Work-up diagnostico-terapeutico
Malattie Demielinizzanti in età pediatrica

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ACQUIRED DEMYELINATING SYNDROME (ADS) IN PEDIATRIC AGE

«An important advance in pediatric demyelinating disorders is the recognition that an acute demyelinating syndrome can represent the first attack of not only multiple sclerosis but also neuromyelitis optica spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein (MOG) antibody–associated demyelinating disease, and other multiphasic disorders in children»

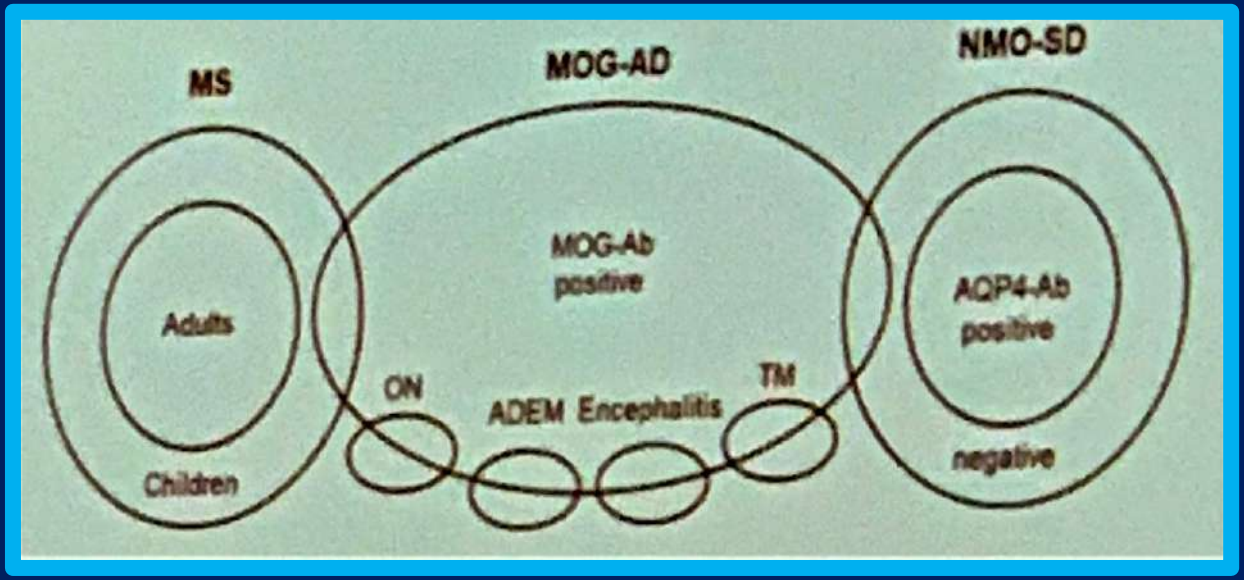
Chitnis 2019

ACQUIRED DEMYELINATIN SYNDROME (ADS) IN PEDIATRIC AGE

EPIDEMIOLOGY

ADS (0,8/100.000 children/years)

- Multiple Sclerosis (MS) 20%
- Neuromyelitis optica spectrum disorder (NMOSD) 5%
- Myelin-oligodendrocite gLycoprotein antibody associated disease (MOGAD) 30%



A female preponderance is present among adolescents but not among younger children

Fadda Lancet Neurology 2021

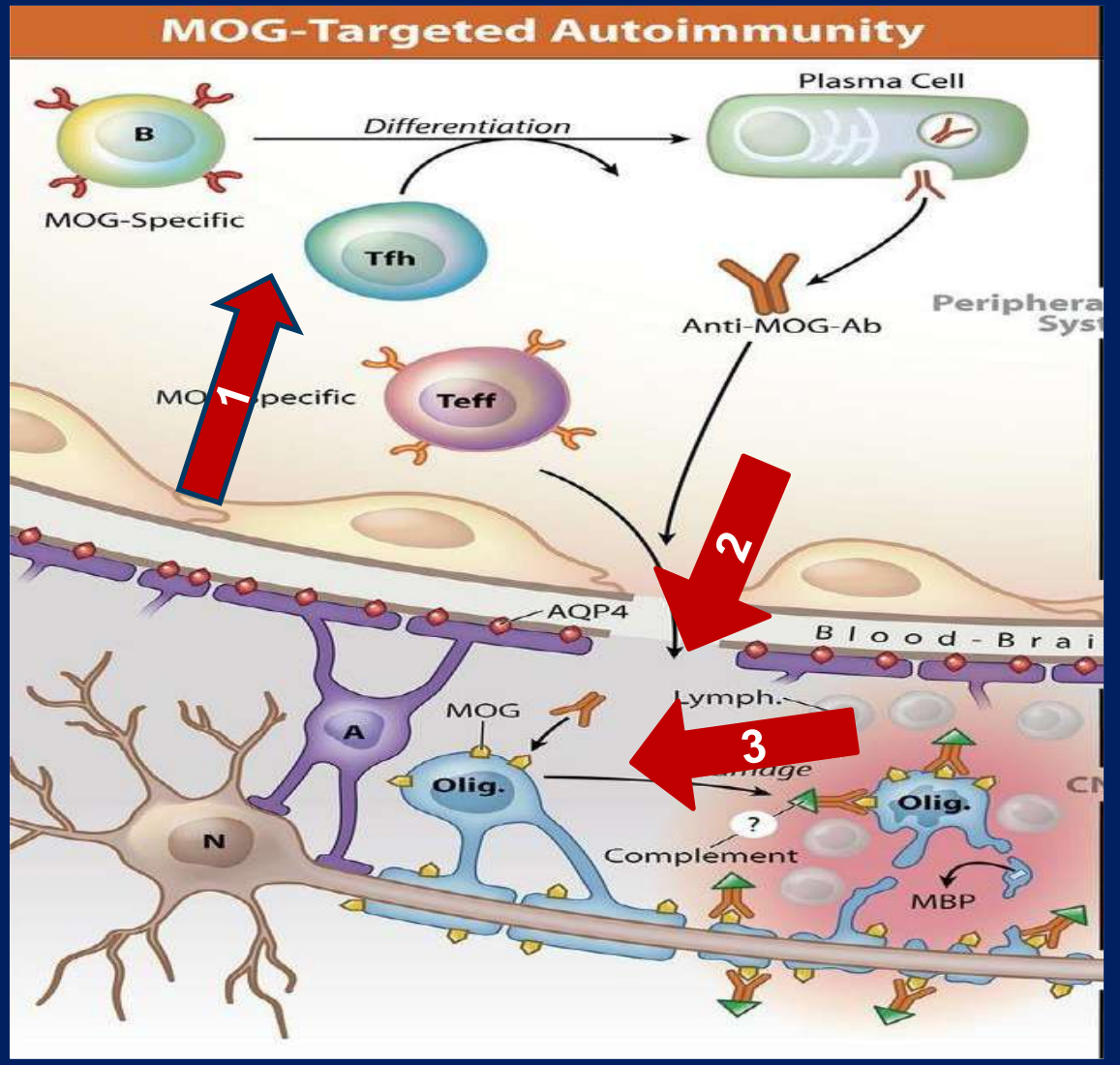
Myelin oligodendrocyte glycoprotein (MOG)-targeted Autoimmunity

1) Anti-MOG autoantibodies are mainly produced in the periphery

2) They cross the BEE altered by infection-activated T lymphocytes or CNS antigens

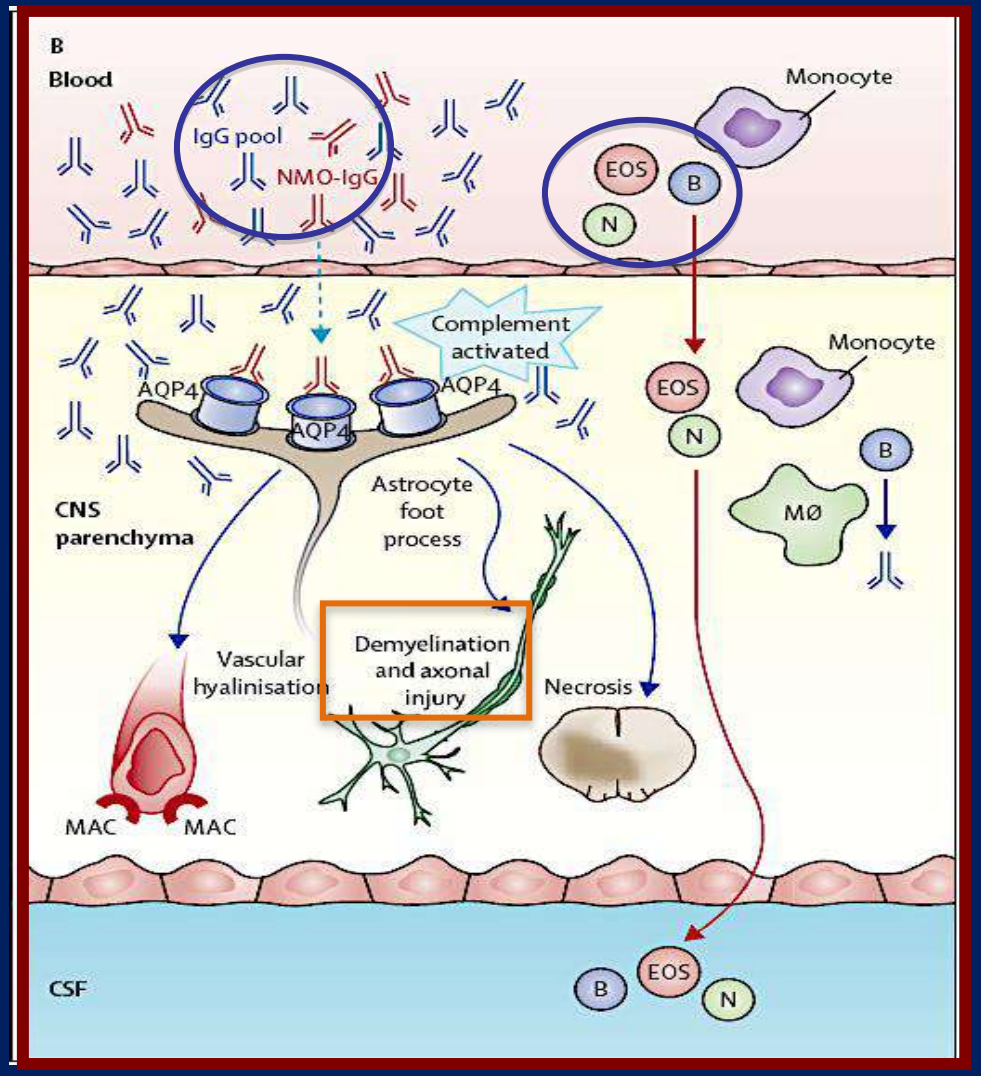
1) They penetrate the CNS where they reach their target

