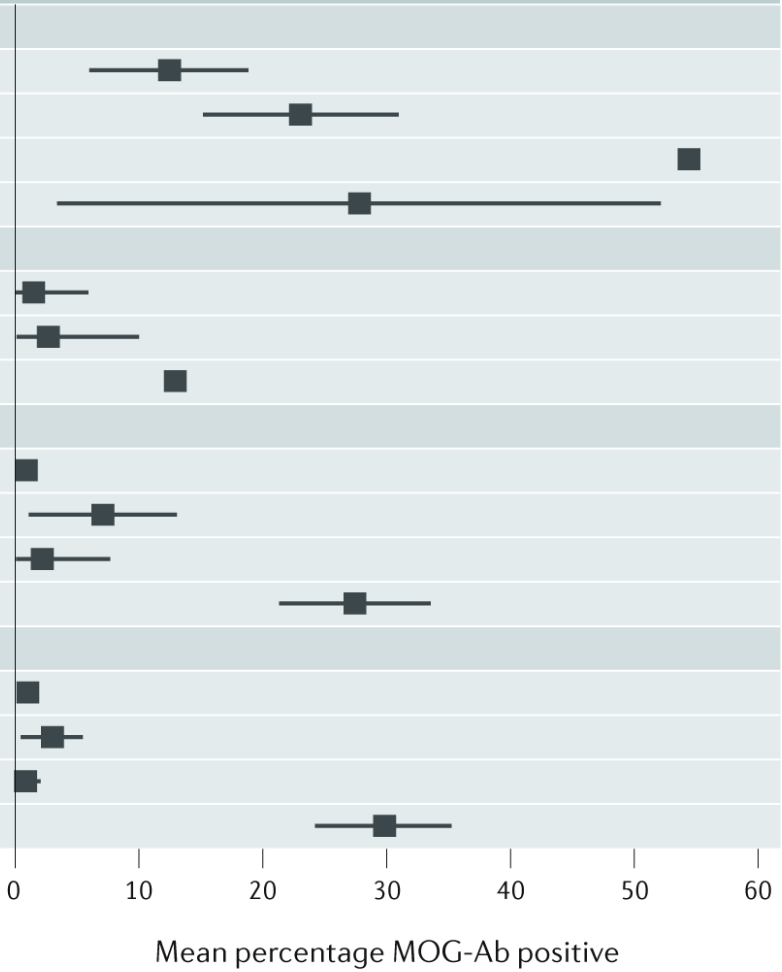
- MOGAD is a **global disease** affecting people of **all age**
  - Incidence = 1.6-3.4/million/year
  - Prevalence = 20/million
  - No sex and racial predominance

- MOGAD is a **distinct entity**, and it differs from MS and NMOSD in histopathological features, imaging features, treatment responses, and outcomes

Banwell et al. Lancet. 2023

a

Disease group	Number of studies	Number of MOG-Ab positive individuals	Mean percentage of MOG-Ab positive cases in all studies (with 95% confidence interval)
IB/ELISA			
Controls	14	221/1726 (12.8%)	
MS	16	423/2111 (20.0%)	
AQP4-Ab⁺NMOSD	1	6/11 (54.5%)	
Other non-MS	7	41/252 (16.3%)	
RIA			
Controls	3	3/236 (1.3%)	
MS	3	8/264 (3.0%)	
Other non-MS	1	13/101 (12.9%)	
CBA-FACS			
Controls	18	15/1173 (1.3%)	
MS	21	105/1771 (5.9%)	
AQP4-Ab⁺NMOSD	6	10/317 (3.2%)	
Other non-MS	20	273/1026 (26.6%)	
CBA-IF			
Controls	17	45/5504 (0.8%)	
MS	25	24/1608 (1.5%)	
AQP4-Ab⁺NMOSD	24	7/1520 (0.5%)	
Other non-MS	41	757/2639 (28.7%)	



By using **cell-based assays** for detection of MOG-Ab, patients who were previously diagnosed with other demyelinating diseases have been now recognized as having MOGAD

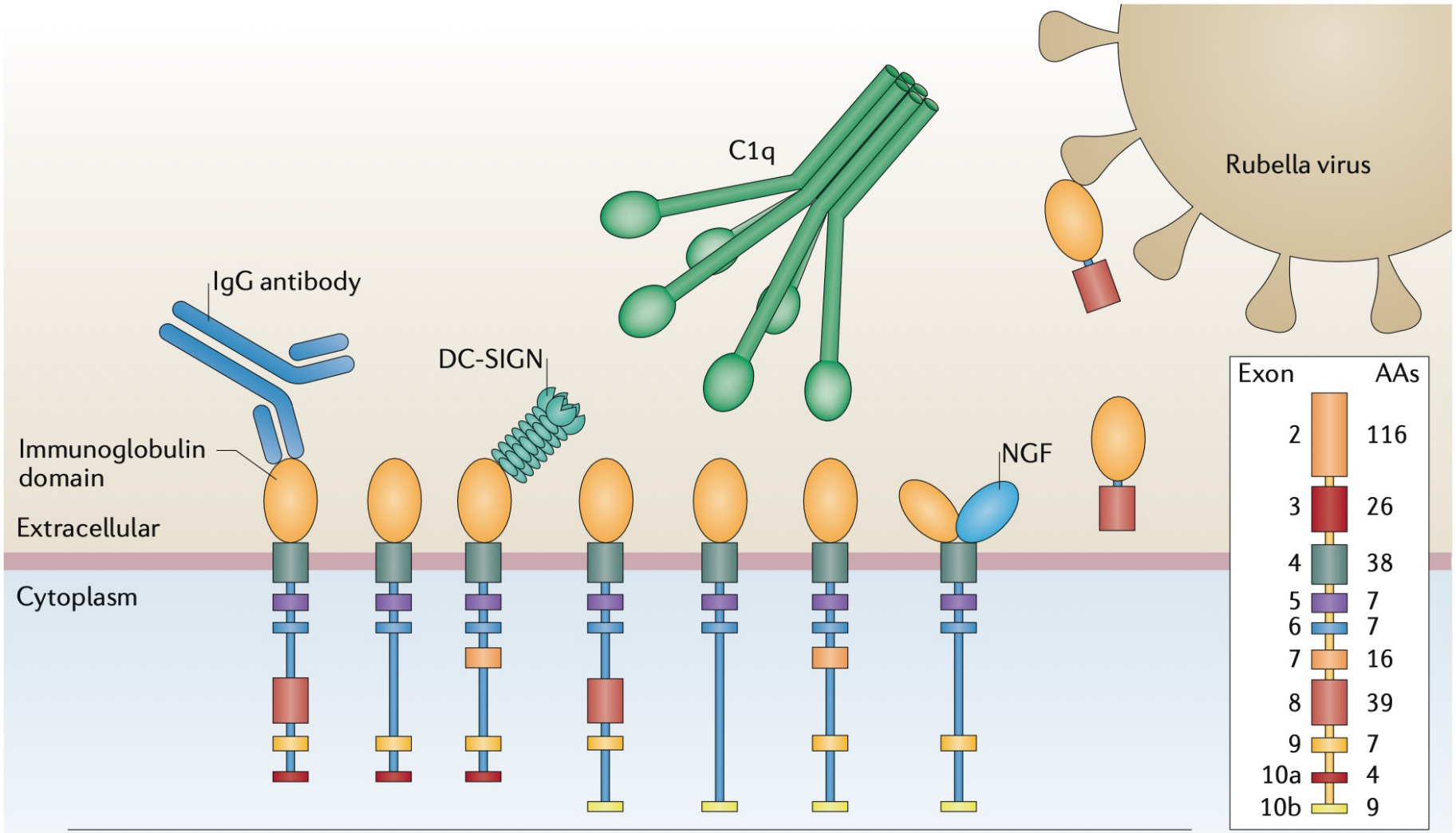
Reindl et al. Nature Reviews Neurology. 2019

Myelin Oligodendrocyte Glycoprotein

Structure and function

- MOG is a myelin component (0.05% of myelin protein) which is present in the **CNS of mammals** only, exclusively on the surface of myelin sheaths and oligodendrocytes
  - It contains 245 amino acids with the molecular weight of 26-28 kilodalton
  - It resides at the **outermost layer** of myelin which results in **encephalitogenic susceptibility**
- **Function**: unknown
  - Myelin maturation and integrity?
  - Immune regulation?
  - Cell surface interaction?

Reindl et al. Nature Reviews Neurology. 2019



Isoforms	α1	α2	α3	β1	β2	β3	β5	α4 and β4
Size kDa	25.1	20.5	22.2	25.6	20.2	22.7	21.0	16.3
Amino acids	218	179	195	223	177	200	184	142

Reindl et al. Nature Reviews Neurology. 2019

Pathogenesis

Experimental autoimmune encephalomyelitis

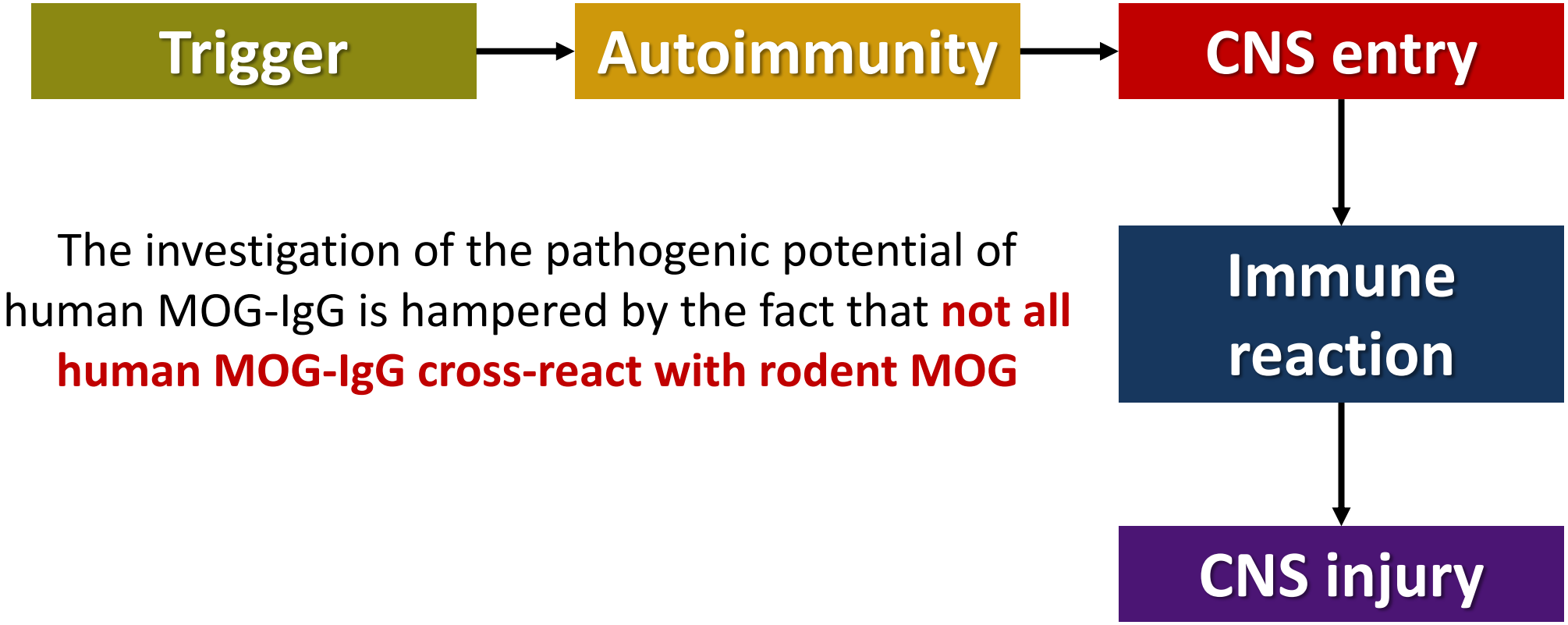
- MOG is frequently used as an **autoantigen** in the experimental autoimmune encephalomyelitis (EAE) model of CNS demyelination
  - In this model, animals are **actively or passively immunized** with different **myelin proteins/peptides** to study the underlying immunopathogenesis

Injection of **MOG antigen** has been shown to result in EAE causing synergy between **encephalitogenic T cells and B cells**

Lerch et al. Journal of Neuroophthalmology. 2023

Pathogenesis

Overview of pathogenesis



The investigation of the pathogenic potential of human MOG-IgG is hampered by the fact that **not all human MOG-IgG cross-react with rodent MOG**

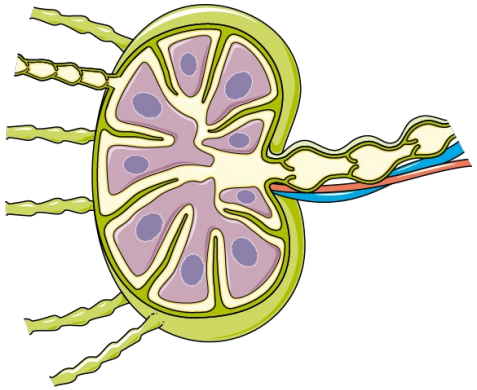
Pathogenesis

Proposed mechanisms of autoimmunity

- **Generation of autoimmune response**: there are 2 possible explanations

Inside-out hypothesis

Primary **damage of oligodendrocytes** → transport myelin antigens as soluble antigens or by DC of the choroid plexus or meninges into the deep cervical LN → activation of T cells



Outside-in hypothesis

Activation of lymphocytes in peripheral LN through **molecular mimicry** or **pan-activation after a systemic viral infection** → cross-reactivity to self-MOG antigen

Incomplete negative thymic selection causing self-intolerance

Lerch et al. Journal of Neuroophthalmology. 2023

Pathogenesis

Proposed mechanisms of CNS entry

- Under normal circumstances, the CNS parenchyma is **free of lymphocytes**
- A **pro-inflammatory environment** enables **opening of the blood-brain barrier** for the
- T-cells home to the brain after priming where they most likely enter the brain parenchyma through the **meninges** or the **choroid plexus**
  - After entry into the **CNS border regions**, T cells need to be **reactivated by antigen-presenting cells** to gain access to the CNS parenchyma across the BBB
  - Production of **cytokines/chemokines** and subsequent activation of nearby tissue including the blood-meningeal barrier and BBB enables the **infiltration of more immune cells** and **MOG-IgG** into the CNS parenchyma that directly damage neurons and glia

