La diagnostica differenziale delle patologie demielinizzanti nelle forme infiammatorie aggressive in età pediatrica

Angelo Ghezzi
Centro Studi Sclerosi Multipla, Gallarate

DISCLOSURES

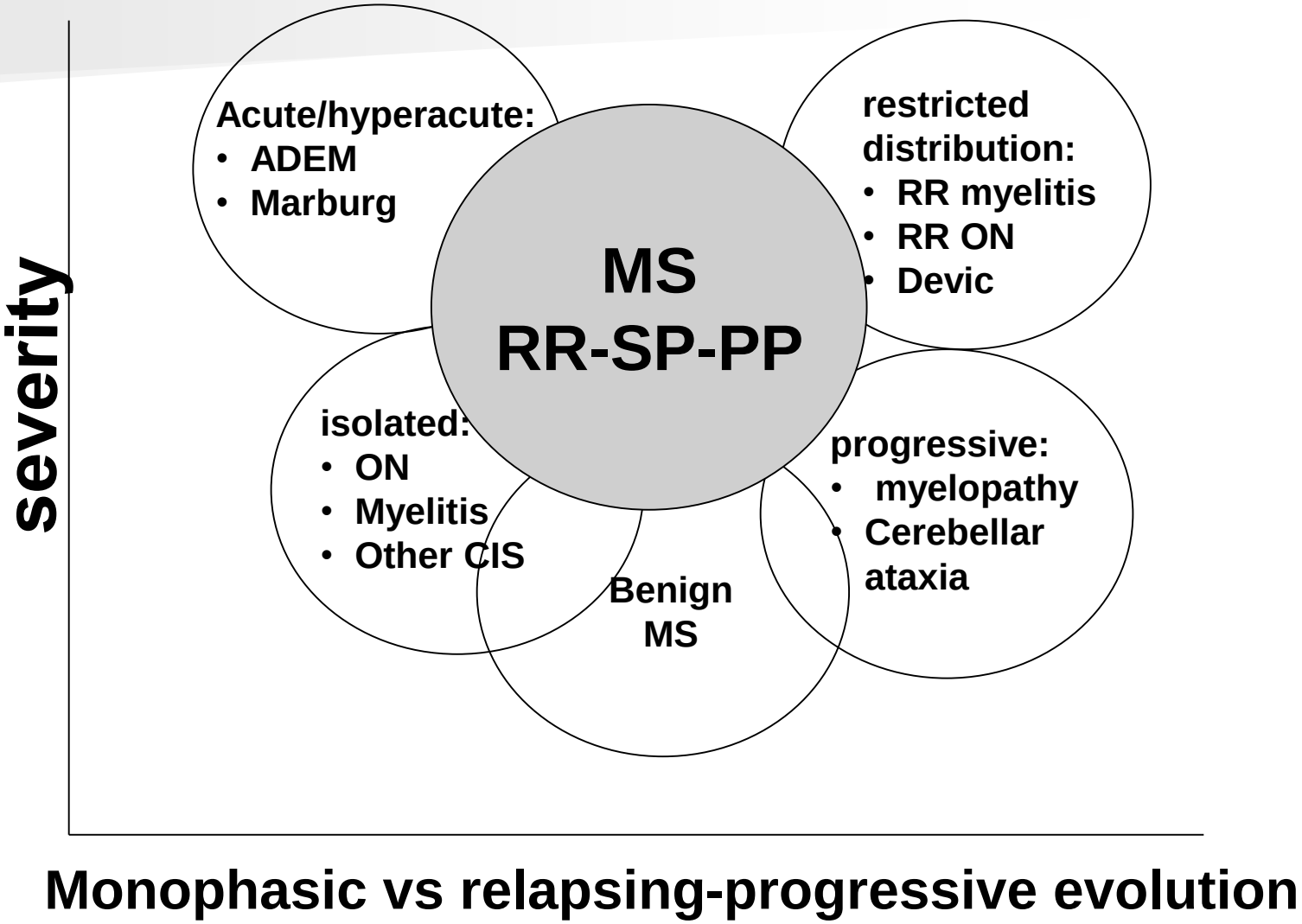
Angelo Ghezzi:

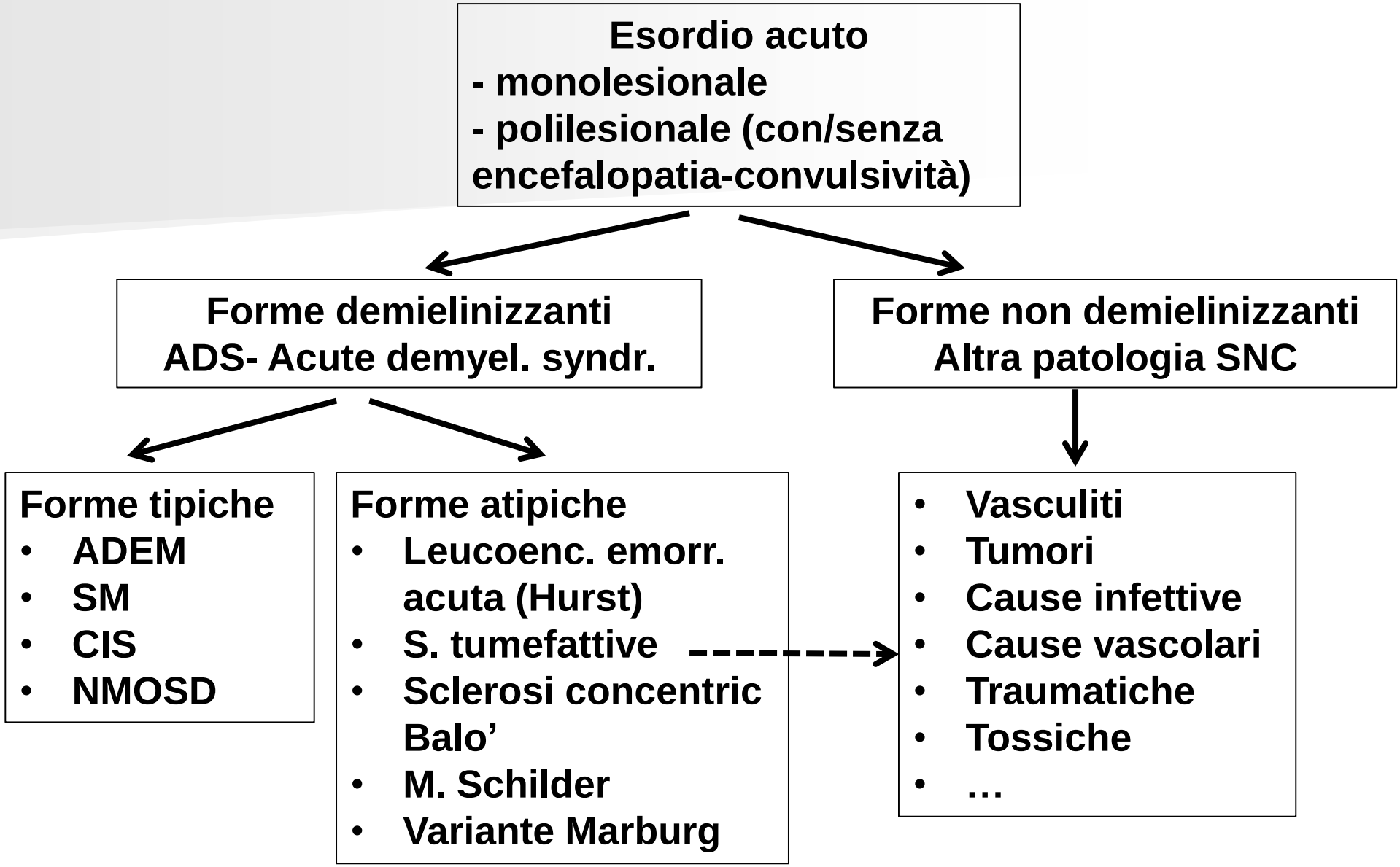
honoraria for speaking from Biogen, Merck Serono, Novartis, Genzyme, Teva, Almirall;