Anti-MOG antibodies, predominantly of class IgG-1 directed against extracellular conformational epitopes of glycosylated MOG, cause demyelination



McLaughlin KA, J Immunol. 2009 ; Rostásy K, Mult Scler. 2013

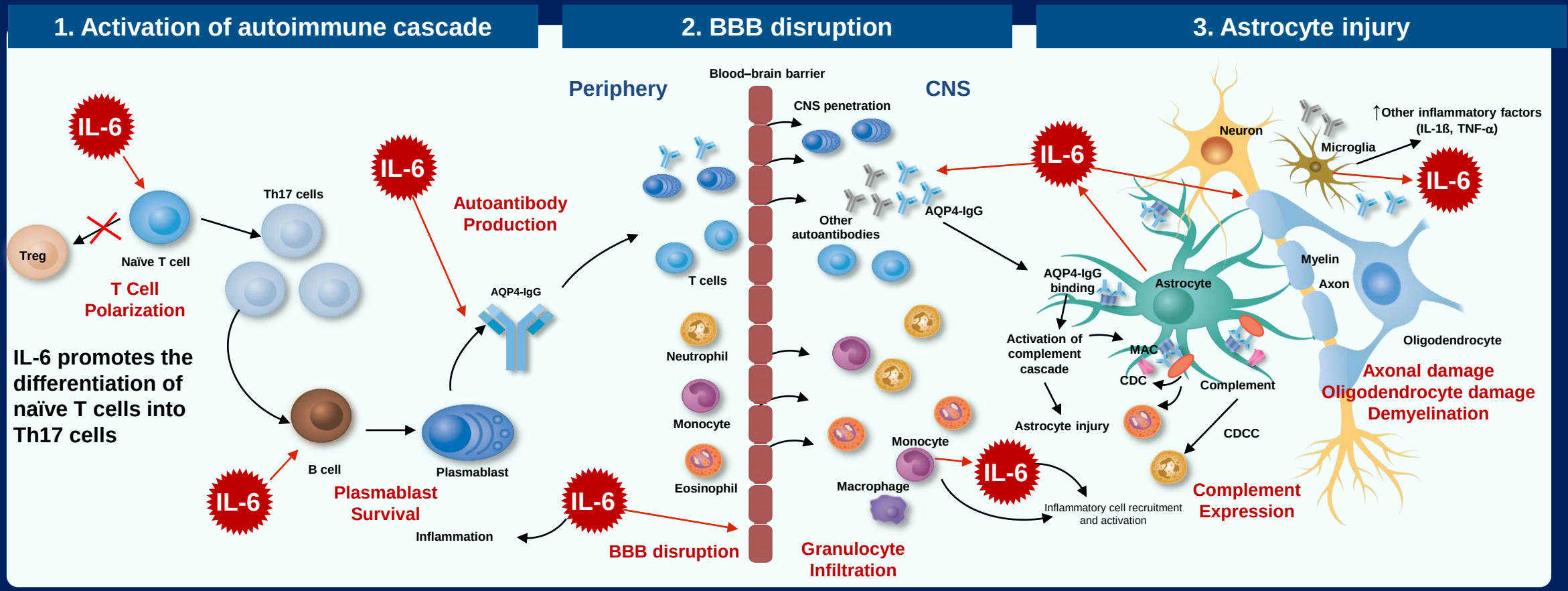
Aquaporin 4 Antibody (AQP-4)-targeted Autoimmunity



- Pathogenesis NMOSD involves generation of AQP4-IgG autoantibody in the periphery and its entry into the CNS.
- The target antigen AQP-4 water channel is located on astrocytic foot process of BBB.
- Serum anti-AQP4-antibodies reach the CNS both through endothelial transcytosis or at areas of relative BBB permeability or injury
- The aquaporin-4 autoantibodies bind to aquaporin 4 expressed on astrocytes, activating the classical complement cascade. This leads to the infiltration of granulocytes and macrophages, astrocyte damage, and, ultimately, demyelination

[Zamvil S and Slavin AJ Neurol Neuroimmunol Neuroinflamm 2015; Wingerchuk et al. 2007]

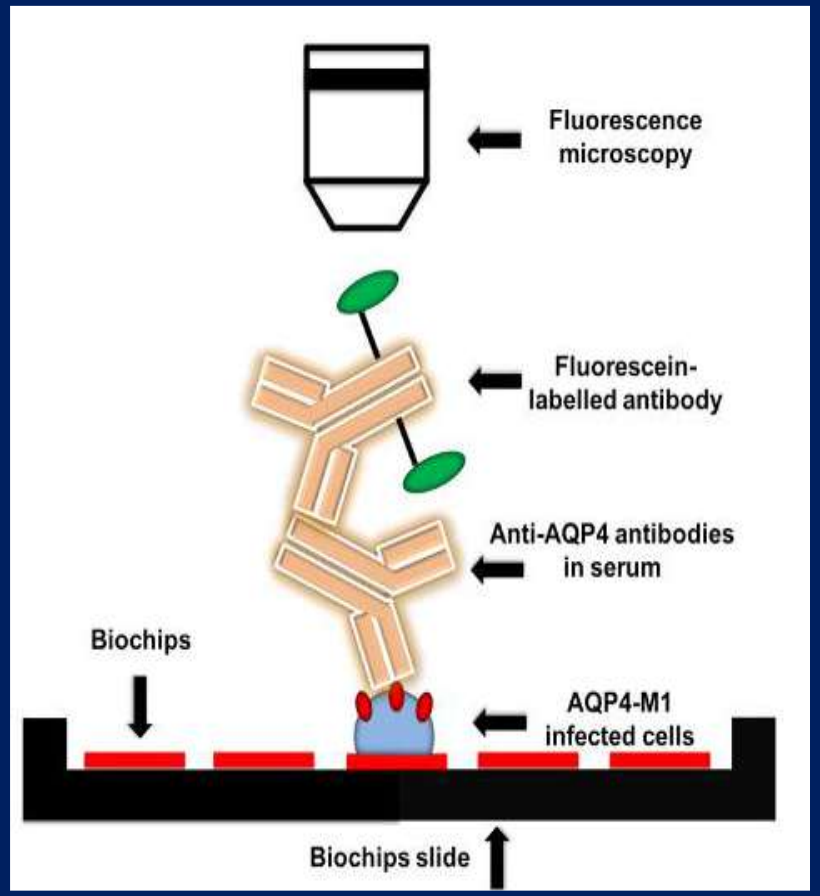
IL-6 is a central driver of NMOSD pathophysiology



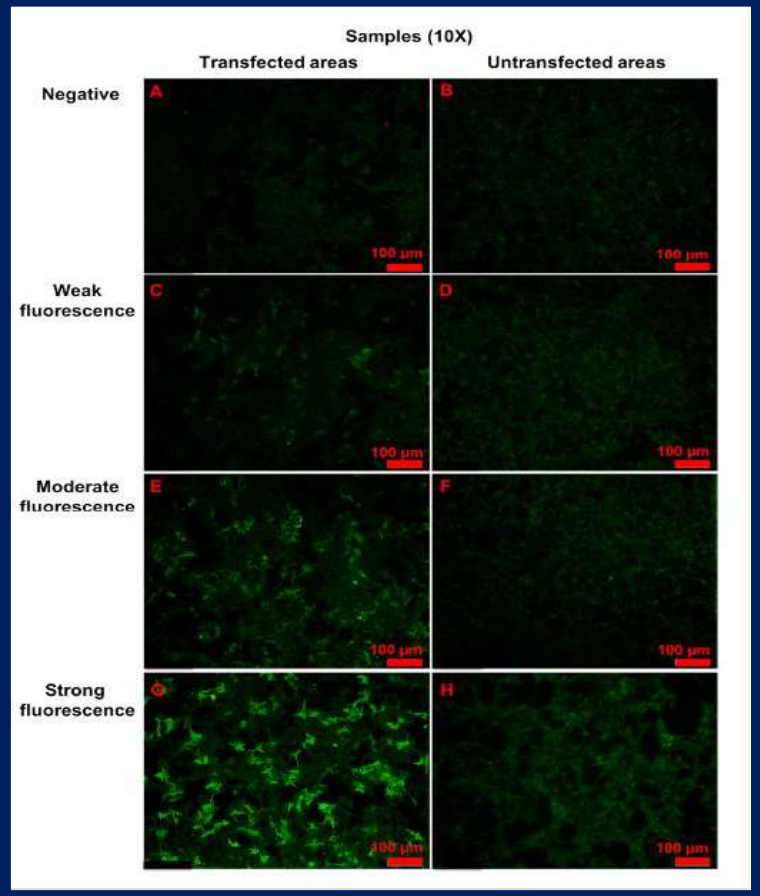
Aquaporin-4; AQP4-IgG, aquaporin-4 immunoglobulin G; BBB, blood-brain barrier; CDC, complement dependent cytotoxicity; CDCC, complement-dependent cellular cytotoxicity; MAC; membrane attack complex; Treg, regulatory T cell

1. Kimura K, et al. Eur J Immunol 2010;40:1830–1835. 2. Lin J, et al. Int J Neurosci 2016;126(12):1051–60. 3. Weinshenker BD, Wingerchuk DM. Mayo Clin Proc. 2017;92(4):663–679. 4. Chihara N, et al. Proc Natl Acad Sci USA 2011;108:3701–3706. 5. Takeshita Y, et al. Neurol Neuroimmunol Neuroinflamm 2017;4:e311. 6. Obermeier B, et al. Nat Med 2013;19:1584–1596. 7. Uzawa A, et al. Clin Exp Neuroimmunol 2013;4:167–172. 8. Kaplin AJ, et al. J Clin Invest 2005;115:2731–2741. 9. Rothhammer V, et al. Semin Immunopathol 2015;37:625–638. 10. Papadopoulos MC, et al. Nat Rev Neurol 2014;10:493–506. 11. Erta M, et al. Int J Biol Sci 2012;8:1254–1266 12. Barnum SR, et al. Glia 1996;18:107–117.