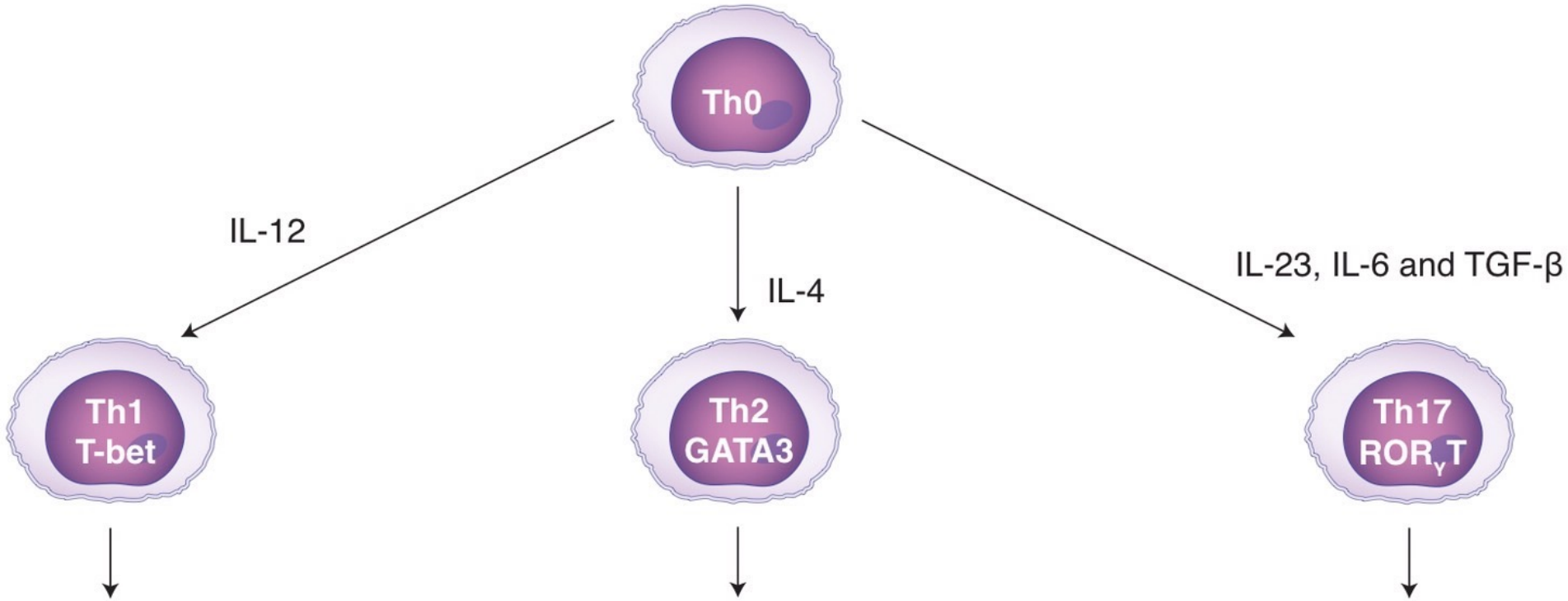
Lerch et al. Journal of Neuroophthalmology. 2023

Pathogenesis

Proposed mechanisms of immune reaction and CNS injury

- **T cell polarization**
  - Different studies examining the **cytokine/chemokine profiles** in patients with MOGAD measured increased levels of **T-helper (Th)17-related cytokines/chemokines (IL-6, IL-8, IL-17a)**, G-CSF, **Th1-related cytokines (INF-γ, TNFα)**, and several B-cell associated factors (a-proliferation-induced ligand, B-cell activating factor, C-X-C motif chemokine ligand 13) in CSF and serum
    - **Tocilizumab** (anti-IL-6 receptor antibody) is used off-label for the treatment of AQP4-IgG seropositive NMOSD and MOGAD

Lerch et al. Journal of Neuroophthalmology. 2023



- Amplifies Th1 response
- Inhibits Th2 response
- Activates classic macrophage
- Drives isotype switching to IgG

- IL-4 amplifies Th2 response
- IL-4 and IL-10 inhibit Th1 response
- IL-5 drives eosinophil maturation
- Activates alternate macrophage
- IL-4 and IL-13 drive isotype switching to IgE and alternative macrophage activation
- IL-5 and TGF-β drive isotype switching to IgA*

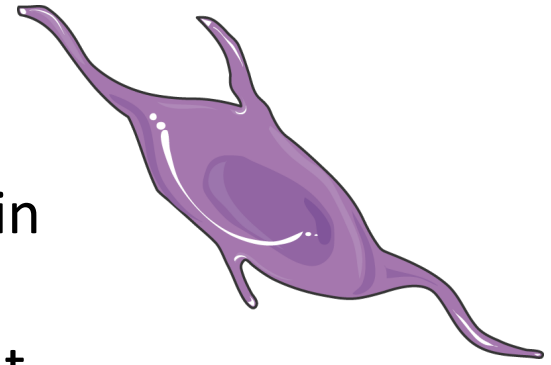
- IL-17 activates tissue cells and leukocytes to secrete inflammatory cytokines leading to recruitment of neutrophils
- IL-17 and IL-22 act on epithelial cells to secrete anti-microbials and improve barrier function

Kaplan, Immunology

Pathogenesis

Proposed mechanisms of immune reaction and CNS injury

- Most MOG-IgG production is believed to take place in the **periphery** as **oligoclonal CSF bands are missing in 90%** of MOGAD patients
- **Pathomechanism of MOG-IgG**
  - Direct pathogenic effects to oligodendrocyte function and structure
  - Increased serum levels of complement products were found in MOGAD compared with MS, and NMOSD
  - After the transfer of human MOG-IgG cross-reactive to rodent MOG into different rat models, **increased T-cell infiltration** or **complement deposition**, together with **MOG- or MBP-specific T cells**



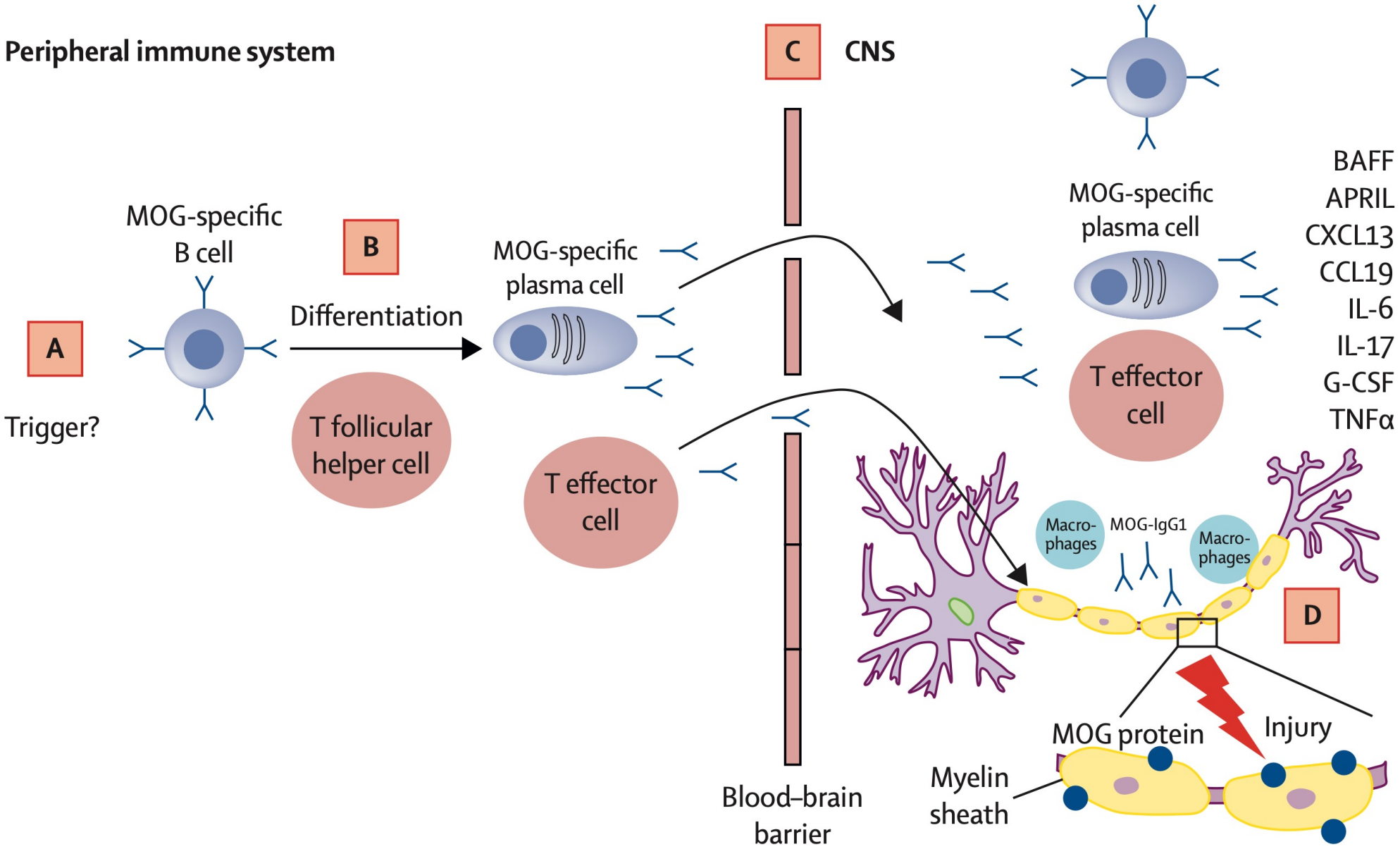
Lerch et al. Journal of Neuroophthalmology. 2023

Pathogenesis

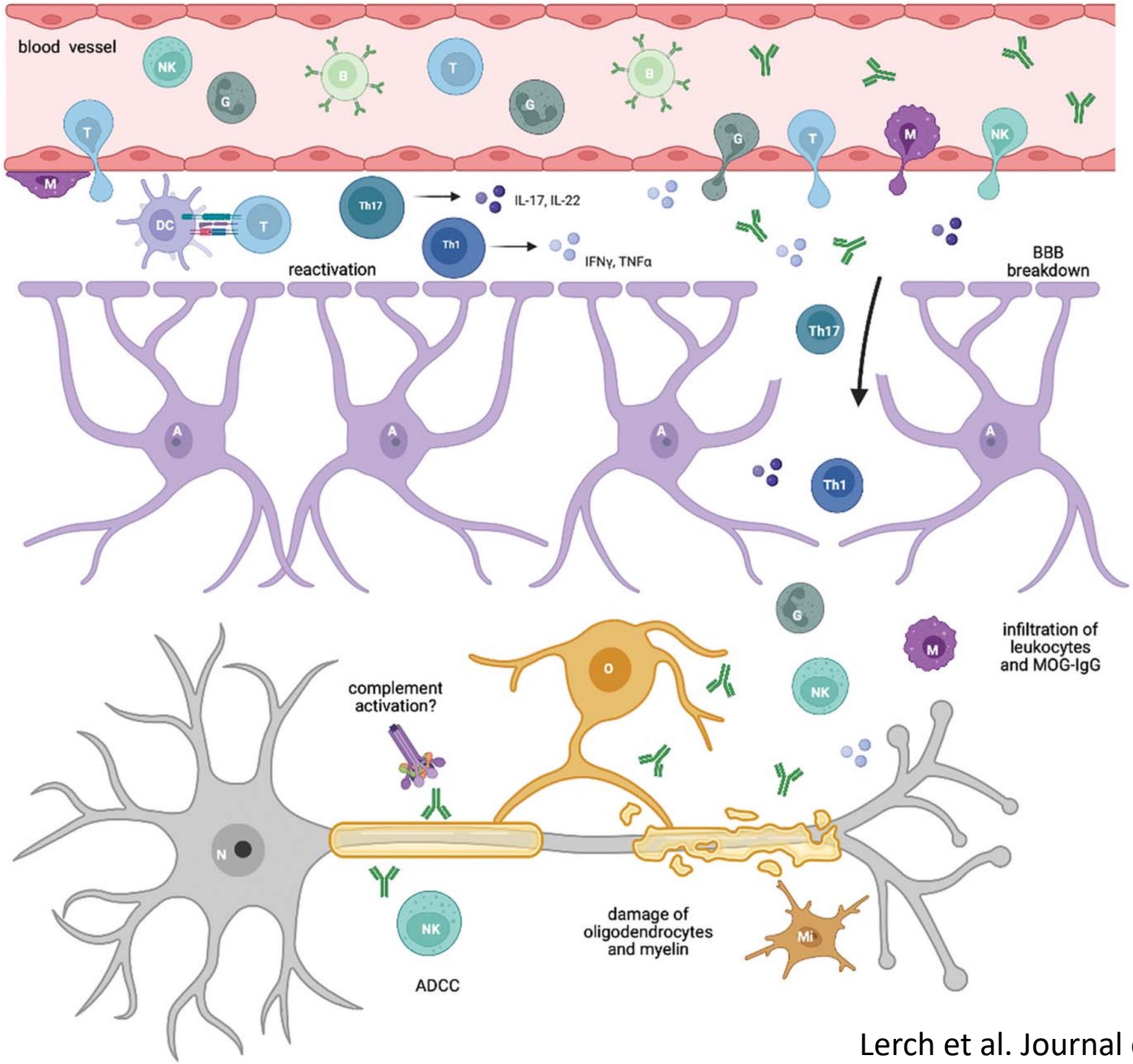
Proposed mechanisms of immune reaction and CNS injury

- **Neuropathological examinations** showed that infiltrating lymphocytes are mainly **CD4+ T cells** with only few B cells and CD8+ T cells
  - **Macrophages and microglial cells** were abundantly found within active demyelinating lesions
  - Low-to-moderate eosinophils and neutrophils
  - Relative axon sparing + reactive astrogliosis
  - **Meningeal inflammation** in 86%
  - **Complement activation** was concentrated in active lesions