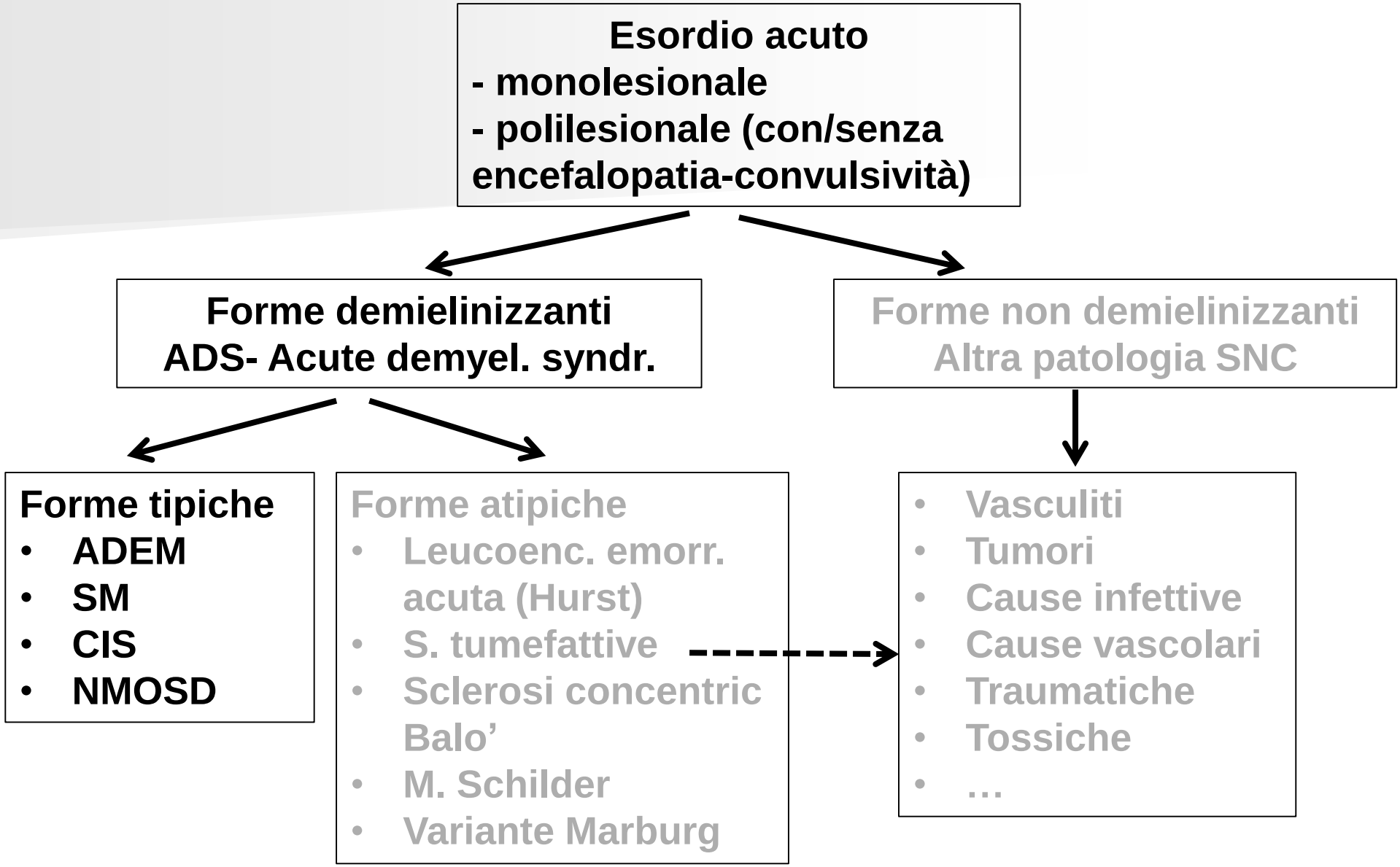
consultancy for Merck Serono, Teva, Novartis, Biogen;

support for participation to national and international congresses from Bayer-Schering, Biogen-Dompè, Merck Serono, Novartis, Sanofi-Aventis

The spectrum of demyelinating disorders




Esordio acuto
- monolesionale
- polilesionale (con/senza encefalopatia-convulsività)
Forme demielinizzanti
ADS- Acute demyel. syndr.
Forme non demielinizzanti
Altra patologia SNC
Forme tipiche
• ADEM
• SM
• CIS
• NMOSD
Forme atipiche
• Leucoenc. emorr. acuta (Hurst)
• S. tumefattive
• Sclerosi concentric Balo'
• M. Schilder
• Variante Marburg
• Vasculiti
• Tumori
• Cause infettive
• Cause vascolari
• Traumatiche
• Tossiche
• …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• Cause infettive
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• Tossiche
• …

INCIDENCE OF ADS

0.9 per 100,000 in Canadian children

Banwell B et al. Neurology 2009;72:232-9

1.66 per 100,000 in a population-based cohort of Southern Californian children

Langer-Gould A et al. Neurology 2011;77:1143-8

0.66 per 100,000 per year in the Netherlands

Ketelslegers IA et al. J Neurol 2012;259:1929-35

2.85 per 100,000 for pediatric-MS cases in Sardinia

Dell'Avvento S et al. Eur J Pediatr. 2016;175:19–29.