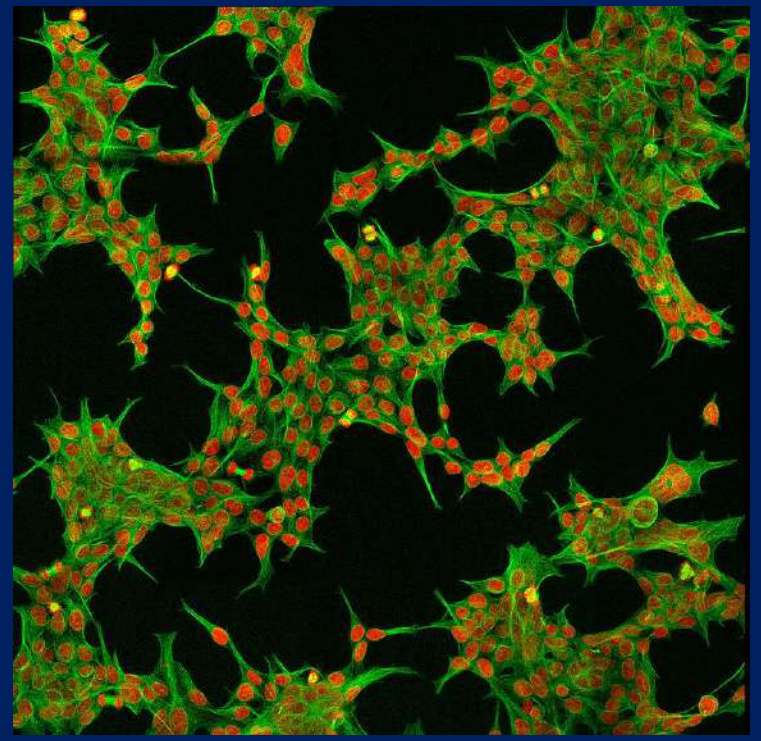
Human Serum Anti-aquaporin-4 Immunoglobulin G and anti-MOG Immunoglobulin G detection by Cell-based Assay



Liu 2019 Jove



anti-AQP4 antibody negative or positive samples.

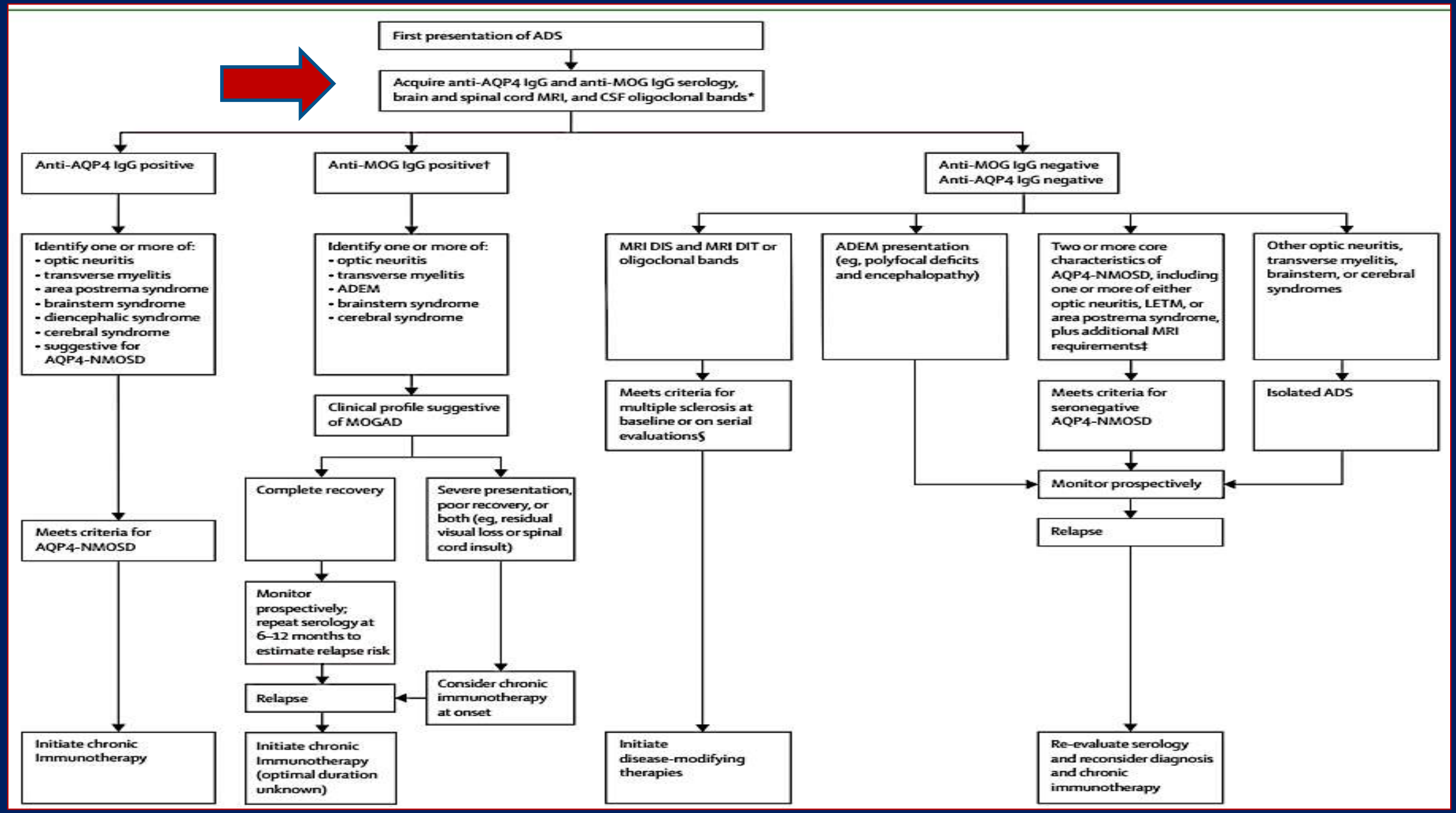


anti-MOG antibody positive samples.

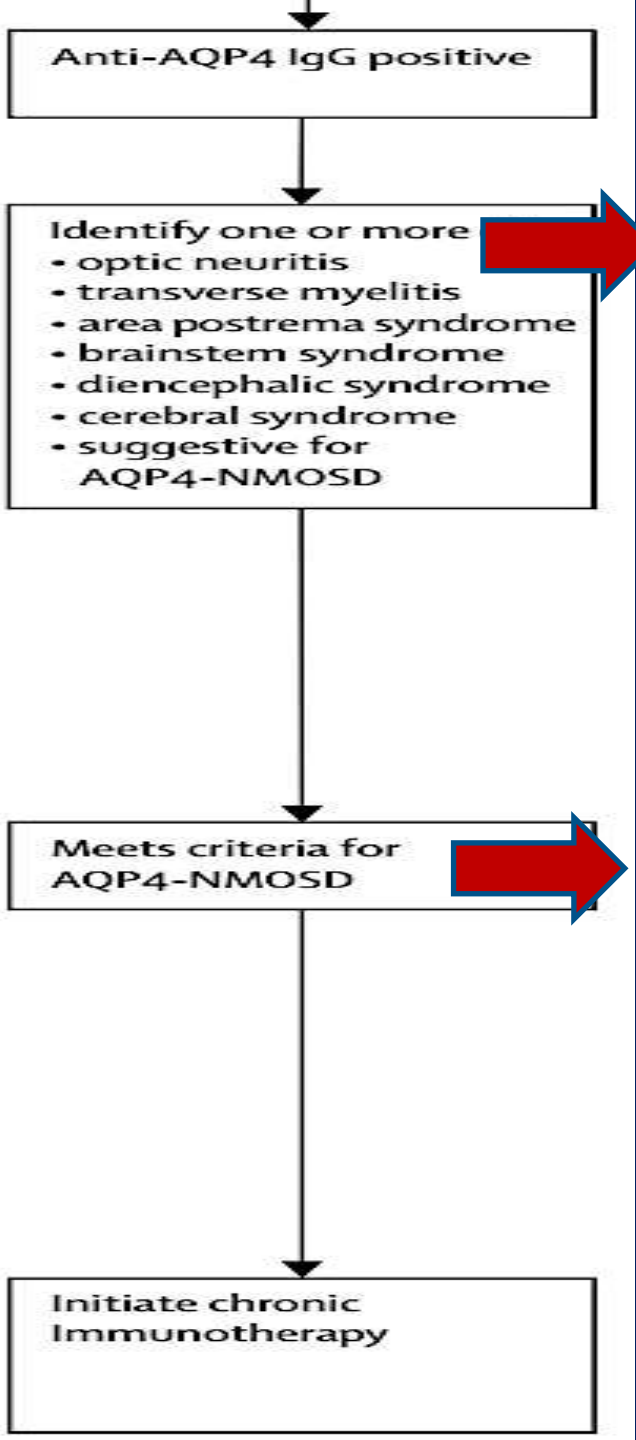
The stably transfected cell line (HEK) is used with the human isoform MOG fused with the fluorescent protein GFP, green, and with the isoform without the fluorescent tag