Hoftberger et al. Acta Neuropathol. 2020



Marignier et al. Lancet. 2021



Lerch et al. Journal of Neuroophthalmology. 2023

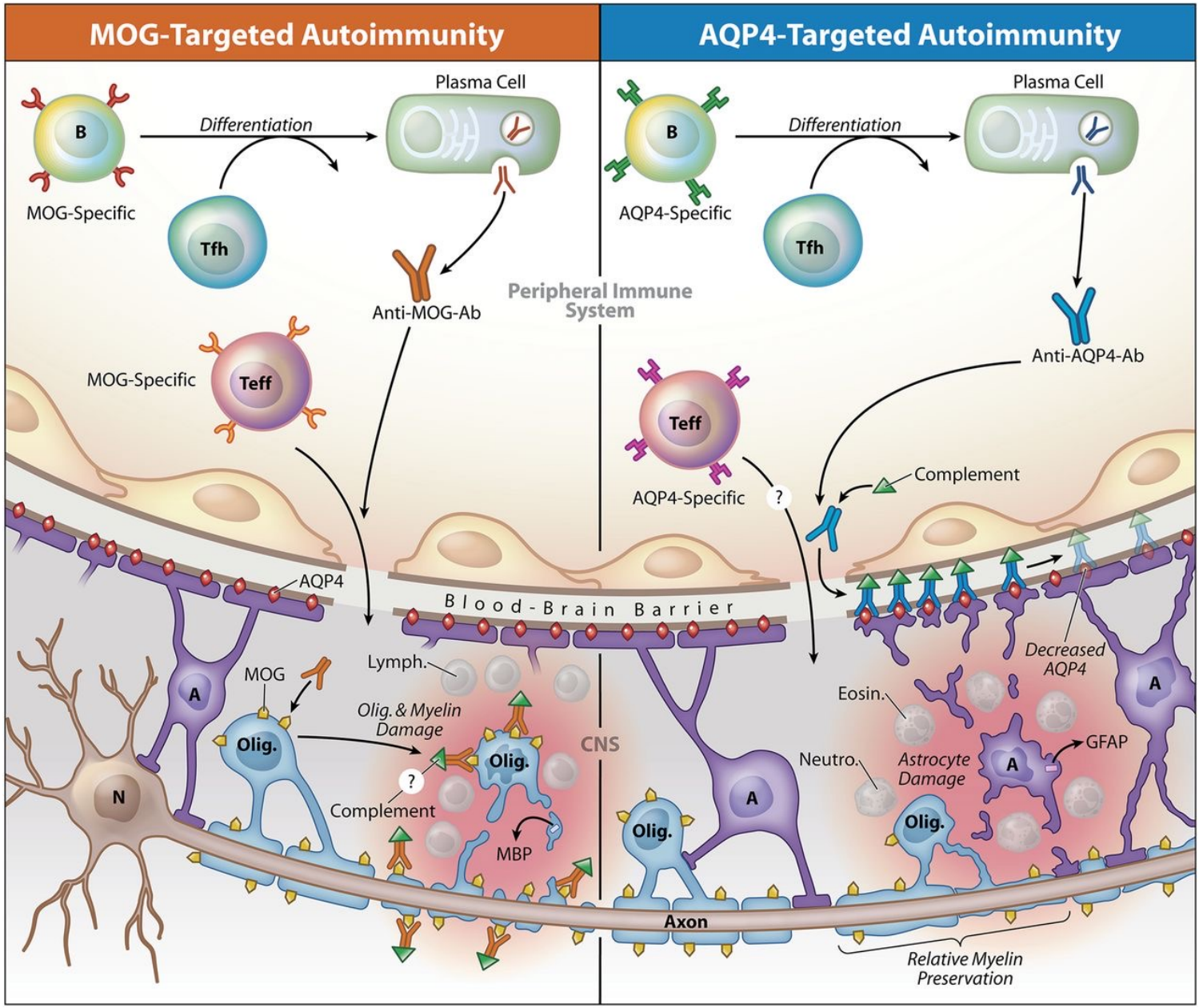
CSF markers

MOGAD

- Increased myelin basic protein (MBP)

NMOSD

- Increased MBP
- Increased GFAP



Kaneko et al. J Neurol Neurosurg Psychiatry. 2016

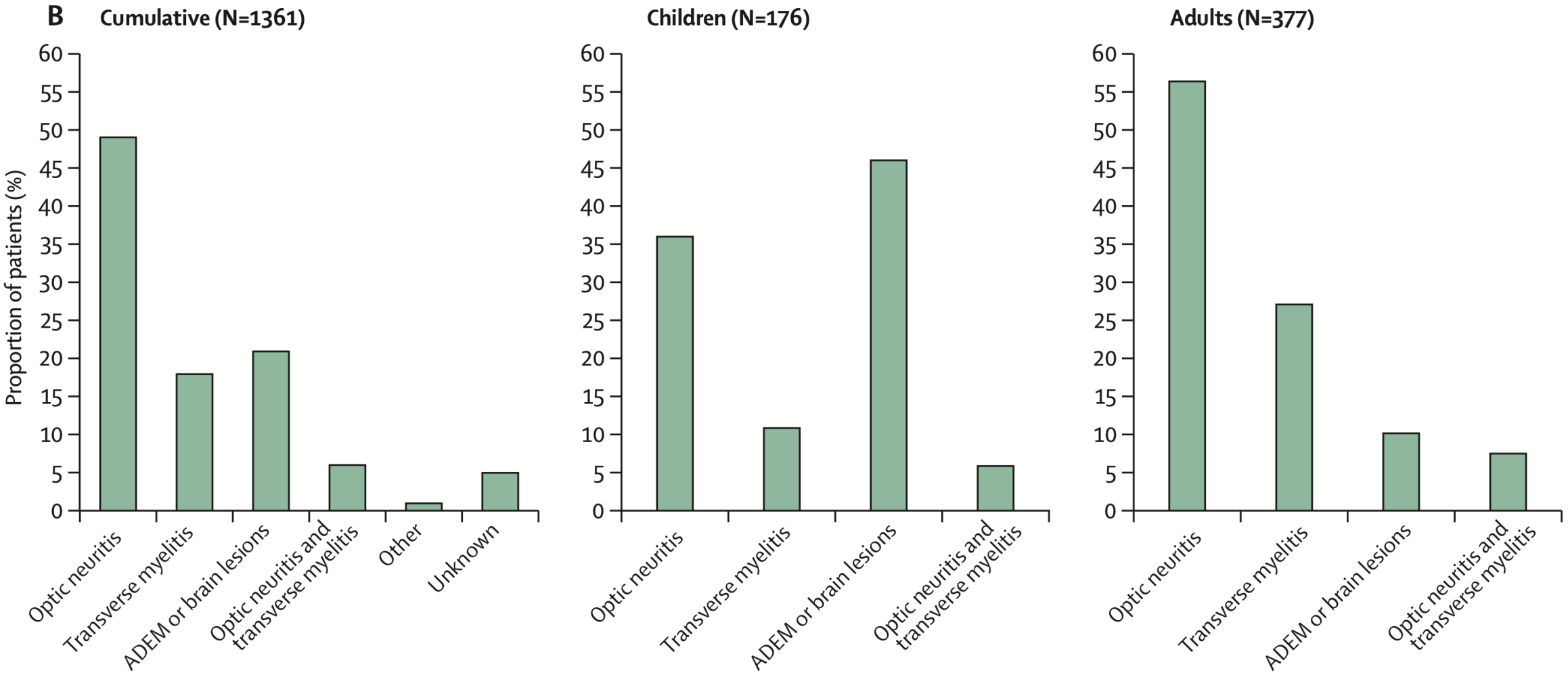
Zamvil et al. Neurology. 2015

Clinical Phenotypes of MOGAD

Phenotypic classification

- **Common phenotypes**
  - Optic neuritis = the most common manifestation in **adults**
  - ADEM +/- ON = the most common manifestation in **children (age <11)**
  - Transverse myelitis
- **Less common phenotypes**
  - Cerebral cortical encephalitis
  - Brainstem and cerebellar demyelinating attacks
  - Tumefactive brain lesions
  - Cerebral monofocal and polyfocal CNS deficits associated demyelinating lesions
  - Cranial neuropathies
  - Progressive white matter damage (leukodystrophy-like pattern)

Banwell et al. Lancet. 2023

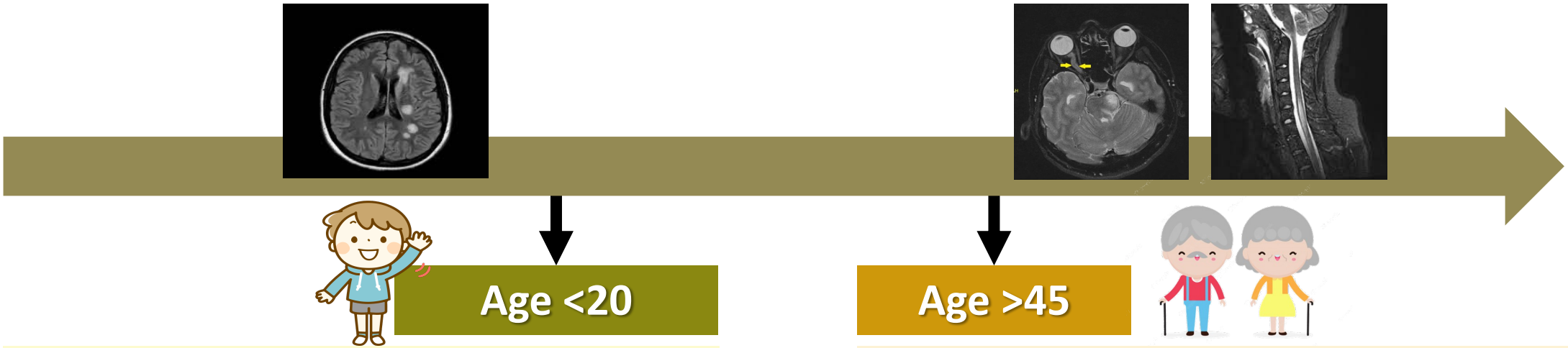


Age-related clinical phenotypes

Banwell et al. Lancet. 2023

Clinical Phenotypes of MOGAD

Age-related phenotypes



Age <20

- ADEM is the most common (36%)
- Better recovery
- 39% relapse rate

Age >45

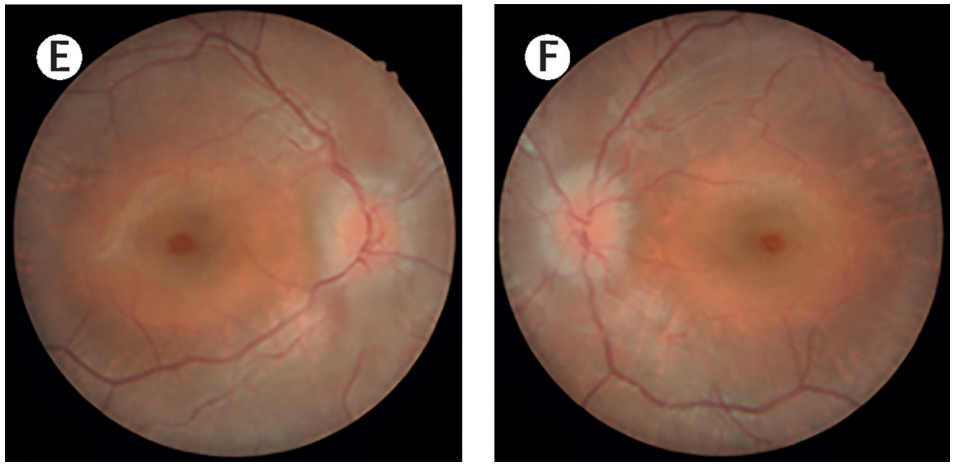
- ON/TM is the most common (>90%)
- More evere course
- Lack of responsiveness to DMT

Pauli et al. Frontiers. 2018

Clinical Phenotypes of MOGAD

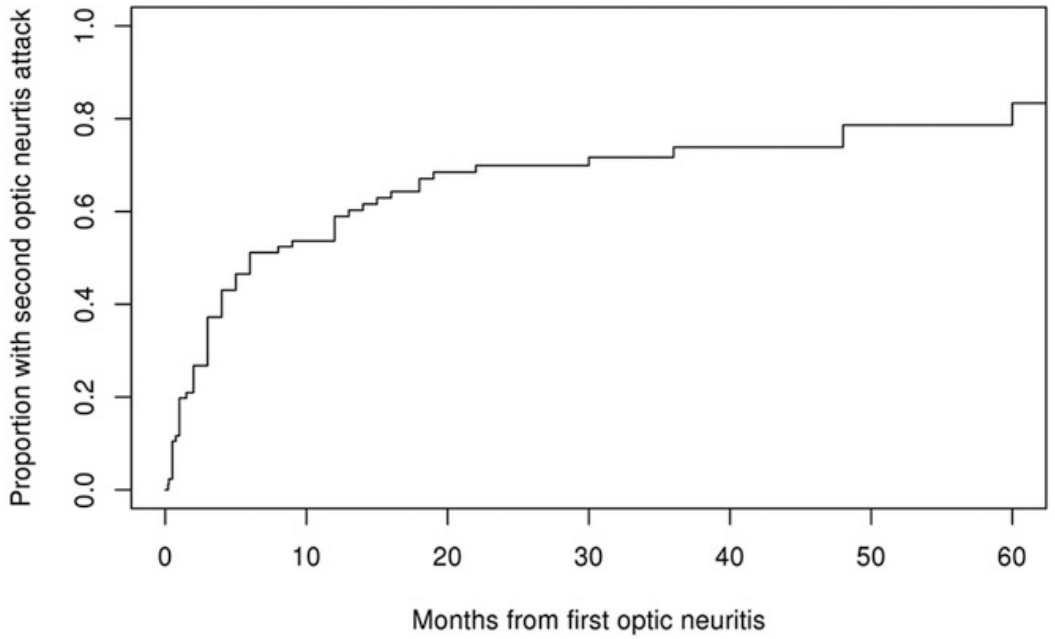
Optic neuritis

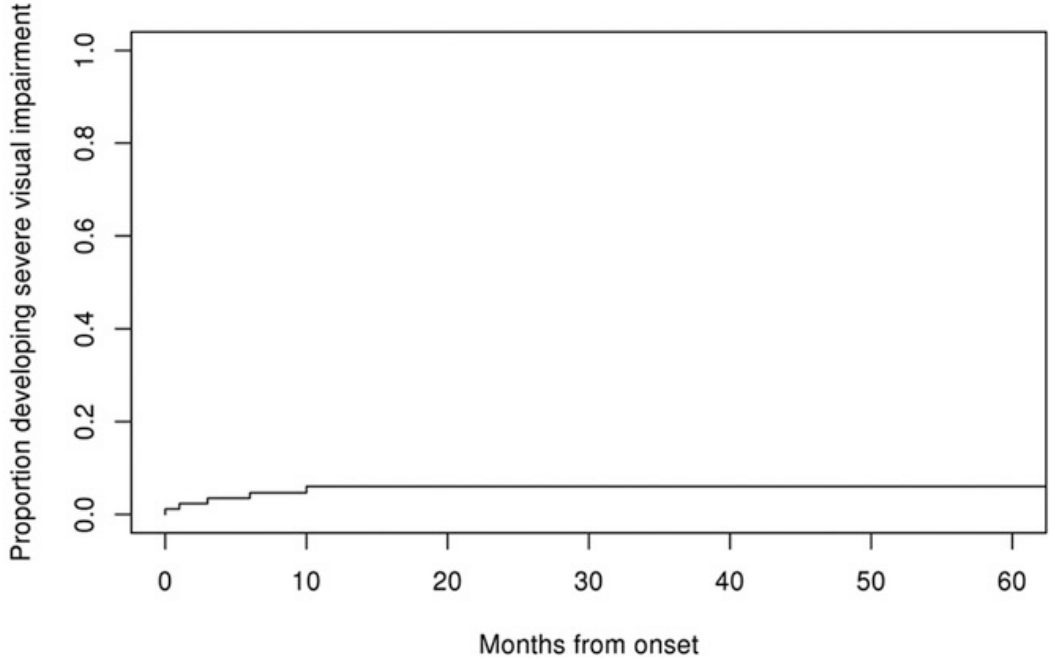
- **Clinical features**
  - **Central acuity loss and color vision loss**
    - VA loss is often worse than 6/60 at nadir with **rapid and dramatic improvement** following acute corticosteroid therapy
  - **Retro-orbital pain**
  - **Afferent pupillary defect**
  - **Bilateral ON** is common at onset (31-58% vs <5% in MS and 13-37% in NMOSD)
  - **Relapses is about 30-50%** which can occur during corticosteroid weaning or shortly after cessation