0.66-2.85 per 100,000 per year

In Italy, 400-1700 new cases per year

Review

MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
0(0) 1–7

DOI: 10.1177/1352458513484547
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International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions

Lauren B Krupp[1*], Marc Tardieu[2*], Maria Pia Amato[3], Brenda Banwell[4], Tanuja Chitnis[5], Russell C Dale[6], Angelo Ghezzi[7], Rogier Hintzen[8], Andrew Kornberg[9], Daniela Pohl[10], Kevin Rostasy[11], Silvia Tenembaum[12] and Evangeline Wassmer[13] for the International Pediatric Multiple Sclerosis Study Group

1. Paediatric Acute Disseminated Encephalomyelitis Syndrome (ADEM)
2. Paediatric MS
3. Paediatric Clinically Isolated Syndrome (CIS)
4. Paediatric Neuromyelitis optica (NMO)

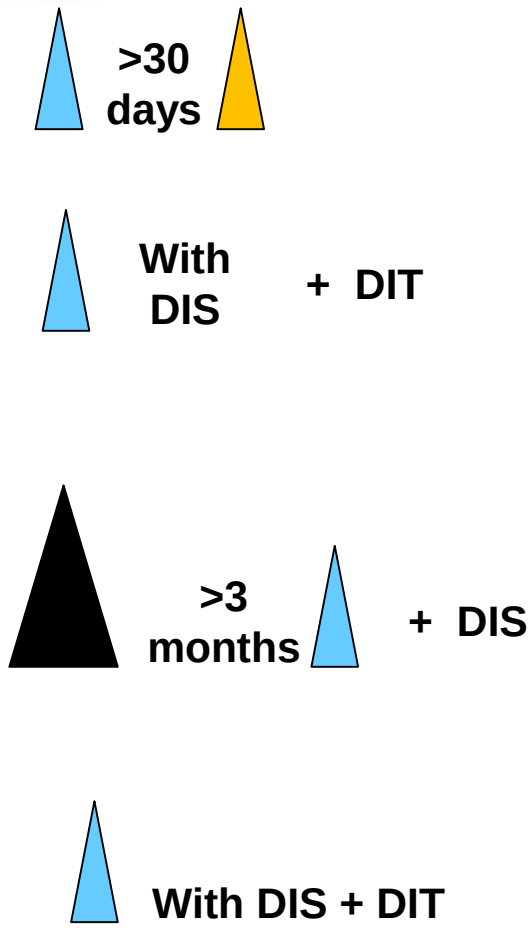
PAEDIATRIC ADEM diagnostic criteria (all are required)

- 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. Mult Scler. 2013;19(10):1261-7

PAEDIATRIC MS diagnostic criteria (can be satisfied by any of the following)

- Two or more nonencephalopathic (e.g. not ADEM-like), clinical CNS events with presumed inflammatory cause, separated by more than 30 days and involving more than one area of the CNS
- One nonencephalopathic episode typical of MS which is associated with MRI findings consistent with 2010 Revised McDonald criteria for DIS and in which a follow up MRI shows at least one new enhancing or nonenhancing lesion consistent with dissemination in time (DIT) MS criteria[4]
- One ADEM attack followed by a nonencephalopathic clinical event, three or more months after symptom onset, that is associated with new MRI lesions that fulfill 2010 Revised McDonald DIS criteria[4]
- A first, single, acute event that does not meet ADEM criteria and whose MRI findings are consistent with the 2010 Revised McDonald criteria for DIS and DIT (applies only to children ≥12 years old)



Krupp et al. Mult Scler. 2013;19(10):1261-7

Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria

Chris H. Polman, MD, PhD,[1] Stephen C. Reingold, PhD,[2] Brenda Banwell, MD,[3] Michel Clanet, MD,[4] Jeffrey A. Cohen, MD,[5] Massimo Filippi, MD,[6] Kazuo Fujihara, MD,[7] Eva Havrdova, MD, PhD,[8] Michael Hutchinson, MD,[9] Ludwig Kappos, MD,[10] Fred D. Lublin, MD,[11] Xavier Montalban, MD,[12] Paul O'Connor, MD,[13] Magnhild Sandberg-Wollheim, MD, PhD,[14] Alan J. Thompson, MD,[15] Emmanuelle Waubant, MD, PhD,[16] Brian Weinshenker, MD,[17] and Jerry S. Wolinsky, MD[18]

ANN NEUROL 2011;69:292–302

The Panel's consensus was that the proposed MAGNIMS-based MRI revisions for DIS will also serve well for most pediatric MS patients, especially those with acute demyelination presenting as CIS, because most pediatric patients will have >2 lesions and are very likely to have lesions in 2 of the 4 specified CNS locations (periventricular, brainstem-infratentorial, juxtacortical, or spinal cord).

However, approximately 15 to 20% of pediatric MS patients, most aged <11 years, present with encephalopathy and multifocal neurological deficits difficult to distinguish from acute disseminated encephalomyelitis (ADEM).[43,50] Current operational international consensus criteria for MS diagnosis in children with an ADEM-like first attack require confirmation by 2 or more non-ADEM like attacks, or 1 non-ADEM attack followed by accrual of clinically silent lesions.[53] Although children with an ADEM-like first MS attack are more likely than children with monophasic ADEM to have 1 or more non-enhancing T1 hypointense lesions, 2 or more periventricular lesions, and the absence of a diffuse lesion pattern,[54] these features are not absolutely discriminatory.

Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria

Alan J Thompson, Brenda L Banwell, Frederik Barkhof, William M Carroll, Timothy Coetzee, Giancarlo Comi, Jorge Correale, Franz Fazekas, Massimo Filippi, Mark S Freedman, Kazuo Fujihara, Steven L Galetta, Hans Peter Hartung, Ludwig Kappos, Fred D Lublin, Ruth Ann Marrie, Aaron E Miller, David H Miller, Xavier Montalban, Ellen M Mowry, Per Soelberg Sorensen, Marc Tintoré, Anthony L Traboulsee, Maria Trojano, Ber

Several studies[34–41] support the applicability of the 2010 McDonald criteria in children. The criteria are generally most applicable to patients who are 11 years of age or older; special care is needed in patients younger than 11 years old, in whom the likelihood of multiple sclerosis is lower.[35] Acute disseminated encephalomyelitis is more common in children than in adults, and, although it is typically monophasic, some children with this disease have recurrent clinical episodes or MRI evidence of accrual of new lesions, which can lead to a diagnosis of multiple sclerosis.[42]

McDonald criteria should not be applied to children at the time of acute disseminated encephalomyelitis presentation and that occurrence of a subsequent attack characteristic of multiple sclerosis is necessary to diagnose multiple sclerosis.[43] Alternative diagnoses, including NMOSDs, need to be excluded in all children in whom the diagnosis of multiple sclerosis is being considered. Tests for antibodies reactive with myelin-oligodendrocyte glycoprotein (MOG) could be useful to aid diagnosis of children with NMOSDs who are aquaporin 4 (AQP4) seronegative, children with acute disseminated encephalomyelitis followed by recurrent optic neuritis, and children with chronic relapsing optic neuritis.[44–4

PAEDIATRIC CIS DIAGNOSTIC CRITERIA (all are required)

- A monofocal or polyfocal, clinical CNS event with presumed inflammatory demyelinating cause
- Absence of a prior clinical history of CNS demyelinating disease (e.g. absence of past optic neuritis [ON], transverse myelitis [TM] and hemispheric or brain-stem related syndromes)
- No encephalopathy (i.e. no alteration in consciousness or behaviour) that cannot be explained by fever
- The diagnosis of MS based on baseline MRI features are not met

Krupp et al. Mult Scler 2013;19(10):1261-7

PAEDIATRIC NMO DIAGNOSTIC CRITERIA

- **Optic neuritis**
- **Acute myelitis**
- **At least two of three supportive criteria:**
  1. **Contiguous spinal cord MRI lesion extending over three vertebral segments**
  2. **Brain MRI not meeting diagnostic criteria for MS**
  3. **Anti-aquaporin 4 IgG seropositive status**

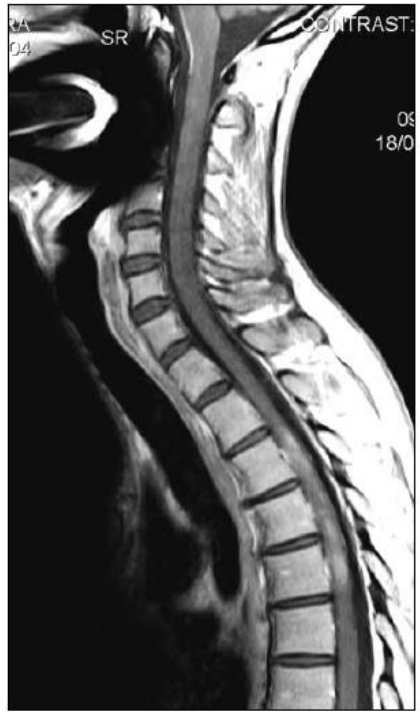


Fig. 1 Spinal cord MRI, showing a diffuse Gadolinium enhancing lesion involving about three vertebral segments

2014: new definition according to anti-aquaporin status

Krupp et al. Mult Scler 2013;19(10):1261-7

Review

MULTIPLE SCLEROSIS JOURNAL | MSJ

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Acute disseminated encephalomyelitis

Updates on an inflammatory CNS syndrome

Daniela Pohl, MD, PhD
Gulay Alper, MD
Keith Van Haren, MD
Andrew J. Kornberg, MD
Claudia F. Lucchinetti, MD
Silvia Tenembaum, MD
Anita L. Belman, MD

Correspondence to Dr. Pohl: dpohl@cheo.on.ca

ABSTRACT

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated demyelinating CNS d with predilection to early childhood. ADEM is generally considered a monophasic disease. Hc recurrent ADEM has been described and defined as multiphasic disseminated encephalon ADEM often occurs postinfectiously, although a causal relationship has never been estat ADEM and multiple sclerosis are currently viewed as distinct entities, generally distinguishab at disease onset. However, pathologic studies have demonstrated transitional cases of yet significance. ADEM is clinically defined by acute polyfocal neurologic deficits including ence athy. MRI typically demonstrates reversible, ill-defined white matter lesions of the brain an also the spinal cord, along with frequent involvement of thalami and basal ganglia. CSF a may reveal a mild pleocytosis and elevated protein, but is generally negative for intrathecal o nal immunoglobulin G synthesis. In the absence of a specific diagnostic test, ADEM is cons a diagnosis of exclusion, and ADEM mimics, especially those requiring a different tre approach, have to be carefully ruled out. The role of biomarkers, including autoantibodies lik myelin oligodendrocyte glycoprotein, in the pathogenesis and diagnosis of ADEM is currentl debate. Based on the presumed autoimmune etiology of ADEM, the current treatment ap consists of early immunotherapy. Outcome of ADEM in pediatric patients is generally fav but cognitive deficits have been reported even in the absence of other neurologic sequela review summarizes the current knowledge on epidemiology, pathology, clinical presentation, imaging features, CSF findings, differential diagnosis, therapy, and outcome, with a focus on advances and controversies. *Neurology*® 2016;87 (Suppl 2):S38-S45

Table 1 ADEM and its convergence with relapsing demyelinating disorders

Diagnosis	Clinical criteria
ADEM, monophasic[7]	Single polyfocal CNS event with encephalopathy and presumed inflammatory demyelination and no new disease activity (clinical or MRI) >3 months after onset
ADEM, multiphasic[7]	ADEM followed at >3 months by second ADEM episode, but no further ADEM or non-ADEM demyelinating events
ADEM-MS[7]	ADEM followed at >3 months by non-ADEM demyelinating relapse and new MRI lesions meeting criteria for dissemination in space[8]
ADEM-NMOSD[9]	ADEM followed at >3 months by events including optic neuritis, longitudinally extensive transverse myelitis, or area postrema syndrome, meeting MRI requirements according to revised NMOSD criteria[9]
ADEM-ON	ADEM, MDEM, or multiple ADEM attacks followed by optic neuritis

Abbreviations: ADEM = acute disseminated encephalomyelitis; MDEM = multiphasic disseminated encephalomyelitis; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder; ON = optic neuritis.