McLaughlin KA, J Immunol. 2009
Rostásy K, Mult Scler. 2013

DIAGNOSTIC AND THERAPEUTIC ALGORITHM FOR PAEDIATRIC ADS



Fadda Lancet Neurology 2021



NMOSD-AQP+

NMOSD < 5% in pediatric pts

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

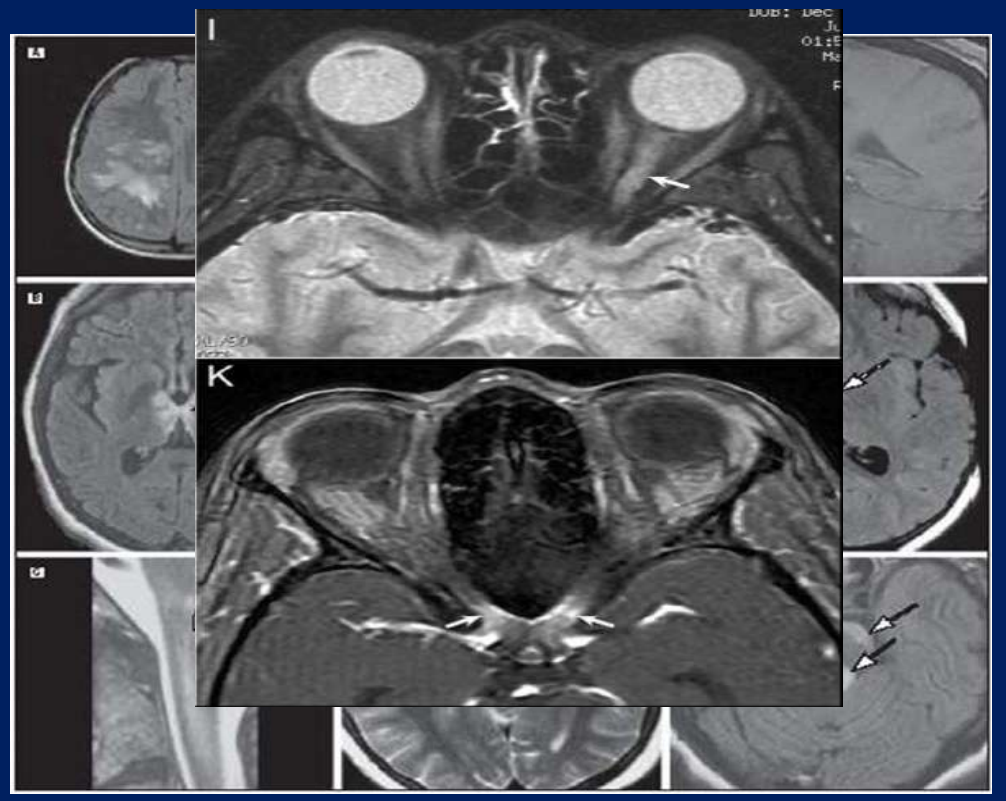
1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm (figure 1)
2. Acute myelitis: 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)

Wingerchuck Neurology 2015

NMOSD-AQP+: CLINICAL AND MRI FEAUTURES

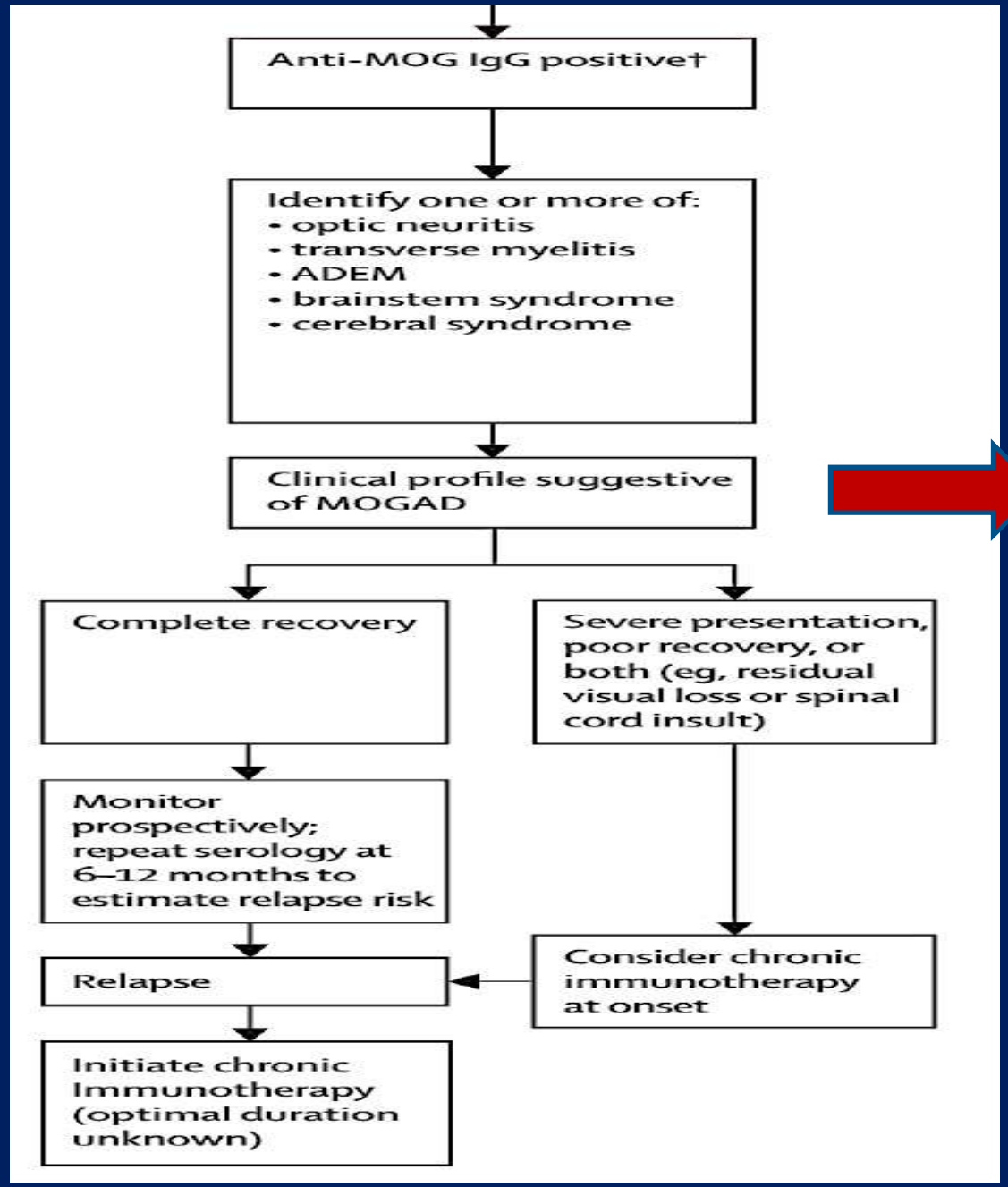
Cole J. et al. Pediatric Neurology 2019

- ON = Often bilateral. Longitudinally extensive with involment of optic tract and chiasma
- TM = Longitudinally extensive transverse myelitis (LETM) with cervic-thoracic spinal cord involvment
- Area postrema syndrome = prolonged and intractable vomiting and hiccups
- Brainstem syndrome = diplopia, facial palsy, hearing loss, hypogeusia, pruritus, trigeminal neuralgia, vestibular ataxia, dysarthria, neurogenic respiratory disfunctions and nystagmus.
- Cerebral syndrome = hemiparesis, visual field involvement and signs of encephalopathy
- Diencephalic syndrome = Hypotension, hypersomnia, hypothermia, behavioral changes, amenorrhea, galactorrhea or narcolepsy



- Neuroimaging =T2-hyperintense; T1-hypointense and contrast-enhanced lesions Long optic nerve >3 contiguous spinal segments myelitis; dorsal brainstem (area postrema lesion), hypothalamic lesion, diencephalic lesion, periependymal destructive lesions

Tenembaum S. et al. Frontiers in Pediatrics 2019



Mog antibody associated disease (MOGAD)

- 30%-40% of ADS in pediatric patients

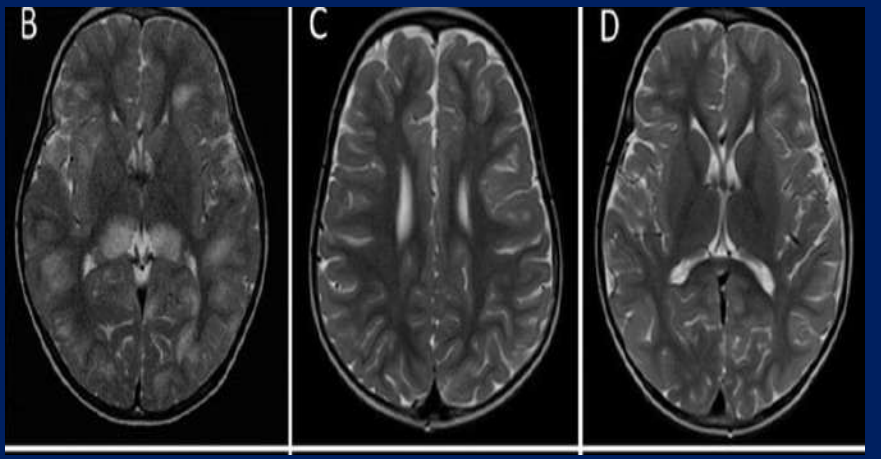
<u>Clinical phenotype</u>

- Optic neuritis 20-60%
- Transverse myelitis 15-20%
- Acute disseminated encephalomyelitis 20-60%