- **Optic disc swelling** (45-95%) (usually **moderate to severe**)

Banwell et al. Lancet. 2023





Clinical features of ON and visual function of MOG-ON

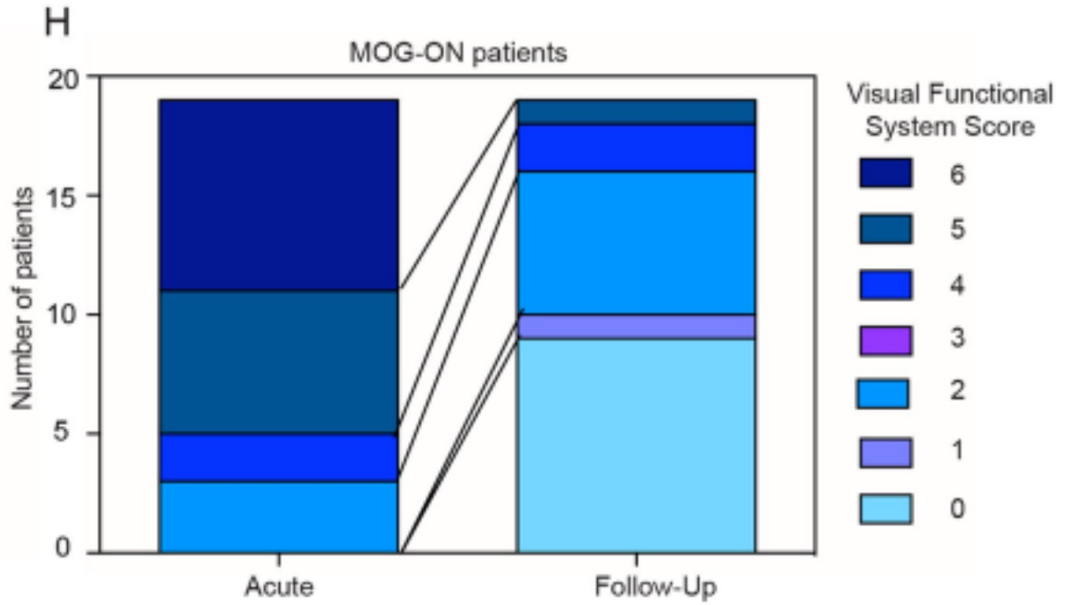
- 87 MOG-IgG-seropositive patients with optic neuritis were included (Mayo Clinic, 76; other medical centers, 11)
- Average VA at nadir of worst attack was count fingers
- Average final VA was 20/30
- Optic disc edema and pain each occurred in 86% of patients
- Median duration of recurrent attack = 4 mo (annualized relapse rate 0.8)
- Severe visual loss <10%

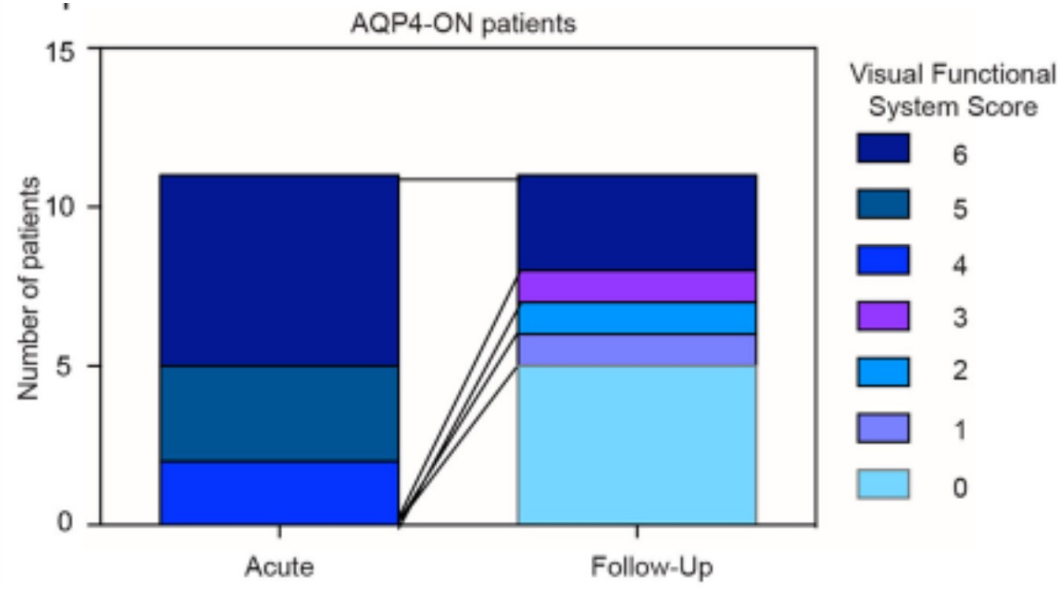
Chen et al. Am J Ophathalmo. 2018

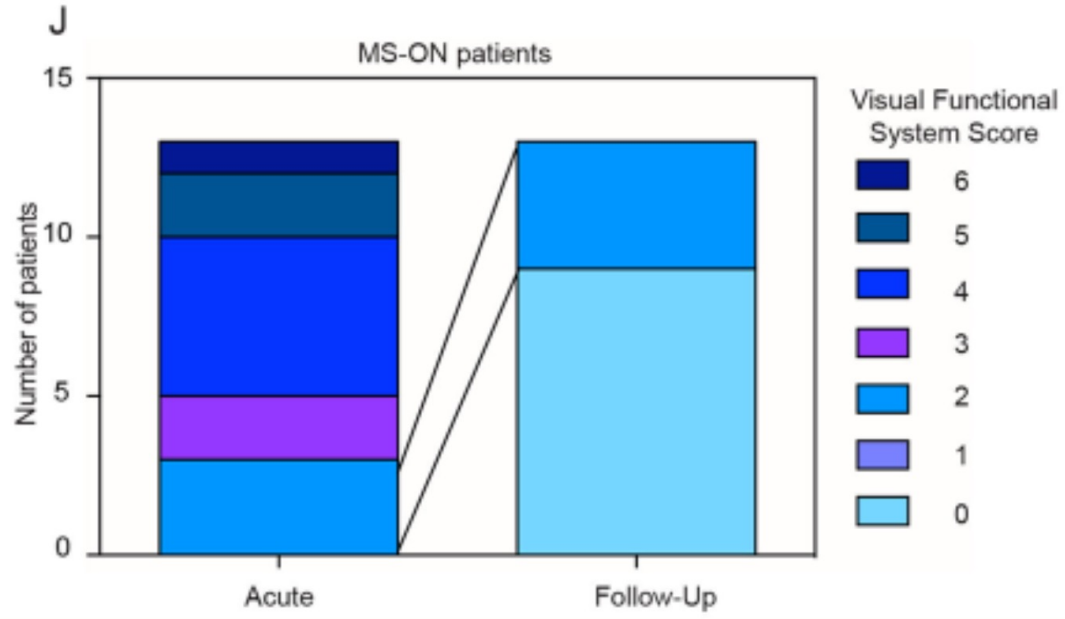
Visual function and recovery in patients with MOGAD, NMOSD and MS

50 patients presenting with first-episode ON

- MOG-ON (n = 19)
- AQP4-ON (n = 11)
- MS-ON (n = 13)
- Unclassified ON (n = 7)





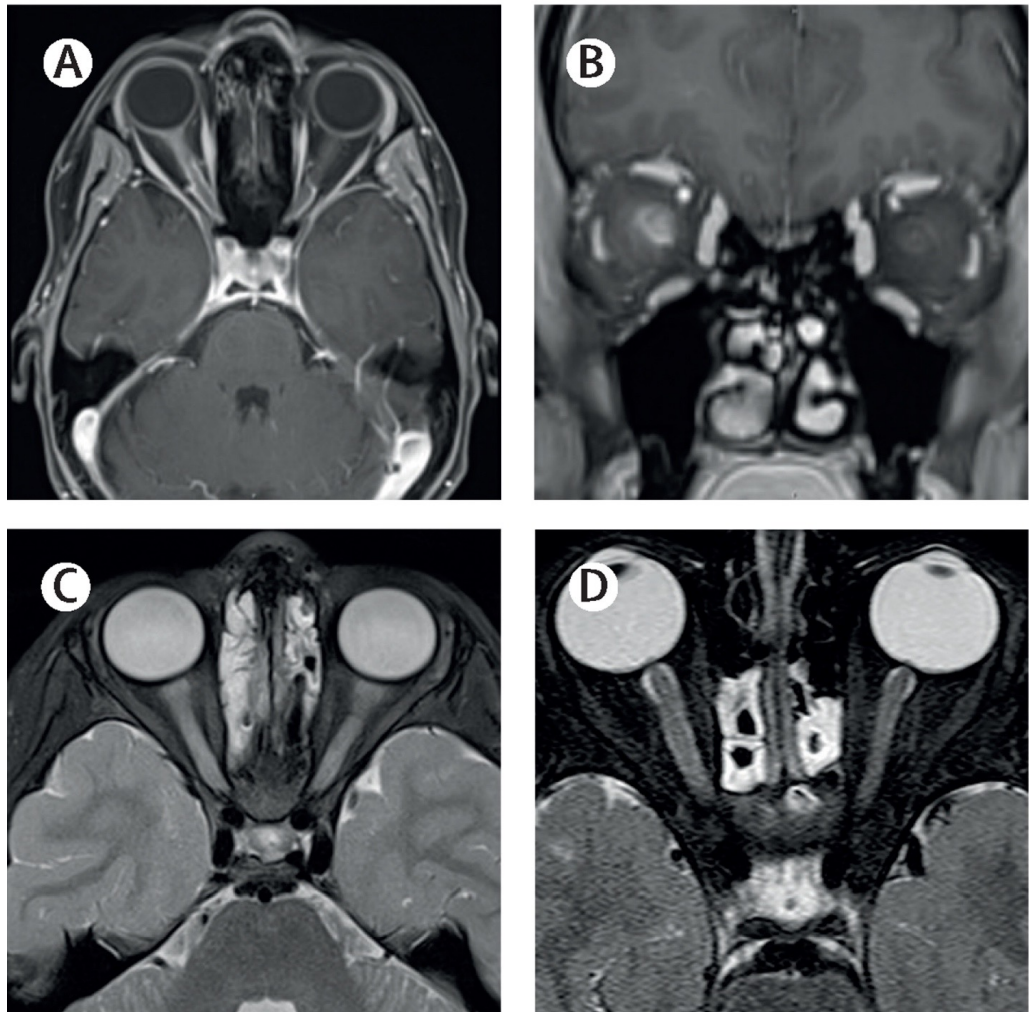


Ramanathan et al. MS Journal. 2015

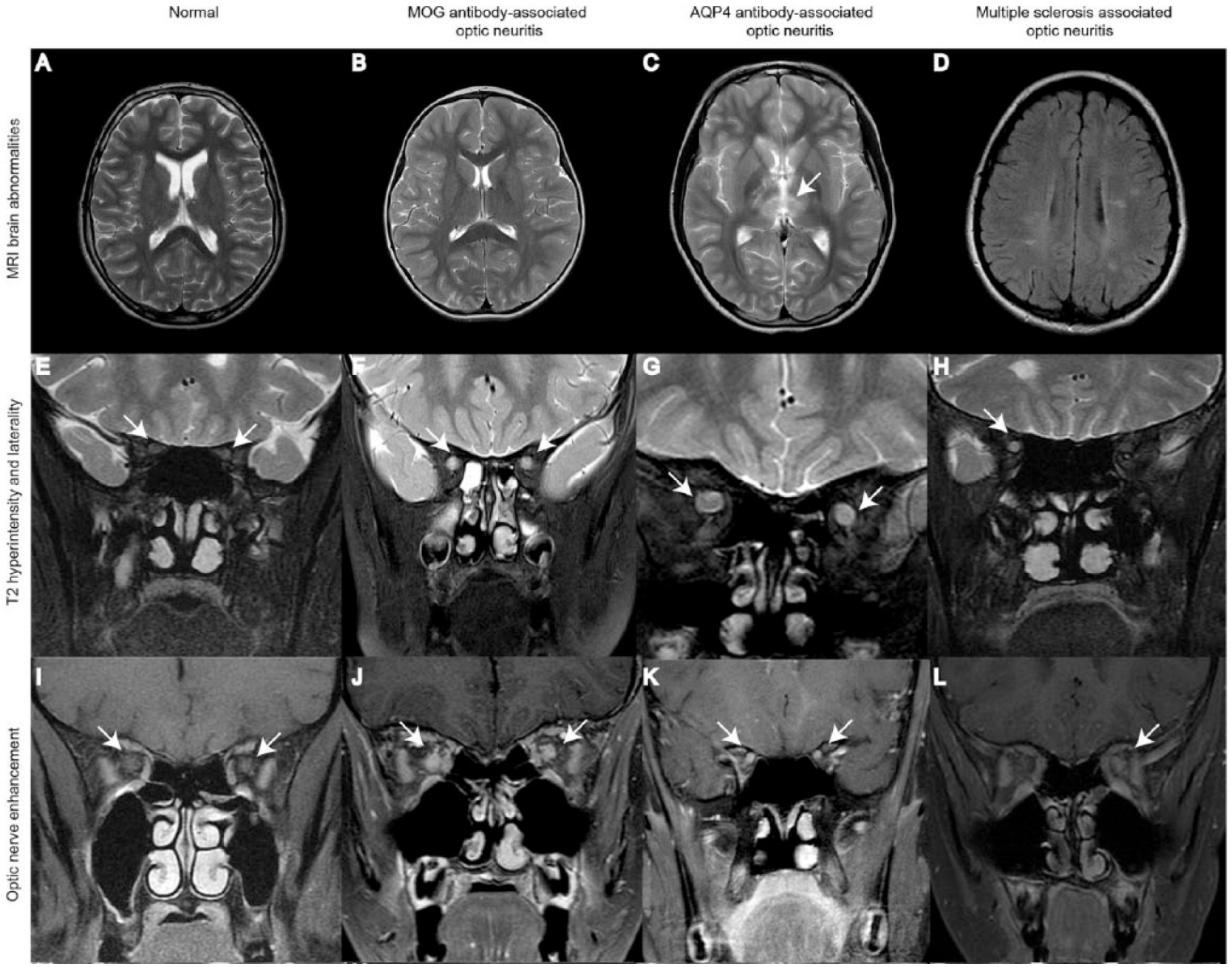
Clinical Phenotypes of MOGAD

Optic neuritis

- **MRI findings**
  - **Optic nerve head swelling**
  - **Lesion extent along the optic nerves >50% of length**
  - **Involvement of perineural tissue**