Table 2 MRI characteristics in ADEM vs MS

MRI characteristics	ADEM: Typical	MS: Typical
Deep gray matter and cortical involvement	Yes	No
Bilateral diffuse lesions	Yes	No
Poorly marginated lesions	Yes	No
Large globular lesions	Yes	No
Periventricular pattern of lesions	No	Yes
Lesions perpendicular to long axis of corpus callosum	No	Yes
Ovoid lesions	No	Yes
Lesions confined to corpus callosum	No	Yes
Sole presence of well-defined lesions	No	Yes
Black holes (on T1 sequence)	No	Yes

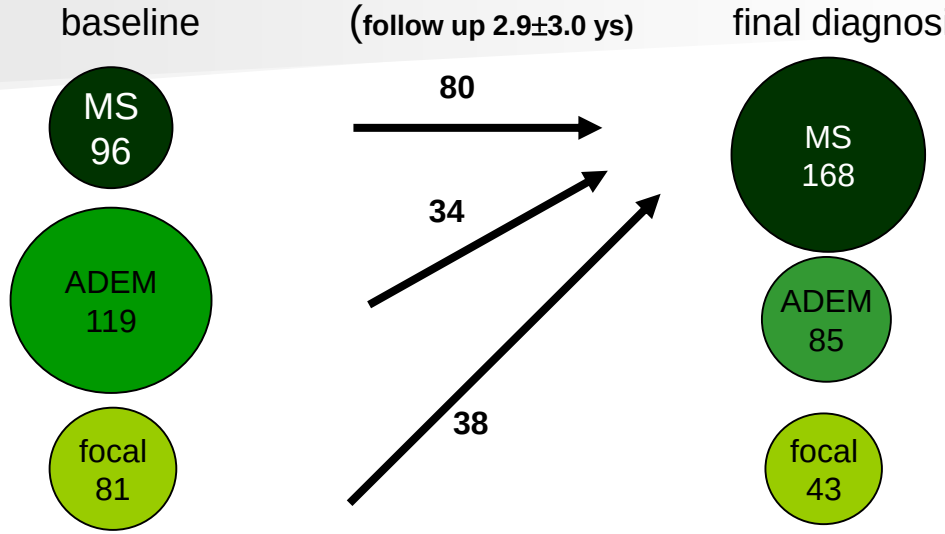
Table 3 Red flags for a diagnosis of ADEM and possible differential diagnoses

	Possible causes
Clinical features atypical for ADEM	
Persistent meningeal signs or headache	Infectious encephalitis, systemic autoimmune disorders (e.g., neurosarcoidosis, SLE), CNS vasculitis
Stroke-like events	CNS vasculitis, antiphospholipid antibody syndrome, mitochondrial diseases (e.g., MELAS, POLG-related disorders)
Recurrent seizures	Infectious or autoimmune encephalitis
Dystonia or parkinsonism	Infectious or autoimmune encephalitis
Neuropsychiatric symptoms	SLE, autoimmune encephalitis
Progressive course	Genetic/metabolic disorders, gliomatosis cerebri, neurosarcoidosis
History of developmental delay or other neurologic abnormalities	Genetic/metabolic disorders
Recurrent encephalopathic events	Genetic/metabolic disorders, systemic autoimmune disorders, autoimmune encephalitis, ANE
CSF features atypical for ADEM	
Cell count >50/mm^3 or neutrophilic predominance or protein >100 mg/dL	CNS infections (e.g., HSV, EBV, enterovirus, West Nile virus, mycoplasma), NMOSD, SLE
Imaging features atypical for ADEM	
Diffuse, symmetric brain lesions	Genetic/metabolic disorders; leukodystrophies, mitochondrial disorders, intoxications (e.g., CO)
Ischemic lesions with restricted diffusion	Stroke, mitochondrial disorders, CNS infections, antiphospholipid antibody syndrome, CNS vasculitis
Mesial temporal lobe lesions	Autoimmune encephalitis

TREATMENT There are no randomized studies for the treatment of ADEM. Thus, management of ADEM is based on expert opinions and observational studies.[20,26,47] Despite the lack of conclusive evidence, high-dose corticosteroids are currently widely accepted as first-line therapy.[48] A typical treatment regimen consists of IV methylprednisolone at a dose of 30 mg/kg/d (maximally 1,000 mg/d) for 5 days, followed by an oral taper over 4–6 weeks with a starting dose of prednisone of 1–2 mg/kg/d. An increased risk of relapse was observed with steroid taper of ≤3 weeks.[49] IV immunoglobulin treatment has been described in case reports and small case series, mostly in combination with corticosteroids or as a second-line treatment in steroid-unresponsive ADEM.[50,51] The usual total dose is 2 g/kg, administered over 2–5 days.[47] Plasma exchange is recommended for therapy-refractory patients with fulminant disease, e.g., using 7 exchanges every other day.[47] In single case reports, patients with fulminant ADEM and cerebral edema have been treated with hypothermia or decompressive craniotomy.[52,53]

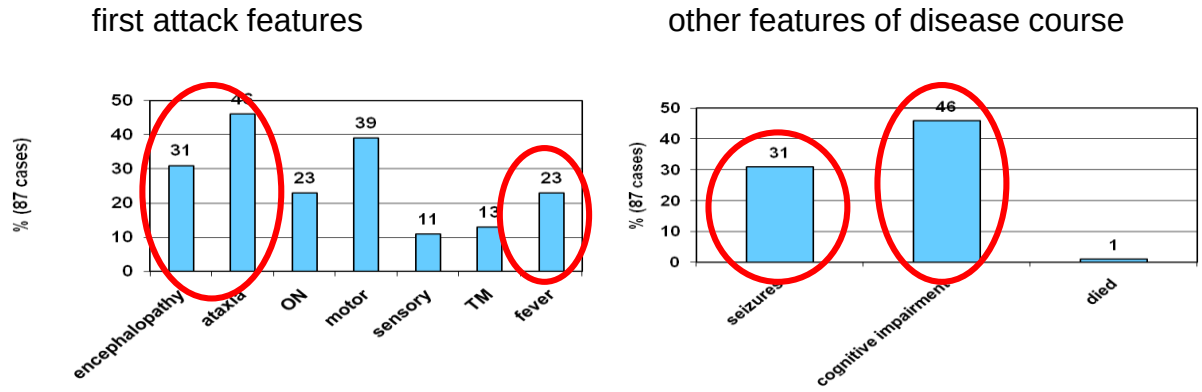
ADEM vs paediatric MS

1- patients with ADEM fail to have a self-limited disease course and experience additional relapses and accumulate MRI lesions. Subsequently, these patients are reclassified as MS



(Mikaeloff et al. 2004)

2- some patients with MS can have an hyperacute onset, resembling ADEM



Brenda Banwell, Angelo Ghezzi, Amit Bar-Or, Yann Mikaeloff, Marc Tardieu *Lancet Neurol* 2007; 6: 887–902

Table I. - *Clinical findings at onset and disease evolution in our MS patients. Neurological impairment and disability were scored according to Kurtzke scales*[10].