MAIN CLINICAL AND PARACLINICAL FEATURES IN MOGAD: ADEM

CSF=Rare oligoclonal bands (<10%)

ADEM	
Clinical features	**Most frequent presentation in children (<18 years);** only in about 5% of adult presentations; **seizures and encephalopathy at onset observed in up to 40% of children.**
Imaging	**Large, hazy, and poorly demarcated asymmetrical bilateral lesions; deep grey matter involvement,** most commonly affecting **the thalamus; lesions might be highly enhancing; corpus callosum, brainstem and cerebellum involved; frequently associated to spinal cord involvement; frequent complete resolution at follow-up scan**
Risk of relapses and outcome	**Up to 50% of children (<18 years) will relapse after acute disseminated encephalomyelitis**; **behavioural and cognitive problems might occur and are more common in relapsing group**; **up to 10% (predominantly very young children [younger than 7 years]) can develop a leukodystrophy-like phenotype**

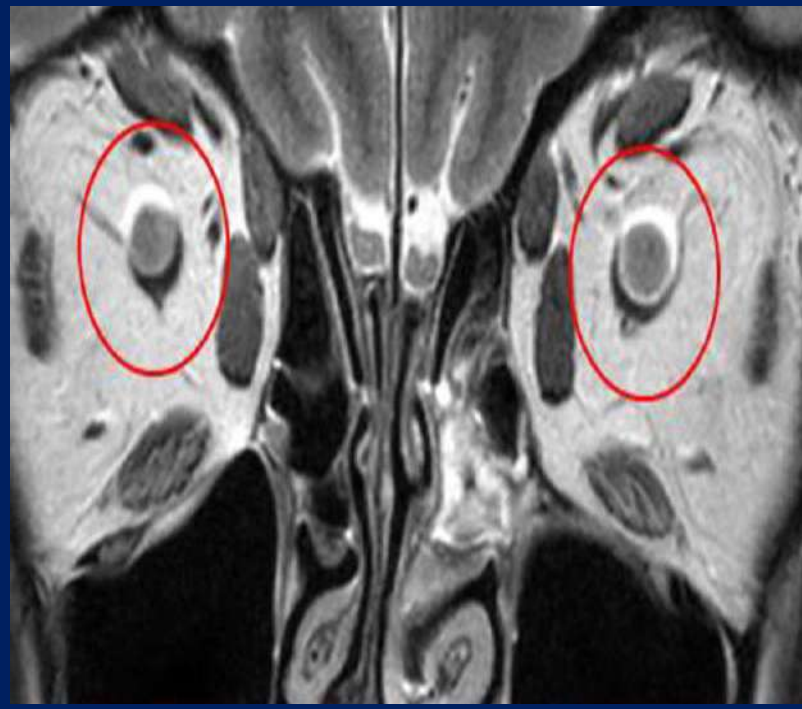


Marignier Lancet Neurology 2021

MAIN CLINICAL AND PARACLINICAL FEATURES IN MOGAD : OPTIC NEURITIS

OPTIC NEURITIS	
Clinical features	Up to 80% of patients, either at onset or during the disease course; **simultaneous bilateral involvement in up to 40%**; average high contrast visual acuity at nadir counting figures; optic nerve head swelling (papillitis); might have peripapillary haemorrhage; **more steroid responsive than in AQP4-NMOSD and multiple sclerosis.**
Imaging	**Extensive T2-weighted and gadolinium enhancing lesion in the optic nerve or chiasm**; **predominates in the anterior parts of nerve but might extend to optic chiasm;** peripapillary retinal nerve fibre layer thinning frequent on OCT but **clinical-radiological paradox** (despite severe atrophy of retinal nerve fibre layer, **visual acuity is preserved**)
Risk of relapses and outcome	**Patients aged <18 years at higher risk of relapse than older ones (>45 years)**

CSF=Rare oligoclonal bands (<10%)

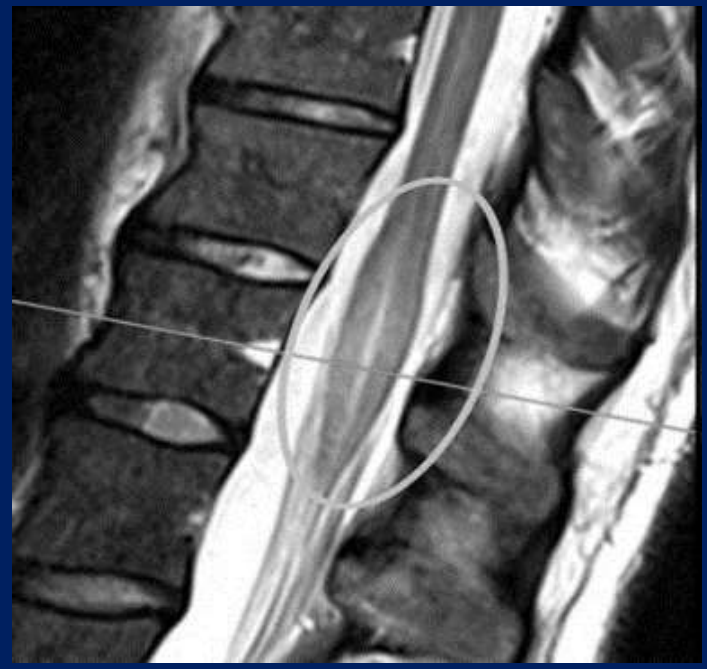


Marignier Lancet Neurology 2021

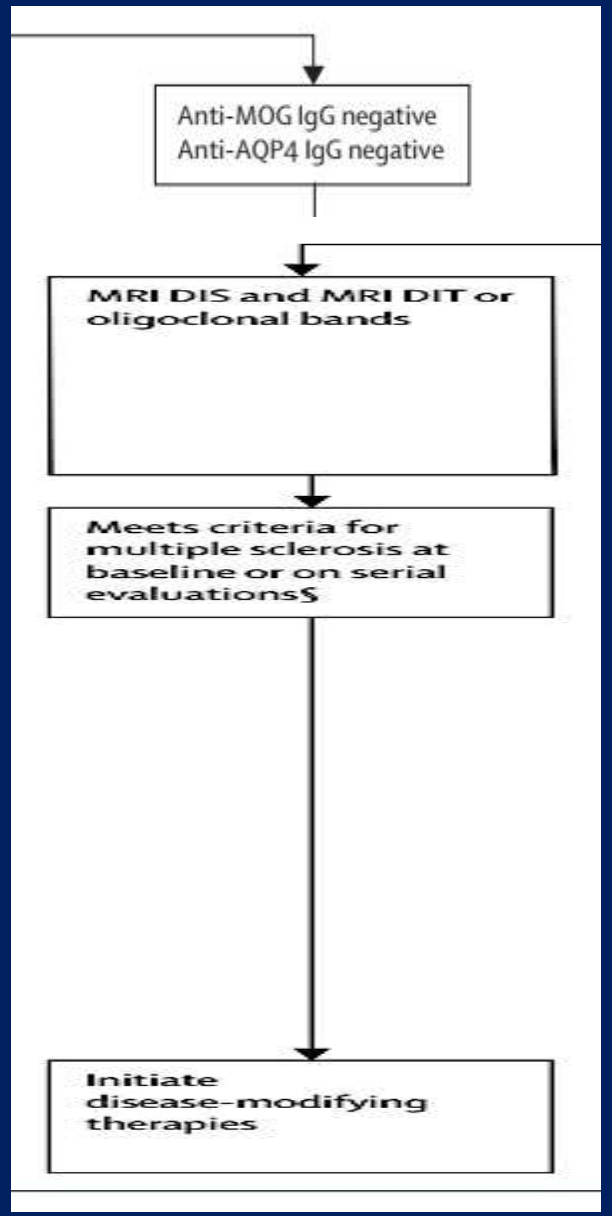
CLINICAL AND PARACLINICAL FEATURES IN MOGAD : TRANSVERSE MYELITIS

CSF=Rare oligoclonal bands (<10%)

TRANSVERSE MYELITIS	
Clinical features	**Spinal cord involvement in 30% of episodes at onset and up to 50% during the disease course; urinary, bowel, and erectile dysfunction are common**; more steroid responsive than AQP4-NMOSD and MS
Imaging	**Short myelitis in up to 40%; involvement of the conus medullaris (more frequent than in MS and AQP4NMOSD)**; abnormalities **confined to grey matter and nerve roots;** less frequent gadolinium enhancement than AQP4-NMOSD and multiple sclerosis; initial spinal cord MRI negative in 10% of patients; frequent complete resolution at follow-up scan
Risk of relapses and outcome	**Good or full recovery from the onset attack in 60% younger patients (<18 years)**; **around 20% of patients had permanent motor disability at 2 years; permanent bowel, bladder, and erectile dysfunction are frequent despite good motor recovery**