Banwell et al. Lancet. 2023



A-D: Presence of MRI brain abnormalities

- No brain changes in a MOG-ON
- Bilateral thalamic and hypothalamic changes in an AQP4-ON
- WMH at periventricular area in an MS-ON

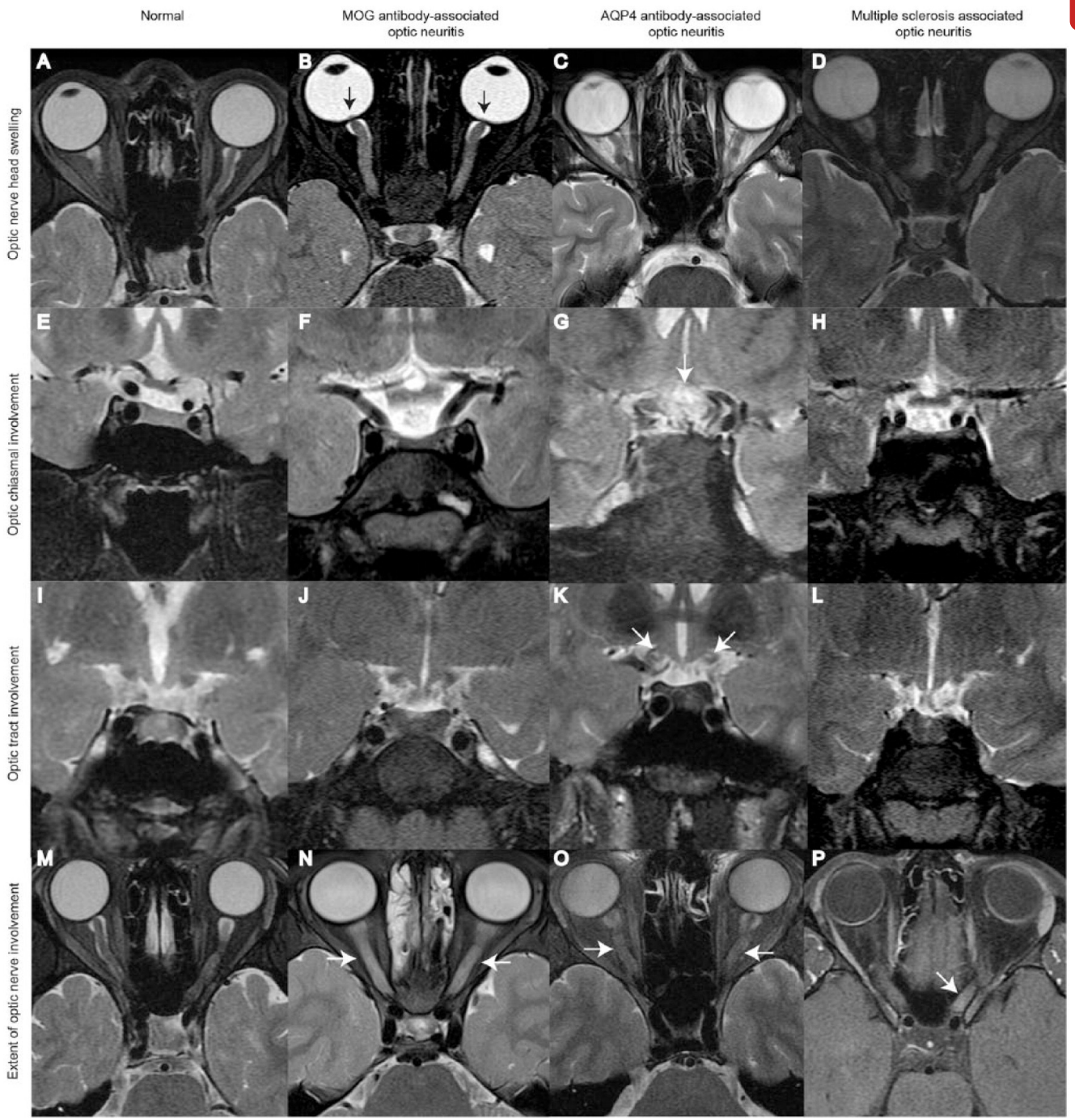
E-H: Coronal T2 hyperintensity of optic nerve

- Bilateral optic nerve T2 hyperintensity in a MOG-ON and AQP4-ON patient
- Unilateral right optic nerve T2 hyperintensity in an MS-ON

I-L: Optic nerve enhancement

- Bilateral retrobulbar enhancement + swelling in a MOG-ON
- Bilateral intracanalicular enhancement in an AQP4-ON
- Unilateral retrobulbar (Lt) enhancement in an MS-ON

Ramanathan et al. MS Journal. 2015



A-D: Optic nerve head swelling

- Bilateral optic nerve head swelling in a MOG-ON
- Absent optic nerve head swelling in an AQP4-ON and an MS-ON

E-H: Optic chiasmal involvement

- No chiasmal involvement in a MOG-ON and an MS-ON
- Chiasmal involvement in an AQP4-ON

I-L: Optic tract involvement

- No optic tract changes in a MOG-ON and MS-ON
- Bilateral optic tract involvement with T2 hyperintensity in an AQP4-ON

M-P: Extent of optic nerve involvement

- Bilateral longitudinally extensive optic nerve involvement in a MOG-ON and an AQP4-ON
- Unilateral focal involvement in an MS-ON

Ramanathan et al. MS Journal. 2015

Clinical Phenotypes of MOGAD

Transverse myelitis and spinal cord involvement

Clinical features

- **Presentations**: TM alone, ADEM with TM, TM with ON
- **Clinical manifestations**: **sensory (pain, dysesthesia)**, motor, and **sphincter disturbance and erectile dysfunction**
  - Painful tonic spasms and severe neuropathic pain as an outcome is less common (more representative of myelitis associated with AQP4-IgG-seropositive NMOSD)
- **Severity**: varies, but typically **moderate to severe at nadir** (EDSS score >4) in >50%
- **Recovery**: **excellent motor recovery** (permanent bladder, bowel, or sexual dysfunction can occur)
- **Recurrence**: recurrent TM without demyelination elsewhere in the CNS are rare
- **Silent lesion** at cord, brain, or optic nerve can be found when an attack affect one site (cord, brain or optic nerve)
  - Silent brain or optic nerve lesions can be detected in 33-50% with clinical TM

Banwell et al. Lancet. 2023

Clinical myelitis in MOGAD patients

- MOG-TM (n = 54)
- AQP4-TM (n = 46)
- MS-TM (n = 26)

Demographics	Myelitis, No./Total No. (%)		MOG-IgG vs AQP4-IgG *P* Value[a]	MS Myelitis, No./Total No. (%)	MOG-IgG vs MS *P* Value[b]
	MOG-IgG	AQP4-IgG			
Age (range), y	25 (3-73)	49.5 (15-75)	<.001	35 (18-59)	.007
Children (<18 y)	16/54 (30)	2/46 (4)	.001	0/26	.002
Female	24/54 (44)	39/46 (85)	<.001	20/26 (77)	.006
White	50/54 (93)	32/46 (70)	.003	26/26 (100)	.15
Clinical features					
Preceding viral-like prodrome or vaccination	33/54 (61)	3/46 (7)	<.001	0/26	<.001
ADEM with myelitis	9/54 (17)	0/46	.004	0/26	.03
History of intractable nausea and vomiting	5/54 (9)	9/46 (20)	.14	0/26	.11
Neurogenic bowel/bladder	45/54 (83)	32/46 (69)	.10	8/26 (31)	<.001
Erectile dysfunction	13/24 (54)	1/7 (14)	.06	0/6	.06
Wheelchair dependent at attack nadir	18/54 (33)	15/46 (33)	.94	0/26	<.001
CSF findings					
CSF elevated white blood cell count, >5 cells/μL	30/42 (71)[c]	21/24 (88)	.13	13/18 (72)	.81
Markedly elevated CSF white blood cell count, >50 cells/μL	22/42 (52)	6/24 (25)	.03	0/18	<.001
Elevated CSF protein, >50 mg/dL	30/42 (71)	16/24 (67)	.69	7/18 (39)	.02
Elevated (≥4) oligoclonal bands	1/38 (3)	3/27 (11)	.16	16/18 (89)	<.001

Dubey et al. JAMA Neurology. 2019

Clinical Phenotypes of MOGAD

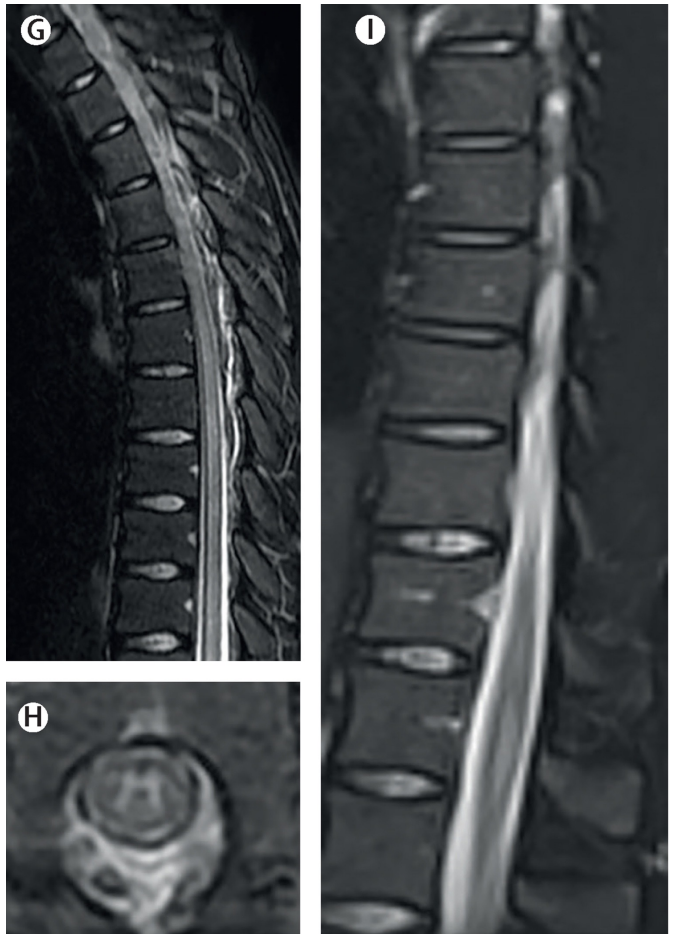
Transverse myelitis and spinal cord involvement

- **LETM** (≥3 or more vertebral segments) in >60% similar to NMOSD (but rare in MS)
- **Conus involvement** is more common (26% MOGAD vs 1.3% MS and 6% NMOSD)
- **Centrally located on axial imaging** (66-75%), and can be **restricted to the grey matter** (30-50%), producing the **H-sign**
- **Contrast enhancement** (50%)
- **Thickening and contrast enhancement of the dorsal nerve roots**

- Resolve or reduce in size substantially at follow-up
- Spinal cord atrophy in severe cases

10% normal at onset

Imaging features



Banwell et al. Lancet. 2023

MRI features of myelitis in MOGAD patients

- MOG-TM (n = 54)
- AQP4-TM (n = 46)
- MS-TM (n = 26)

Clinical outcome

MRI spine features					
Longitudinally extensive sagittal T2 lesion (>3 vertebral segments)	37/47 (79)	28/34 (82)	.52	0/26	<.001
≥2 cord lesions	29/47 (62)	0/34	<.001	17/26 (65)	.76
Gadolinium enhancement	14/54 (26)	31/40 (78)	<.001	19/26 (73)	<.001
Concurrent H sign and linear sagittal hyperintensity	15/51 (29)	3/39 (8)	.007	0/26	.002
Involvement of conus	21/51 (41)	5/38 (13)	.004	5/15 (33)	.59
Clinical outcomes					
Gait aid at last follow-up	3/54 (6)	17/46 (37)	<.001	1/26 (4)	.74
mRS at last follow-up, median (range)	1 (0-4)	2 (0-6)	<.001	1 (0-4)	.61
Duration of follow-up, median (range), mo	24 (2-120)	34 (1-118)	.39	90 (1-166)	<.001

Dubey et al. JAMA Neurology. 2019

Table. Demographic, Clinical, and Magnetic Resonance Imaging (MRI) Characteristics Among Patients With MOG-Ab Disease or AQP4-Ab Disease (continued)