EDSS at onset	EDSS at 1 y	EDSS at 4 ys	Course
3	6.5	6.5	RP
2	2	2	RP
–	6	6.5	P
2	1	1	R
3	1	–	R
3	0	–	R
2	0	0	R

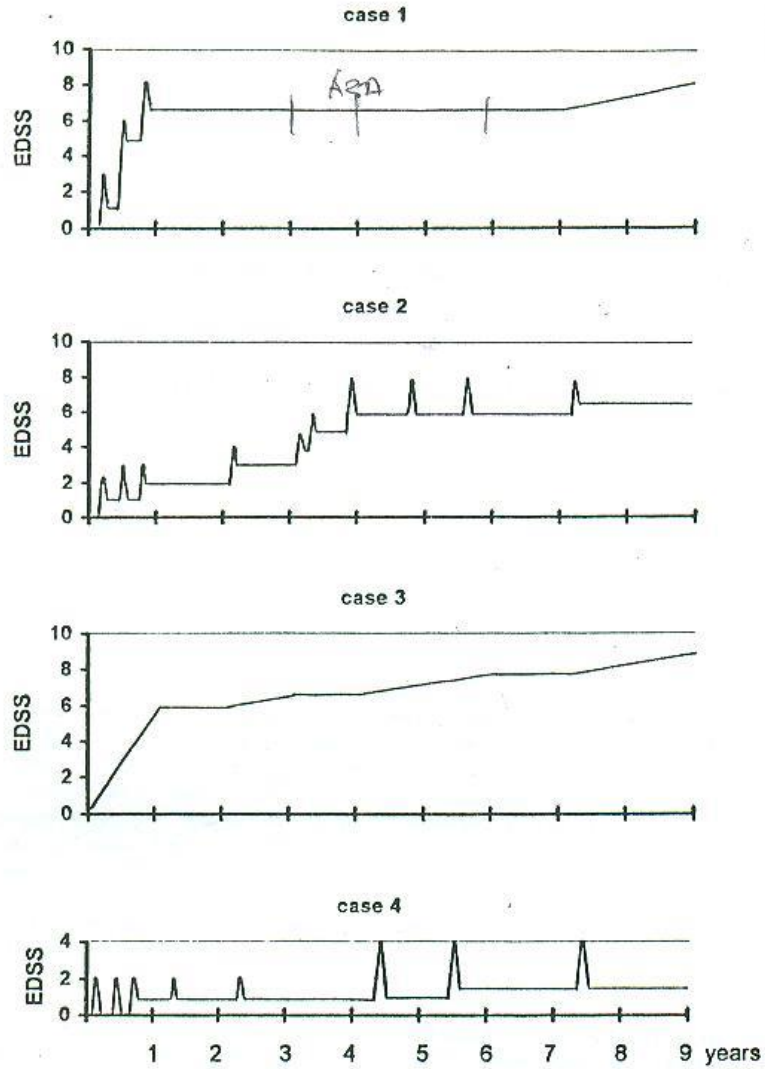
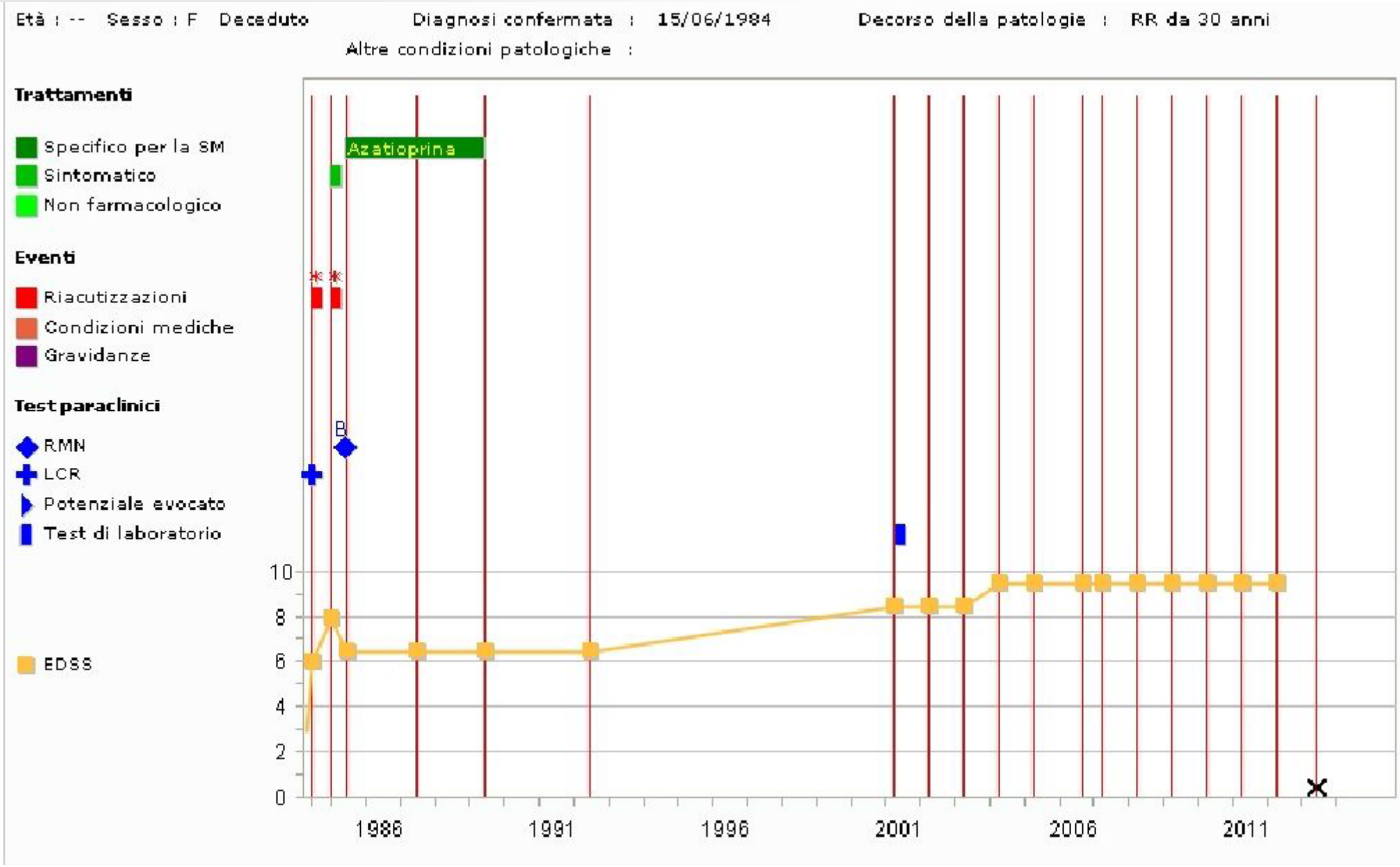