Marignier Lancet Neurology 2021

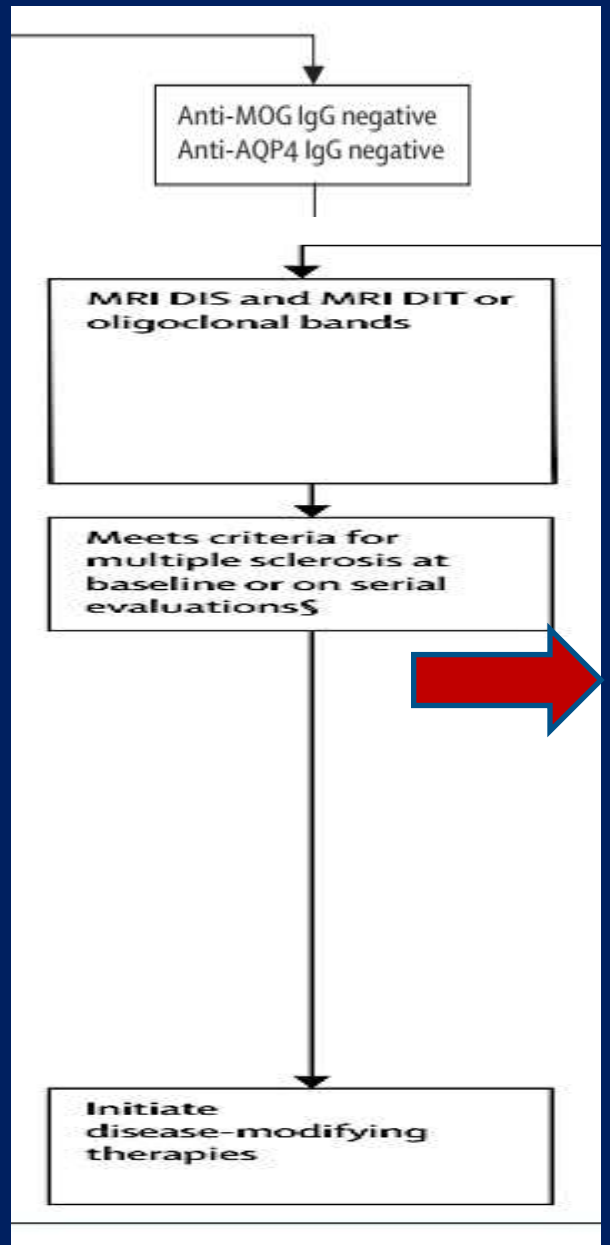


Pediatric onset Multiple Sclerosis (POMS)

- 20% ADS in pediatric patients

- 3-10% of total MS population
- Higher relapse rate
- Greater accumulation of MRI disease activity
- Earlier age of disability
- Greater long term cognitive impairment
- Not a benign disease

DIAGNOSTIC CRITERIA POMS



Diagnostic criteria

Demonstration of **dissemination in space** by the presence of two or more T2 lesions, either:

- One or more periventricular
- One or more cortical or juxtacortical
- One or more infratentorial
- One or more in the spinal cord

And either:

- Demonstration of **dissemination in time** by one or more contrast-enhanced lesions and one or more non-contrast enhanced lesions
- CSF oligoclonal bands
- Follow-up MRI showing at least one new enhanced or non-enhanced lesion
- Two or more episodes typical of multiple sclerosis, each lasting more than 24 h and separated by more than 30 days

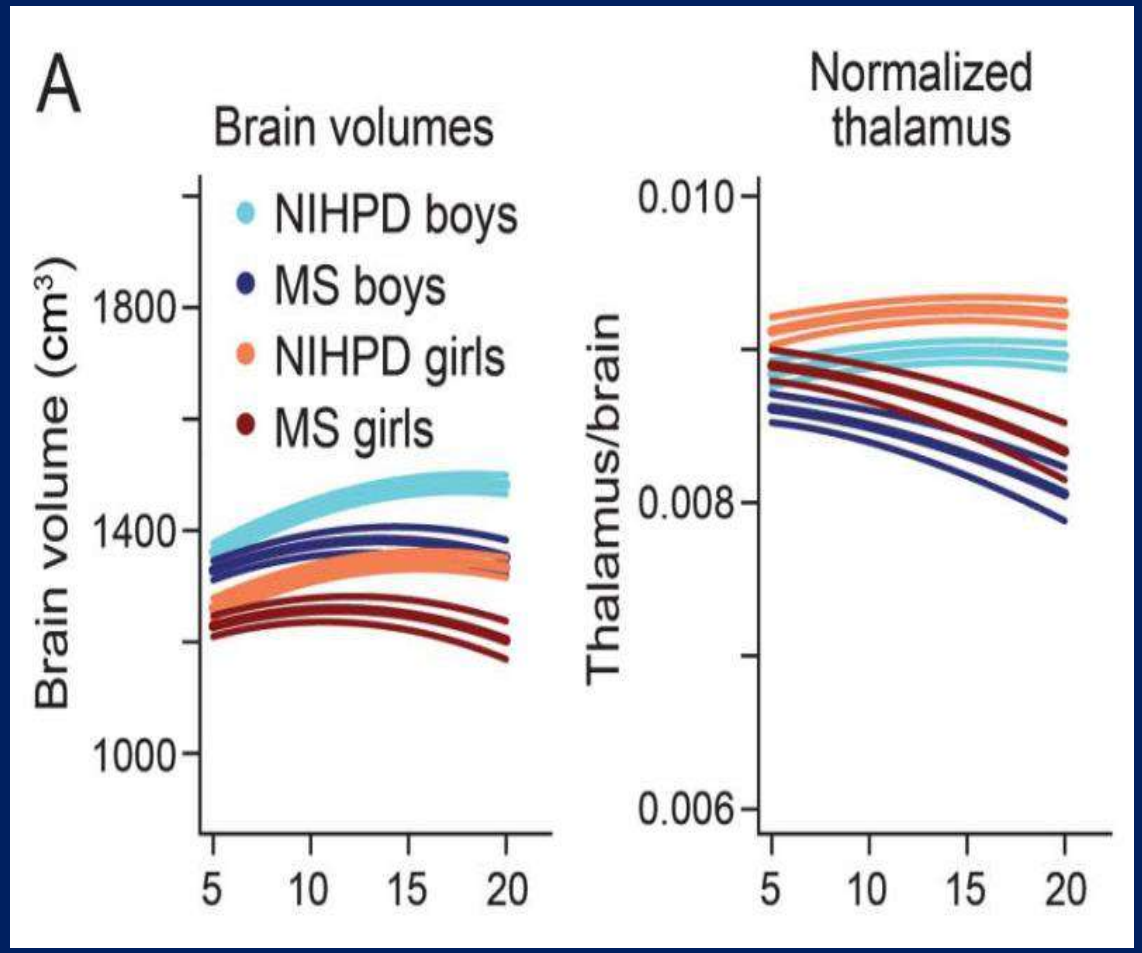
Thompson Lancet Neurol 2018

Diagnostic criteria : caveats for pediatric onset

1. **Particular caution should be applied for children presenting before 11 years of age**
2. **The criteria should not be applied at the time of an incident event with ADEM phenotype.**
3. **In children who present with ADEM, a future diagnosis of MS must be supported by additional clinical events typical of MS**

Hacohen Mult Sclerosis 2020

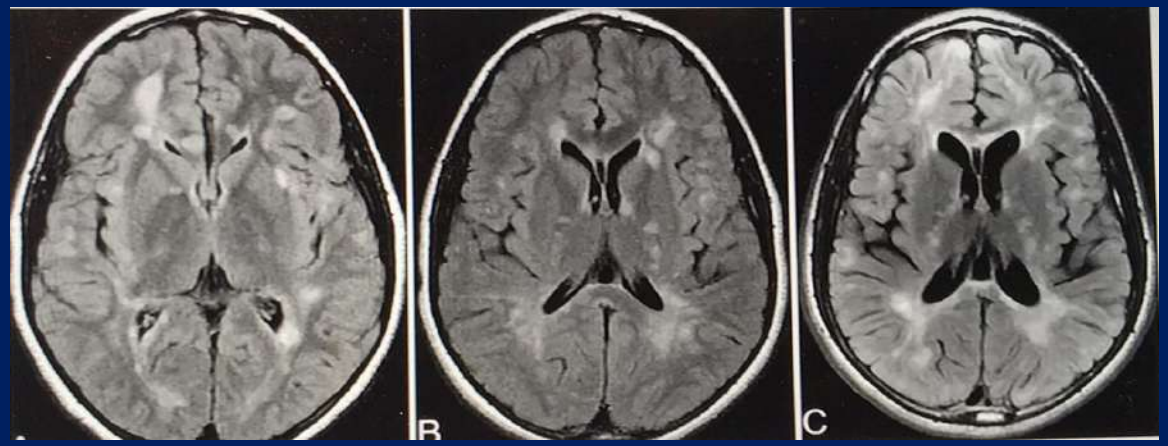
The impact of MS onset during childhood on brain growth



Aubert-Broche et al. Neurology 2014

Onset of MS during childhood and adolescence limits age-expected primary brain growth and leads to subsequent brain atrophy, implicating early neurodegeneration

Progression of atrophy (12 year old boy)



Presentation **1 year later** **2 years later**

POTENTIAL BIOMARKERS FOR DIFFERENTIAL DIAGNOSIS IN ADS

BIOMARKER	MOGAD	MS	AQP4 positive NMSOD	NOTES/COMMENTS
OCB	7-11%	>80%	15-30%	Rare in MOGAD, high positive predictive value in MS
Nfl	++	+++	+++	Increases during relapses and correlates to EDSS; possible biomarker for treatment response
Tau protein	++	+	+	Increases during relapses in MOGAD and correlates to EDSS.
GFAP	+	+	+++	Elevated in AQP4 but not in MOG positive NMSOD. Increases during relapses particulary in AQP4 positive NMSOD and correlates to EDSS.
MBP	++	+	++	Little data in MOGAD; one study found higher levels in MOGAD and AQP4 positive NMSOD than in MS
IL-6	+++	+	+++	Correlates with MOG-abs titers

Armangue et al. Eur. J Paediatr. Neurol 2020

Frontiers Neurol 2021

Serum Neurofilament Light Chain Levels and Myelin Oligodendrocyte Glycoprotein Antibodies in Pediatric Acquired Demyelinating Syndromes

Marta Simone[1], Claudia Palazzo[2], Mariangela Mastrapasqua[2], Luca Bollo[2], Francesco Pompamea[1], Alessandra Gabellone[1], Lucia Marzulli[1], Paola Giordano[1], Andrea De Giacomo[2], Antonio Frigeri[2], Maddalena Ruggieri[2] and Lucia Margari[1]*

sNfL levels and MOG-Abs have been measured by ultrasensitive single-molecule array and cell-based assay in a cohort of 37 children with ADS and negativity for serum anti-aquaporin 4 (AQP4) antibodies.