Characteristic	Patients, No. (%)		*P* Value
	MOG-Ab Group (n = 46)	AQP4-Ab Group (n = 69)	
MRI features			
Spinal cord			
Short lesions only	11 (24)	8 (12)	.12
Long lesions only	24 (52)	59 (86)	<.001
Long and short lesions	11 (24)	2 (3)	<.001
Total lesion length, mean (SD), vertebral levels	6.8 (6.5)	7.7 (5.2)	.38
Single lesion	28 (61)	62 (90)	<.001
Multiple lesions	18 (39)	7 (10)	<.001
Conus involvement	18 (39)	8 (12)	.001
Contrast enhancement, No./total No. (%)	17/24 (71)	38/48 (79)	.55
Axial cord			
No.	16	24	
Central	12 (75)	17 (71)	>.99
Lateral	3 (19)	3 (13)	.67
Posterior	0	0	>.99
Anterior	1 (6)	4 (17)	.63
Brain			
No.	45	62	
Normal	19 (42)	47 (76)	<.001
Brain lesion	24 (53)	14 (23)	<.001
Brainstem lesion	11 (24)	11 (18)	.47

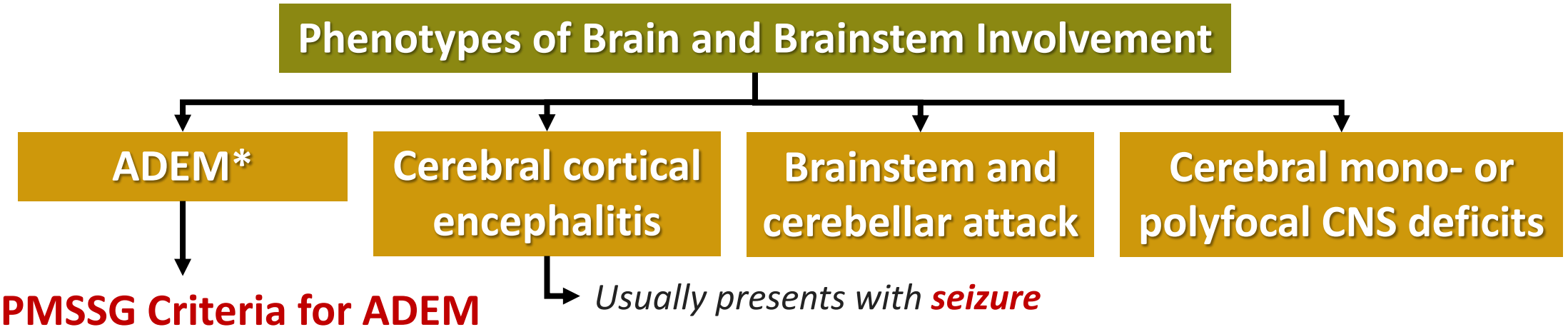
MRI features of myelitis in MOGAD patients

- MOG-TM (n = 46)
- AQP4-TM (n = 69)

Mariano et al. JAMA Neurology. 2019

Clinical Phenotypes of MOGAD

Brain and brainstem involvement



IPMSSG Criteria for ADEM

- First attack of CNS inflam + multifocal + polysymptomatic + encephalopathy (acute behavioral change or AOC) + subsequent improvement + no other causes
- **Characteristic MRI**
  - **Brain**: large (>1-2 cm) multifocal (bilateral asymmetric), hyperSI WM lesion ± hemorrhage ± deep GM involvement (no prior destructive lesion)
  - **Cord**: confluent intramedullary ± enhancement

Other phenotypes

- **Leukodystrophy-like pattern**
- Tumefactive brain lesions *(which can lead to brain herniation)*
- Cranial neuropathies
- Silent lesions in pts with ON/TM

Banwell et al. Lancet. 2023

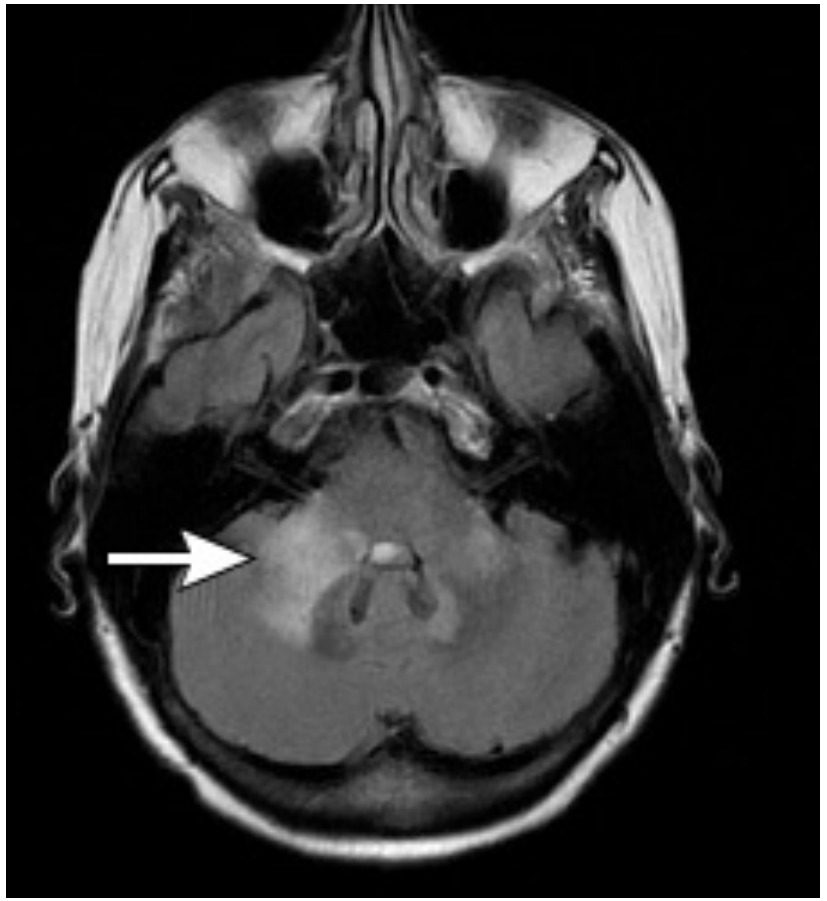
Clinical Phenotypes of MOGAD

Brain and brainstem involvement

- **In patients with ON or TM**: MRI brain T2-hyperintense lesions are absent in 47-68% (whereas in MS, MRI brain is normal in only 8-16%)

Characteristic imaging features

- **Bilateral**, **ill-defined**, and **large**, often with **deep grey matter and pons involvement**, **no black holes** (= persistent T1-hypointense lesions) and **no MS features**
- **Large middle cerebellar peduncle lesion*** (rare in MS or AQP4-IgG-seropositive NMOSD)



Jurynczyk et al. Brain. 2017

Clinical Phenotypes of MOGAD

Brain and brainstem involvement | **ADEM**

- **ADEM in pediatrics** = 50% MOG-IgG positive (lower positivity in adults) especially if **age <10 years**
  - Children with ADEM and MOG-IgG are on average **2-3 years younger** than children with seronegative ADEM
  - **Preceded by an infectious episode** (mainly respiratory) and fever (40-75%)
  - **70% complete (or almost complete) clinical and radiological resolution** but poorer in leukodystrophy-like brain imaging pattern

- **ADEM in adults** = presenting syndrome in only 5.6% MOGAD adult patients
- **TM and ataxia** occur more commonly in MOG-IgG-positive ADEM (than in seronegative ADEM)

Banwell et al. Lancet. 2023

Age-related presentation of MOG-IgG positive ADEM

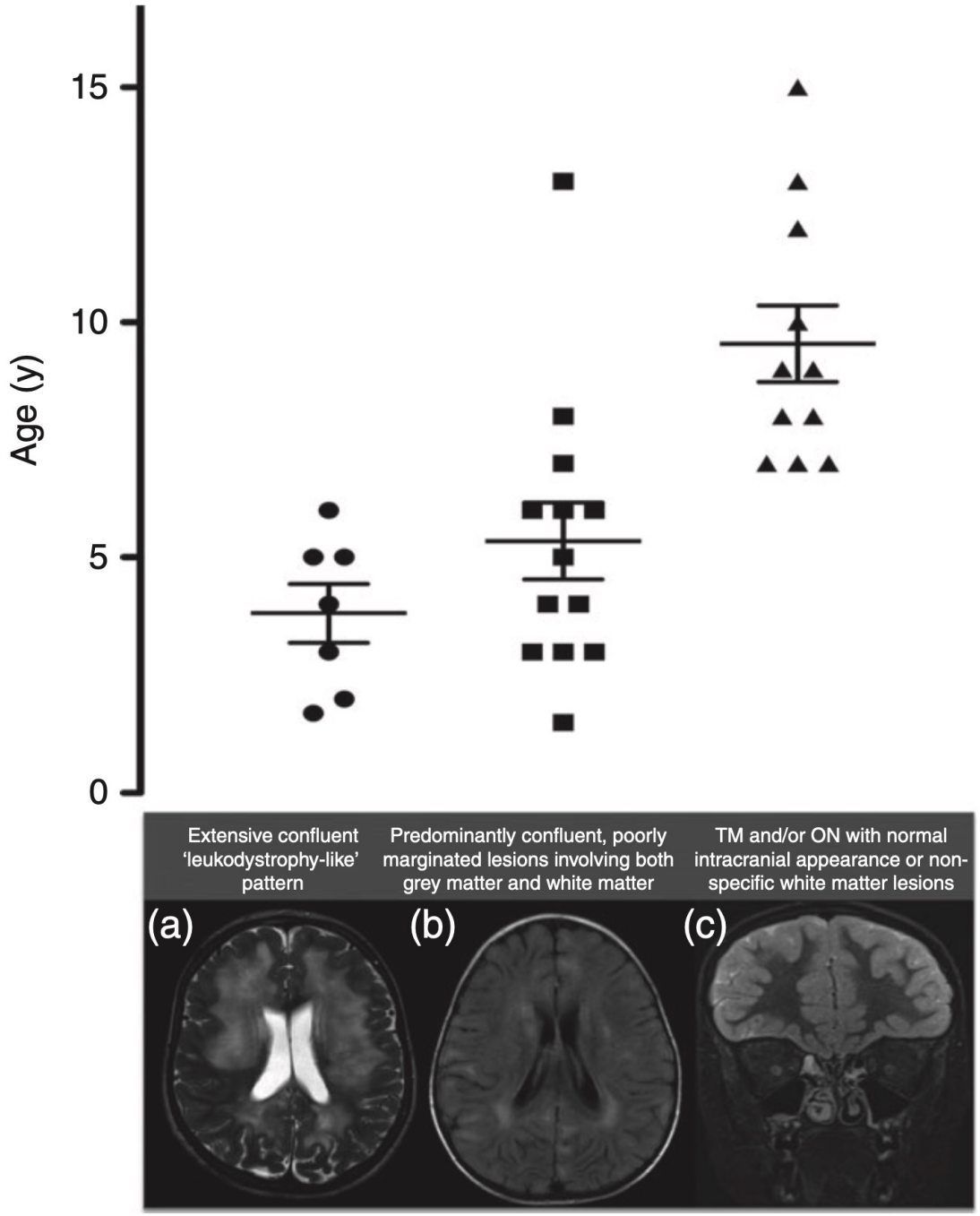
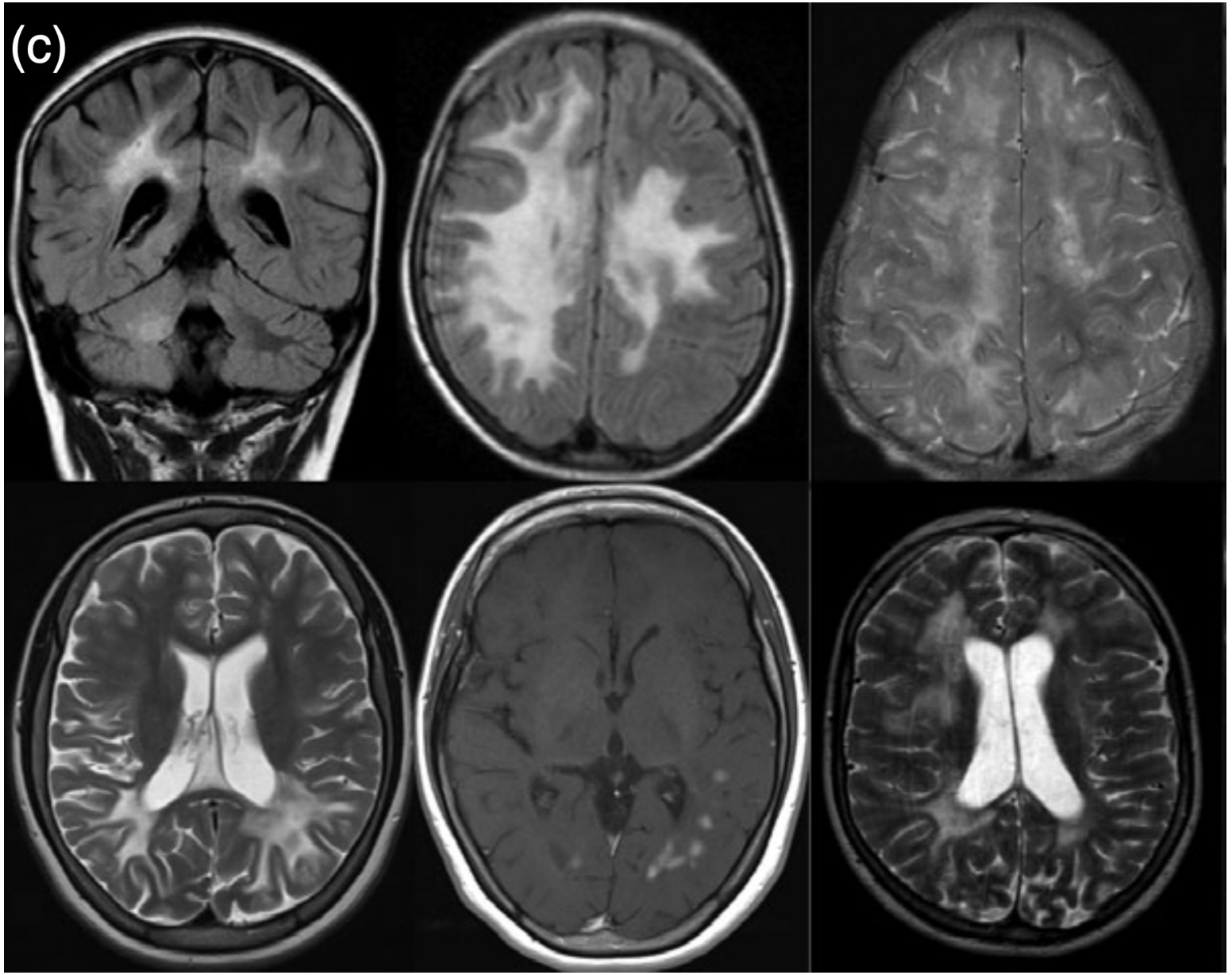


Figure 1: Association between age at onset and magnetic resonance imaging patterns in myelin oligodendrocyte glycoprotein antibody-associated disease. The box-plot (showing median and interquartile range) demonstrates the relationship between the predominant imaging pattern and the age group. (a) The 'leukodystrophy-like' pattern was predominantly seen in younger children; (b) confluent, hazy/poorly marginated lesions involving both grey and white matter were seen in the middle-age group; (c) the spinal cord/optic nerve (ON) involvement with normal or non-specific brain imaging was seen in the older group. TM, transverse myelitis.