Figure 2. -


Età : -- Sesso : F Deceduto
Diagnosi confermata : 15/06/1984
Decorso della patologie : RR da 30 anni
Altre condizioni patologiche :
Trattamenti
Specifico per la SM
Sintomatico
Non farmacologico
Eventi
Riacutizzazioni
Condizioni mediche
Gravidanze
Test paraclinici
RMN
LCR
Potenziale evocato
Test di laboratorio
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1991
1996
2001
2006
2011

ADEM vs paediatric MS

Typical features	ADEM	MS
Demographic	More frequent in young patients (aged <10-12 years); no gender predilection	More frequent in adolescents; girls more affected than boys
Prior flu-like illness	Very frequent	Variable
Symptoms ▪ Seizures ▪ Encephalopathy ▪ Discrete event	 Variable Required in definition A single event can fluctuate over the course of 12 weeks	 Rare Rare early in the disease Discrete events separated by >4 weeks
MRI: ▪ Large lesions involving gray and white matter ▪ Enhancement • Longitudinal MRI findings	 Frequent Frequent Lesions typically either resolve or show only residual findings*	 Rare Frequent Typically associated with development of new lesions
CSF ▪ Pleocytosis ▪ Oligoclonal bands	 Variable Variable	 Rare, white blood cell count almost always <50 Frequent

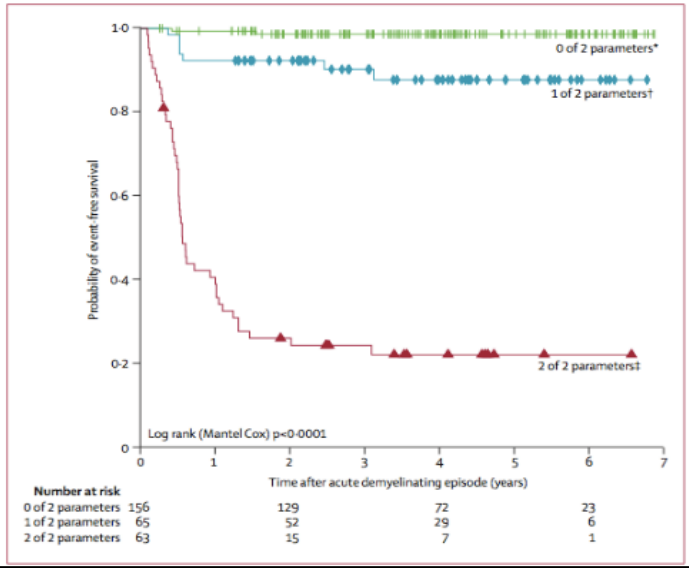
*** A subset of patients with ADEM fail to have a self-limited disease course and experience additional relapses and accumulate MRI lesions. Subsequently, these patients are reclassified as MS**

Krupp et al. Neurology. 2007;68(16 Suppl 2):S7-12.

The role of MRI in identifying subjects at risk of MS

The role of T2 and T1 hypointense lesions

Verhey et al. Lancet Neurol 2011;10:1065-73



The diagnostic and prognostic role of CSF examination

Oligoclonal Bands Predict Multiple Sclerosis in Children with Optic Neuritis

ANN NEUROL 2015;77:1076–1082

Nicole Heussinger, MD,[1]

Multiple regression analysis 1, analyzing cMRI and CSF as separate factors[b]				
Sex (female)	0.95	0.74	1.23	0.701
Age (per year of age)	1.08	1.02	1.13	0.003
Laterality (bilateral)	1.15	0.80	1.64	0.447
cMRI (abnormal)	5.94	3.39	10.39	<0.001
CSF OCB (positive)	3.69	2.32	5.86	<0.001

Prognostic factors after a first attack of inflammatory CNS demyelination in children

R. F. Neuteboom, M. Boon, C. E. Catsman Berrevoets, J. S. Vles, R. H. Gooskens, H. Stroink, R. J. Vermeulen, J. J. Rotteveel, I. A. Ketelslegers, E. Peeters, B. T. Poll-The, J. F. De Rijk-Van Andel, A. Verrips and R. Q. Hintzen

Table 2 Clinical and CSF features at baseline of children with a final diagnosis of CIS, PCIS, and MS

	Final diagnosis at end of follow-up			
	Monophasic CIS	PCIS	MS	*p* Value*
Encephalopathy (%)	0	60	16	<0.001
Meningism (%)	3	20	11	NS
Headache (%)	3	34	8	0.005
Fever (%)	7	42	8	<0.001
Seizures (%)	0	28	3	0.02
Preceding infection (%)	27	50	24	0.015
CSF data				*p* Value†
IgG index	n = 17	n = 26	n = 29	
>0.68 (%)	17	27	66	<0.001
Oligoclonal banding	n = 16	n = 19	n = 26	
Present (%)	0	16	46	0.001