The sNfL levels were compared in MOG-Ab+/MOG-Ab– and in two subgroups MOG-Ab+ with/without encephalopathy.

40% ADS resulted MOG-Ab+.

Higher sNfL levels were found in MOG-Ab+ and MOG-Ab– compared to age-matched controls without significant difference.

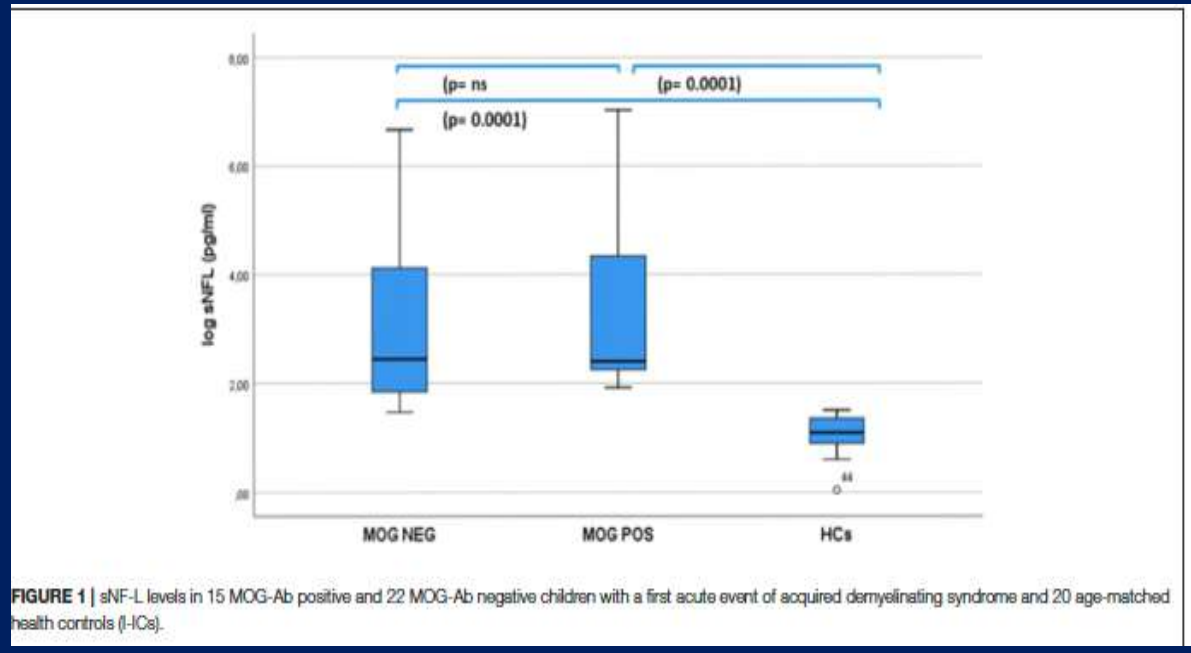


FIGURE 1 | sNF-L levels in 15 MOG-Ab positive and 22 MOG-Ab negative children with a first acute event of acquired demyelinating syndrome and 20 age-matched health controls (I-ICs).

Frontiers Neurol 2021

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TABLE 2 | Comparison of baseline demographic and laboratory features between MOG-Ab positive (+) ADS with encephalopathy and MOG-Ab positive (+) ADS without encephalopathy.

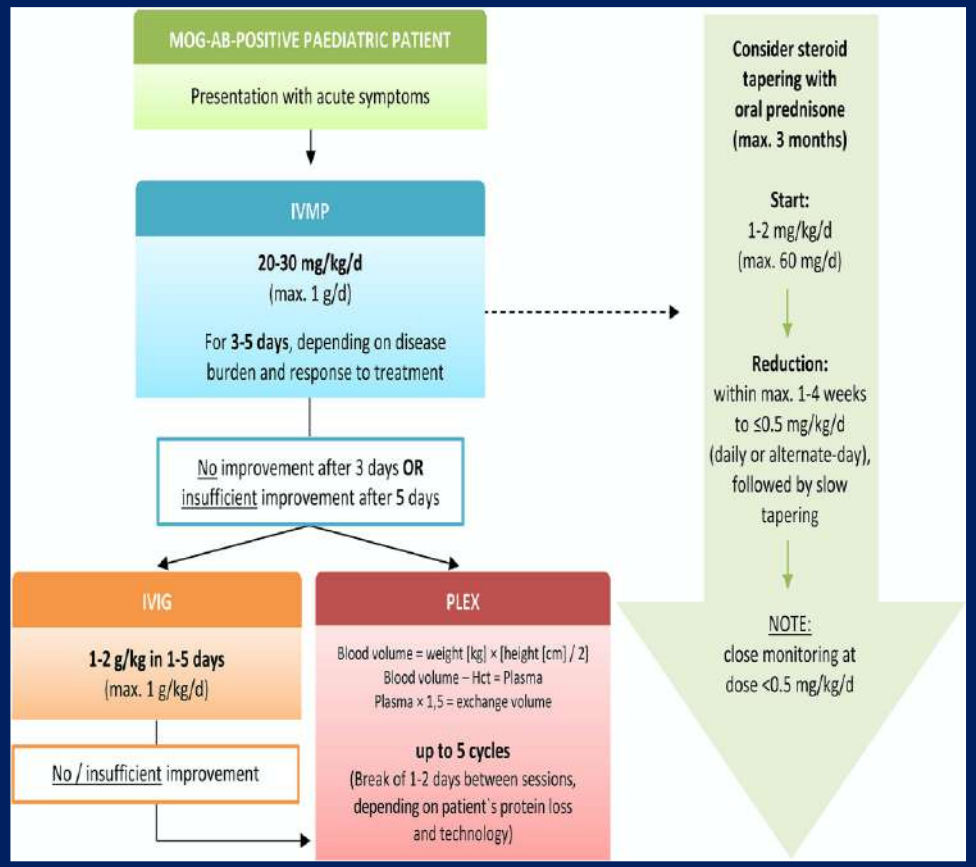
	ADS MOG+ without Encephalopathy	ADS MOG+ with Encephalopathy	*p*-value
Number	7	8	
Gender (F/M)	2/7	3/8	ns
Age at sampling, median (range), years	14.16 (9.8–17.5)	4.5 (2.17–11.17)	0.004
MOG-Ab titre, median (range)	0.05 (0.04–0.28)	0.28 (0.04–0.69)	0.1
sNfL median (range) pg/ml	10.22 (6.83–50.53)	75.24 (9.1–1.129)	0.043

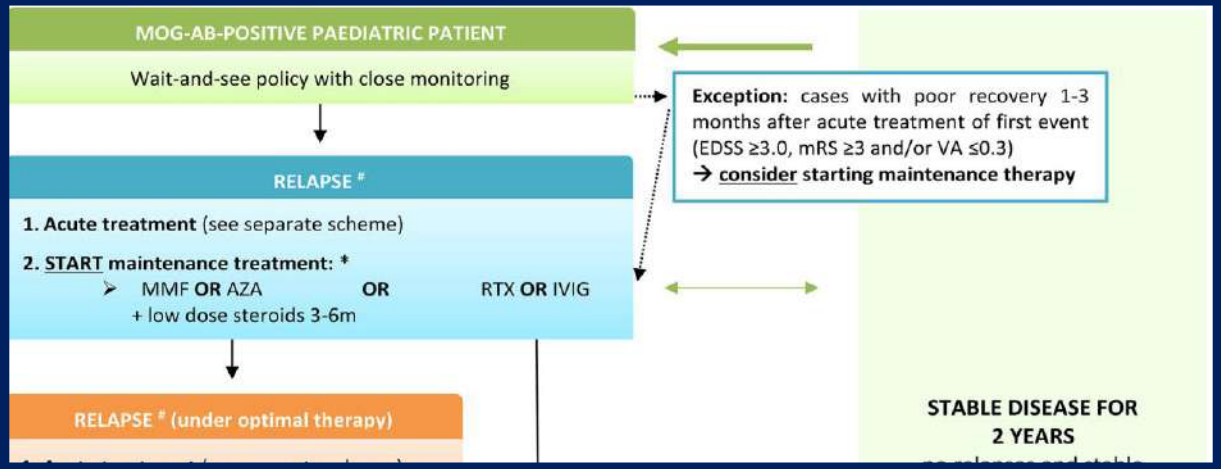
MOG-Ab+ with encephalopathy resulted significantly younger at sampling (median/range: 4.5/2.17–11.17 vs. 14.16/9.8–17.5; p = 0.004), had higher sNfL levels and showed a trend for higher MOG-Ab titer in comparison to those without encephalopathy.