Hacohen et al. Developmental Medicine & Child Neurology . 2018

MOG-IgG positive ADEM with leukodystrophy-like pattern on MRI brain



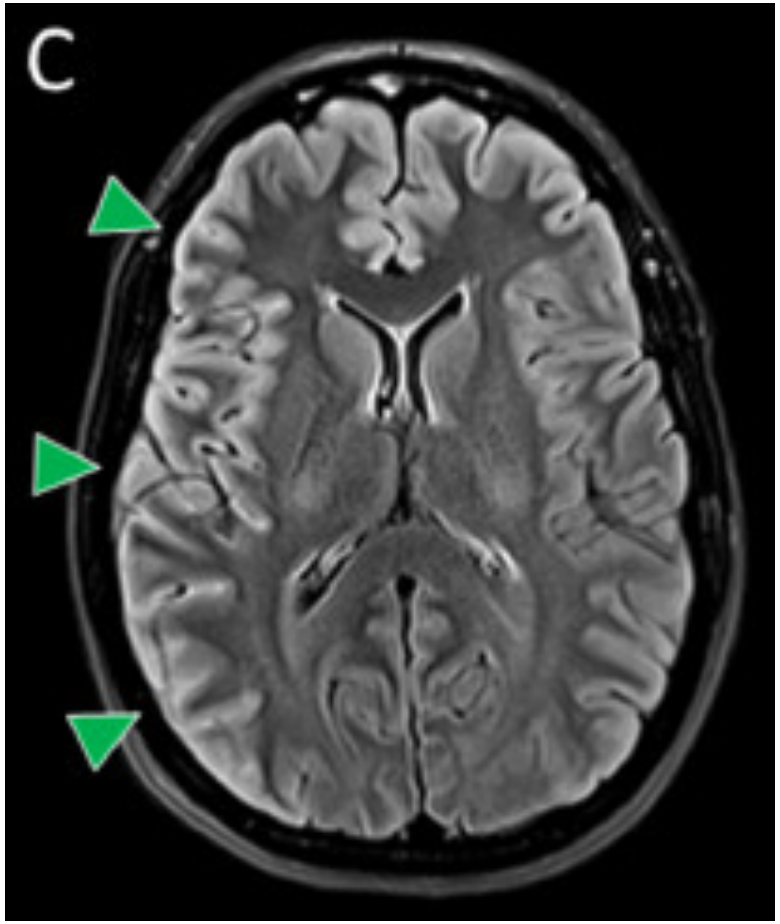
Hacohen et al. Developmental Medicine & Child Neurology . 2018

Clinical Phenotypes of MOGAD

Brain and brainstem involvement

Cerebral cortical encephalitis

- Occurs in 6.7% (19 of 285) patients with MOG-IgG
- **Presentation**: fever, **headache**, reduced consciousness, **seizures** (focal or generalized), or **status epilepticus**
  - Symptoms of raised intracranial pressure can also occur and can be life-threatening
  - **FLAMES (FLAIR hyperintense lesions in anti-MOG encephalitis with seizures)** = cortical lesions with MOG-IgG and seizures (which are more apparent with FLAIR sequences)
  - Overlying leptomeningeal enhancement (89%)
- **NMDAR Ab** should be tested (co-positive in 4-7.5%)



Valencia-Sanchez et al. Annals of Neurology. 2022

Budhram et al. MS and Related Disorders. 2020

Clinical Phenotypes of MOGAD

Relapses

Definition

- a new clinical attack occurring **>30 days following onset of a previous attack**

  - More common in the **first 6 months** than later after the first attack
  - Relapses can occur **within 2 months following oral corticosteroid therapy tapering or cessation**
  - Cluster of early relapses may occur
- **Relapses in adults**: 2 studies showed similar relapse risks
  - 16 (36%) of 44 patients with a median follow-up of 15.5 months
  - 37 (27%) of 139 patients with a median follow-up of 10.78 months
  - Relapse risk was greatest over the first few months from the initial attack (but the follow-up duration was short)

Banwell et al. Lancet. 2023

Clinical Phenotypes of MOGAD

Relapses

- **Relapses in pediatrics**: 17-20% of the 200 patients experienced relapsing disease over a median observation period of 1-7 years (the median time to first relapse was 11 months)

- **Study with longer follow up (UK)**: 183 patients with MOG-IgG (68 pediatric onset and 115 adult onset) followed for a median of 24.4 months (range 1.2-235.1 months), **the 4-year risk of relapse was 31.7% and the 8-year risk was 36.3%**

Summary

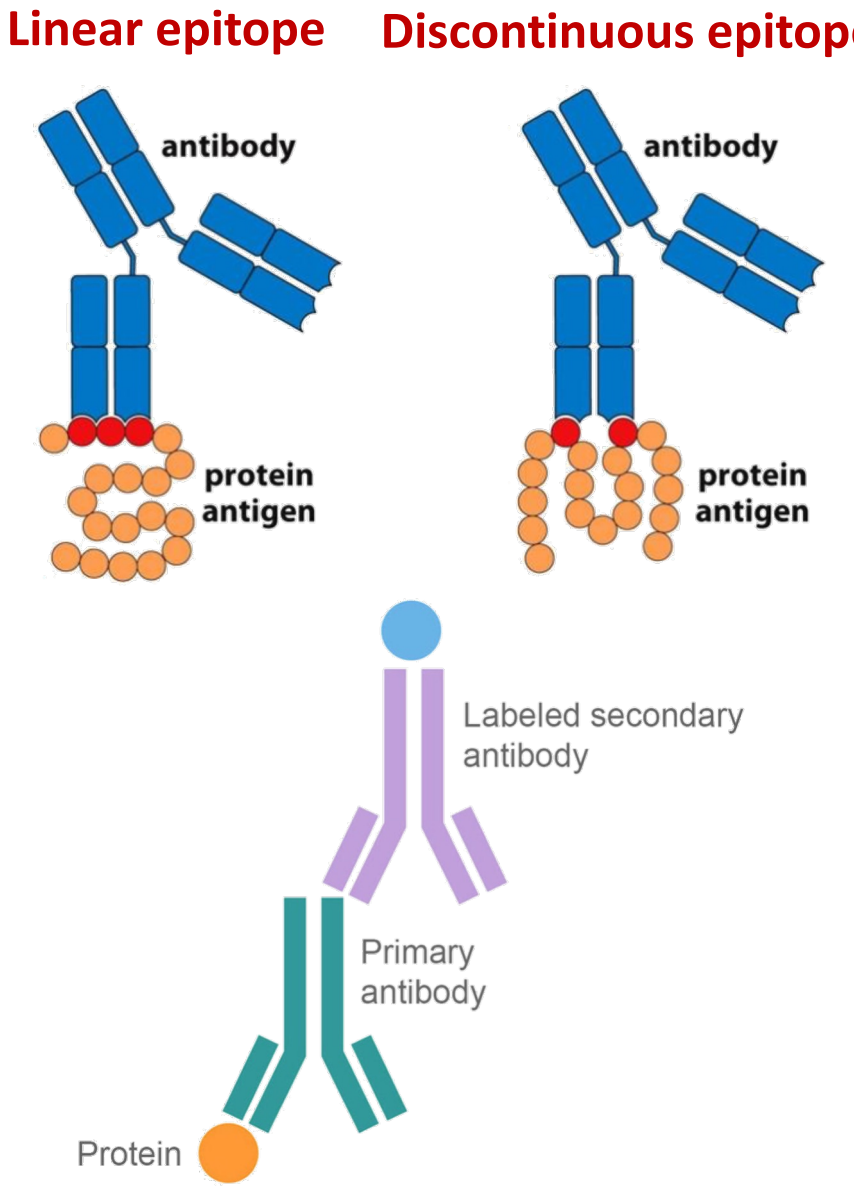
Relapse rate of MOGAD is about 27-37% over the first 1-2 years
Risk of relapse is higher in ON and NMOSD phenotypes

Banwell et al. Lancet. 2023

Laboratory Investigations

MOG-IgG testing | **Method**

- As pathogenic MOG IgG is conformational (discontinuous) epitope antibodies, **cell-based assay** (with **full-length human MOG**) is more sensitive and specific
  - **Live CBA is preferred** (to fixed CBA which carries lower Se and Sp)
- **Serum** is preferred specimen type for MOG-IgG testing (positive CSF alone = 3-4%; paired serum-CSF positive in 42-89%)
- **MOG-IgG are IgG1**: **IgG1 Fc secondary Ab** is recommended



Sechi et al. JAMA Neurology. 2021

Laboratory Investigations

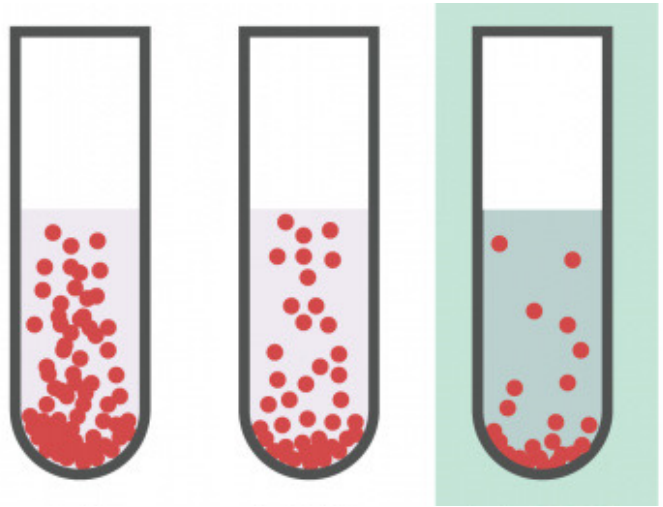
MOG-IgG testing **Method**

- Titer or semi-quantitative results should be reported *(rationale: **higher titers are more reproducible**)*

- An international, multicenter, blinded comparative study of 7 live cell-based assays from 4 centers: **excellent interlaboratory agreement for clear positive results** whereas low positive samples were more frequently discordant
- PPV for clinical features consistent with MOGAD increased with increasing titer of MOG-IgG

Definition of clear positive

- **Live CBA**: at least two doubling dilutions above the assay cutoff
- **Fixed CBA**: titers ≥1:100

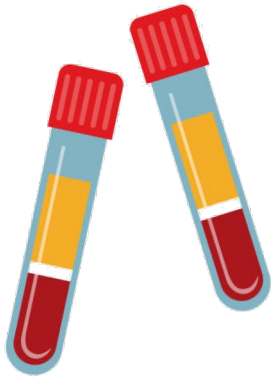


Sechi et al. JAMA Neurology. 2021

Laboratory Investigations

MOG-IgG testing | **Timing**

- Highest likelihood of MOG-IgG seropositivity when tested **at the time of attack**, ideally **before treatment** with of steroids, IVIg, or apheresis *(as observed in AQP4-IgG testing)*



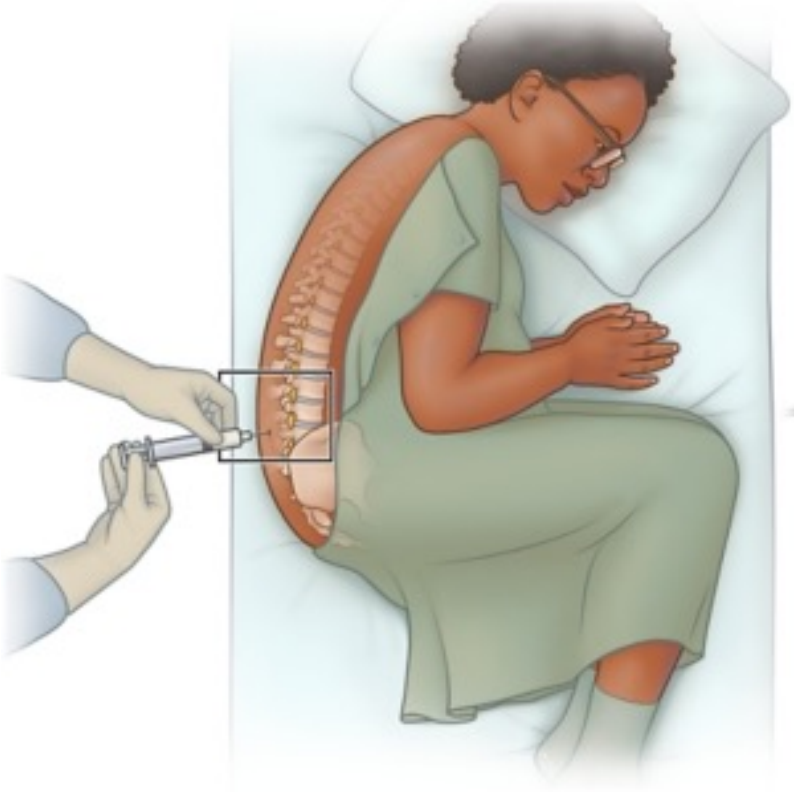
- If initial testing was negative but obtained after administration of acute therapies → **repeat at 3 months** or at the time of relapse
- MOG-IgG titers usually **decline with time** (but can remain positive for years, or become seronegative with or without immunotherapy)
- Seroconversion from negative to positive is extremely rare if initial test at the onset is negative
- **Repeated testing if initial positive**: persistent positivity is associated with an **increased risk of relapse by a factor of 2-10** (timing at 6 mo?)

Jarius et al. Brain. 2008

Laboratory Investigations

CSF analysis

- **CSF pleocytosis**: WBC >5 per µL, occurs in >50% in the first attack of MOGAD (12% have >100 WBC/HPF) especially in **ADEM or TM** (less common in ON alone)
- **CSF protein**: elevated in 30% of patients with a first demyelinating attack and MOG-IgG (not different from other neuroinflammatory disorders)
- **CSF OCB**: strongly favor a diagnosis of MS (but can be detected transiently in up to **20% of MOGAD**)
- **CSF Ab to measles, rubella, and VZV**: absent in MOGAD but very common in MS



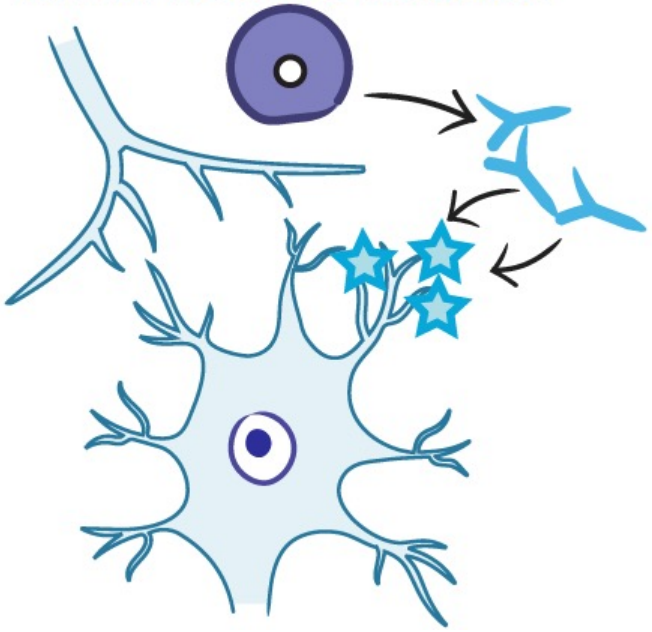
Banwell et al. Lancet. 2023

Laboratory Investigations

Other antibody testing

- **MOG-IgG and AQP4-IgG**: dual positivity is very rare, and when it occurs, the **AQP4-IgG titers are nearly always high** whereas the MOG-IgG titers are low

- **MOG-IgG + anti-NMDAR Ab**: can be found in MOGAD and anti-NMDA receptor encephalitis overlap syndrome
  - **History of episodes** of encephalitis or demyelination, or can have **concurrent** serum MOG-IgG and CSF NMDA receptor antibodies and manifest with clinical features of anti-NMDA receptor encephalitis (including encephalopathy, psychosis, seizures, and dyskinesias) + clinical and MRI features of CNS demyelination



Banwell et al. Lancet. 2023

Diagnosis

Diagnostic criteria

(A) Core clinical demyelinating event

- Optic neuritis
- Myelitis
- ADEM
- Cerebral monofocal or polyfocal deficits
- Brainstem or cerebellar deficits
- Cerebral cortical encephalitis with seizures

(B) Positive MOG-IgG test

- Clear positive in serum
- Low positive or positive without reported titer or CSF positive alone requires the following:
  - Negative AQP4-IgG
  - At least 1 supportive features of ON, TM

(C) Exclusion of better diagnosis including MS

Supporting features

- **ON**: bilat, longitudinal (>50%), perioptic sheath enhancement, disc edema)
- **Myelitis**: LETM, central lesion or H-sign, conus
- **Brain/brainstem**:
  - Multiple ill-defined T2 lesions in supratent + infratent WM
  - Deep gray involvement
  - Ill-defined T2 lesions at pons, MCP, or medulla
  - Cortical lesion + meningeal enhancement

Banwell et al. Lancet. 2023

Diagnosis

Red flag against MOGAD

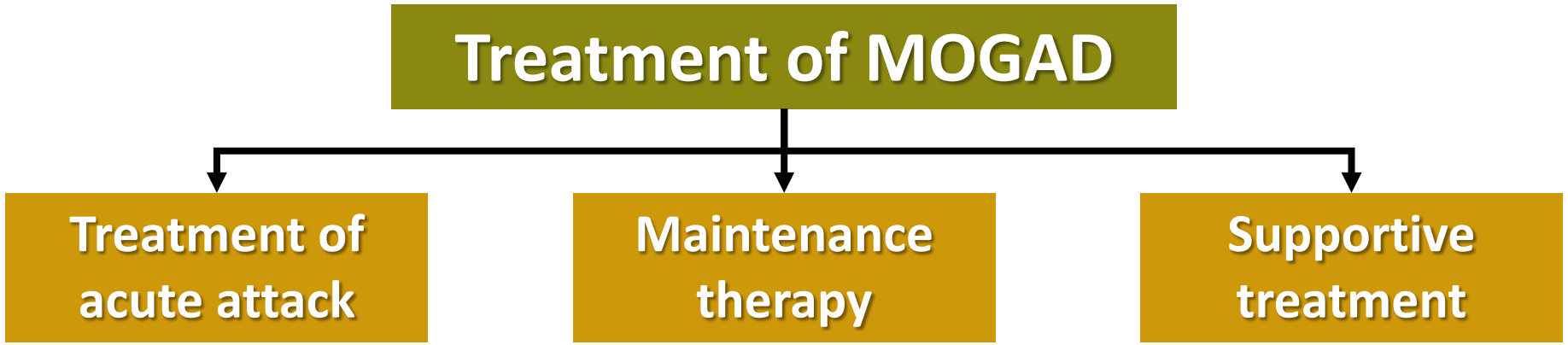
- Progressive course
- Rapid worsening within minutes to hours
- No improvement with high-dose corticosteroid therapy
- MRI with MS features
- Positive OCB
- Persistent contrast enhancement

Banwell et al. Lancet. 2023

Treatment

General principles

- There are **no RCTs** available in MOGAD
- Existing recommendations for treatment are mostly derived from data on AQP4-IgG+NMOSD, and retrospective studies
- Some drugs that are typically very effective in AQP4-IgG+NMOSD, such as **rituximab**, seem **less effective in MOGAD**

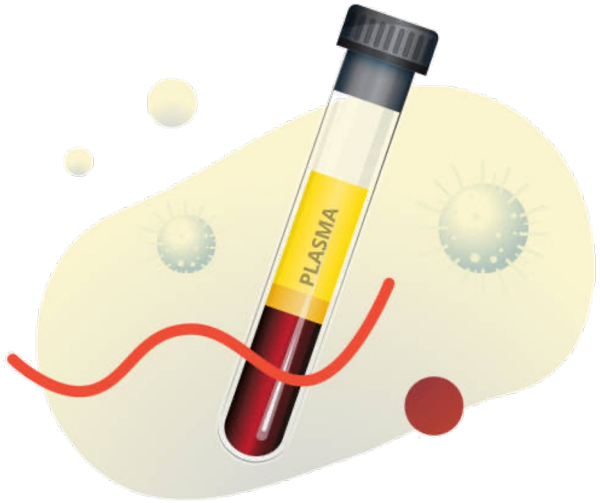


Sechi et al. Frontiers Neurology. 2022

Treatment

Treatment of acute attacks

- **High dose corticosteroids**: most patients respond briskly (earlier treatment may lead to better outcomes)
  - **Dosage**: IVMP 1 g OD for 5 days or oral prednisone 1250 mg/d for 5 days
- **PLEX**: early IV corticosteroids + PLEX 5-7 exchanges every other day in patients with **severe attacks** and **high disability at attack nadir** is reasonable
- **IVIg**: limited data in MOGAD attacks but may represent a reasonable treatment option after PLEX in very **severe/refractory cases**
  - **Dosage**: 0.4 g/Kg/day for 5 days

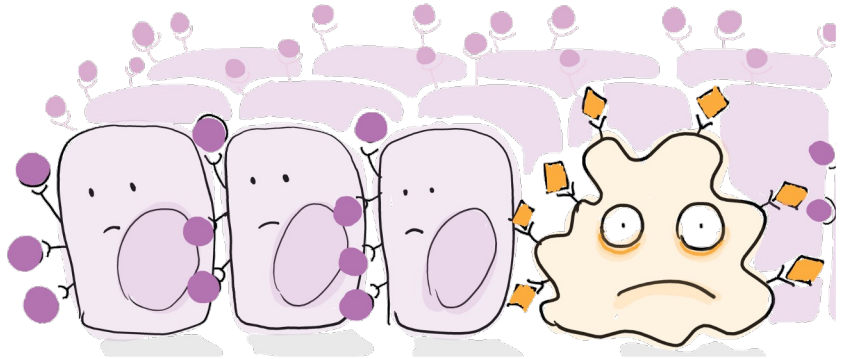


Sechi et al. Frontiers Neurology. 2022

Treatment

Maintenance therapy

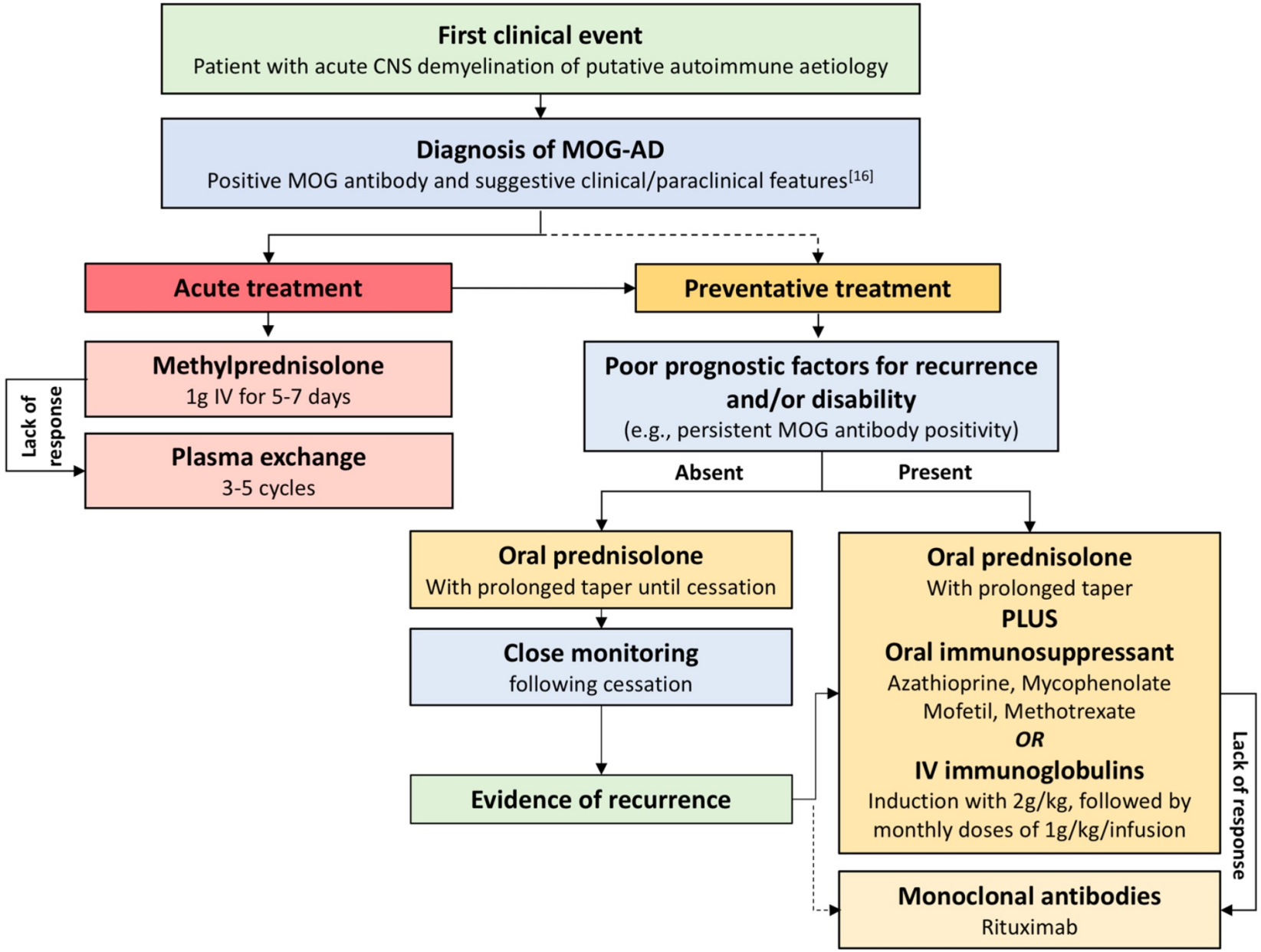
- Attack-prevention therapy is offered to those that have had 2 or more attacks, but not initiated after the first attack to avoid over treatment of monophasic disease (which is about 40-50%)
  - Exceptions in patients with **severe residual deficits** following the presenting attack, to prevent further disability



Maintenance immunotherapy

- Maintenance IVIg
- Rituximab
- Azathioprine
  MMF
- IL-6 targeting therapy

Sechi et al. Frontiers Neurology. 2022



Wynford-Thomas et al. Journal of Neurology. 2018

Treatment

Supportive treatment

- **Chronic pain and depression** (with strong correlation with each other) have been reported in up to 51 and 42% of patients with MOGAD, respectively
- **Mechanisms**: neuropathic, spasticity-associated, and/or painful tonic spasms
- **Treatment**: non-opioid analgesics, antidepressants (e.g., duloxetine), and antiepileptic agents (e.g., gabapentin, pregabalin)
  - **Painful tonic spasms** generally respond well to low dose **carbamazepine** (200-300 mg/day)
  - **Immunosuppressive treatment** has also been reported to improve pain
  - **Muscle relaxants** (e.g., baclofen, benzodiazepines) and physical rehabilitation should be offered for spasticity

Sechi et al. Frontiers Neurology. 2022

Summary

Epidemiology	**No sex and race predilection**		**Unknown genetic?**
Pathogenesis	**Outside-in**	**B cell + Th cell**	**MOG-IgG**
	Complement activation	**Oligodendrocyte injury**	**Demyelination**
Clinical features	**ON (adults)**	**TM**	**Brain**
	Bilateral	Central, H-sign	ADEM (children)
	Retrobulbar	LETM	Cerebral cortical encephalitis
	Peri-optic involvement	Conus medullaris	Brainstem or cerebellar (MCP lesion, no MS signs)
Diagnosis	**Core clinical features**	**Serum MOG-IgG (CBA)**	**No MS features**
Treatment	**IVMP for acute attacks**	**DMT for recurrent or high-risk pts**	**Supportive treatment**


Thank you!