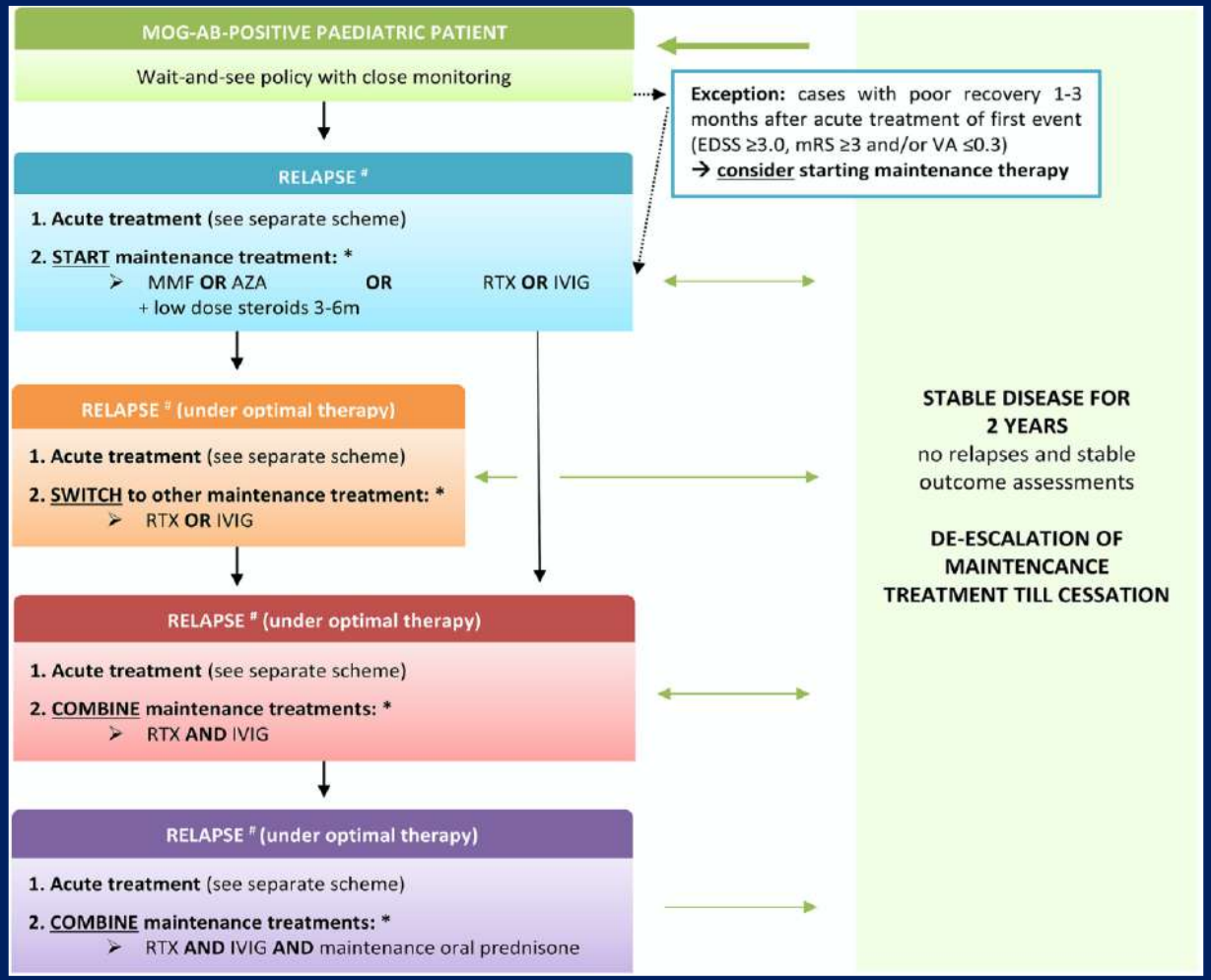
These findings suggest a role of acute demyelination in association with axonal damage in the pathogenesis of encephalopathy in pediatric ADS.

TREATMENT ALGORITHMS

MOGAD







E.U. paediatric MOG consortium consensus.
European Journal of Paediatric Neurology 2020

Acute treatment

Confirm NMOSD
Treat with high IVMP
Add on PLEX

The mainstay of acute treatment is high-dose IVMP with 1000 mg for 3–5 days

For severe and steroid refractory cases, an escalation therapy with PLEX alone or in combination with steroids can be considered.

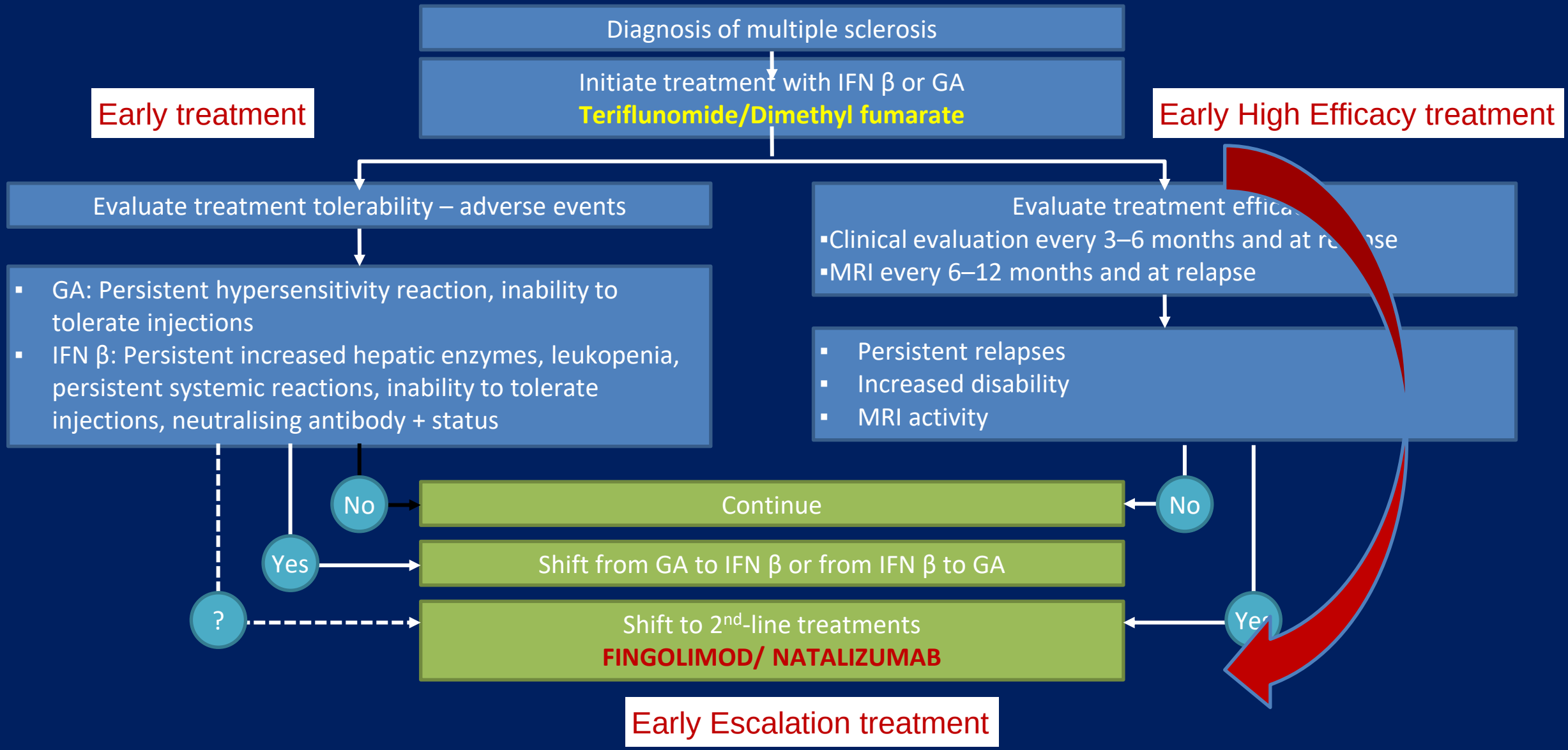
Maintenance therapies for NMOSD

	Therapy	Type	Mechanism	Route	Safety
Off-label	Azathioprine	Small molecule	Inhibits lymphocyte proliferation	PO	Increased incidence of malignancy (3%) or rare bone marrow suppression
	Mycophenolate mofetil	Small molecule	Inhibits lymphocyte proliferation	PO	Teratogenicity, hair loss, rare skin cancer
	Rituximab	Chimeric monoclonal antibody	CD20 B-cell depletion	IV	Infusion related reactions; lower immunoglobulins over time
FDA approved	Eculizumab	Humanized monoclonal antibody	Inhibits complement 5 component	IV	Risk of infection with encapsulated organisms; requires pre-treatment vaccination for Neisseria meningococcus
	Inebilizumab	Humanized monoclonal antibody	CD19 B-cell depletion	IV	No short term concerns; long term potential concern for hypogammaglobulinemia and impaired immunity.
	Satralizumab	Humanized recycling monoclonal antibody	IL6 receptor blocker	SC	Injection site … hyperlipidem … k of

Newly approved for pediatric NMOSD

Yi-Ching Chu, Tzu-Lun Huan Taiwan J Ophthalmol 2022*

Current algorithm to treating children with MS



TAKE HOME MESSAGES

- A first episode of acquired demyelinating disorder (ADS) in children is a diagnostic challenge as different diseases can express similar clinical features.
- Antibodies to MOG and to AQP4 have emerged as biomarker of ADS, which clearly allows for the identification of monophasic and relapsing forms of ADS other than MS predominantly in children.
- The main challenge is to identify early those patients who are at high risk of relapse and long-term disability in whom long-term immunotherapy can improve outcome.
- The development of assays to detect immune responses to other CNS antigens, peripheral blood research to define disease-specific circulating new biomarkers and more advanced MRI techniques might aid in the identification of as yet unrecognised neuroimmune diseases.

Thank you for your attention!

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