Review

MULTIPLE SCLEROSIS JOURNAL | MSJ

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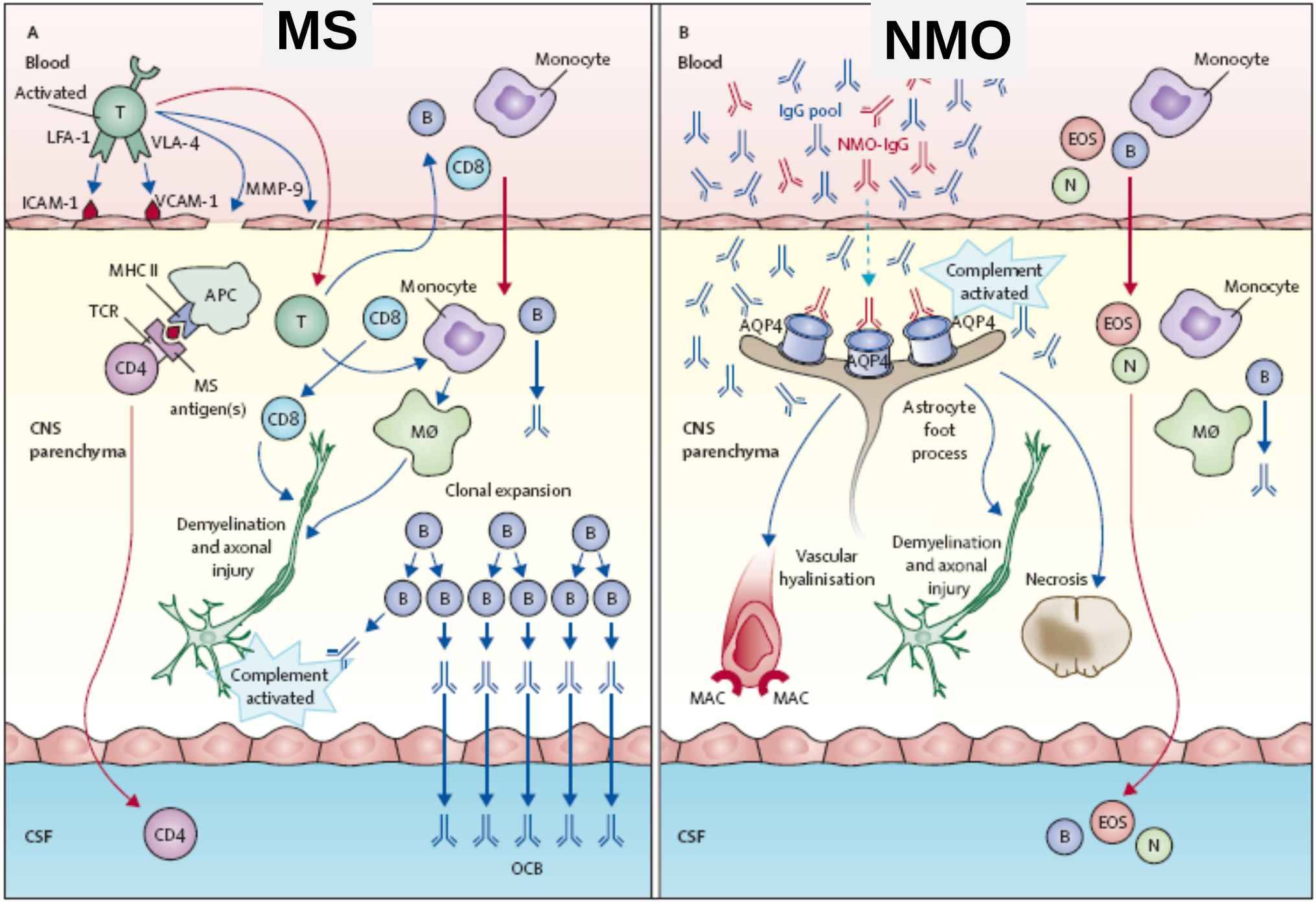

MS
NMO
A
Blood
Activated
T
LFA-1
VLA-4
ICAM-1
VCAM-1
MMP-9
Monocyte
B
CD8
MHC II
APC
TCR
CD4
MS antigen(s)
CNS parenchyma
Demyelination and axonal injury
Clonal expansion
Complement activated
MØ
CSF
OCB
B
Blood
IgG pool
NMO-IgG
EOS
N
Monocyte
AQP4
Astrocyte foot process
Vascular hyalinisation
Demyelination and axonal injury
Necrosis
MAC

Neuromyelitis optica spectrum disorders in children and adolescents

Silvia Tenembaum, MD
Tanuja Chitnis, MD
Ichiro Nakashima, MD
Nicolas Collongues, MD, PhD
Andrew McKeon, MD
Michael Levy, MD, PhD
Kevin Rostasy, MD

ABSTRACT

Neuromyelitis optica (NMO) is a severe autoimmune disease of the CNS characterized by recurrent inflammatory events primarily involving the optic nerves and spinal cord. NMO is infrequent in children, but early recognition is important to start adequate treatment. In this article, we review the evolving diagnostic criteria of NMO and provide an update on the clinical and neuroimaging spectrum of the disorder in pediatric patients, including current knowledge on immunopathogenesis and treatment recommendations for children with NMO. *Neurology®* 2016;87 (Suppl 2):S59–S66

NMOSD with AQP4-IgG

1. ≥1 Core clinical characteristic
2. Positive AQP4-IgG testing using best available method
3. Exclusion of alternative diagnoses

NMOSD without AQP4-IgG or with unknown AQP4-IgG status

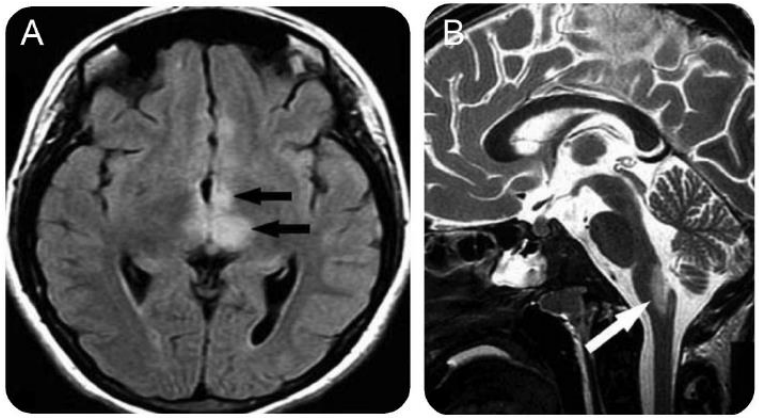
1. ≥2 Core clinical characteristics occurring as a result of ≥1 clinical attacks and meeting all of the following:
   a. At least 1 clinical characteristic: Must be optic neuritis, LETM, or area postrema syndrome
   b. Dissemination in space (≥2 different core clinical characteristics)
   c. Fulfillment of additional MRI requirements
2. Negative tests for AQP4-IgG using best available or testing unavailable
3. Exclusion of alternative diagnoses

Core clinical characteristics

1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome
4. Acute brain stem syndrome
5. Symptomatic narcolepsy or acute diencephalic syndrome with typical diencephalic MRI lesions
6. Symptomatic cerebral syndrome with typical brain lesions

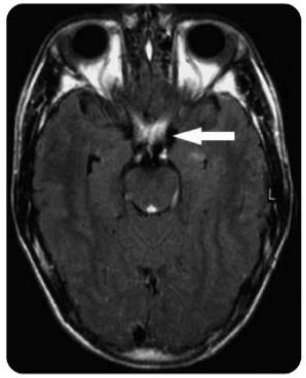
D. Additional MRI requirements	
1. Acute optic neuritis	a. Brain MRI normal or showing nonspecific white matter lesions and
	b. Optic nerve MRI with T2-hyperintense or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm
2. Acute myelitis	Requires intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) or ≥3 contiguous segments of spinal cord atrophy in patients with history compatible with acute myelitis
3. Area postrema syndrome	Requires associated dorsal medulla/area postrema lesions
4. Acute brainstem syndrome	Requires associated periependymal brainstem lesions

Figure 1 Diencephalic and area postrema lesions in pediatric neuromyelitis optica spectrum disorder



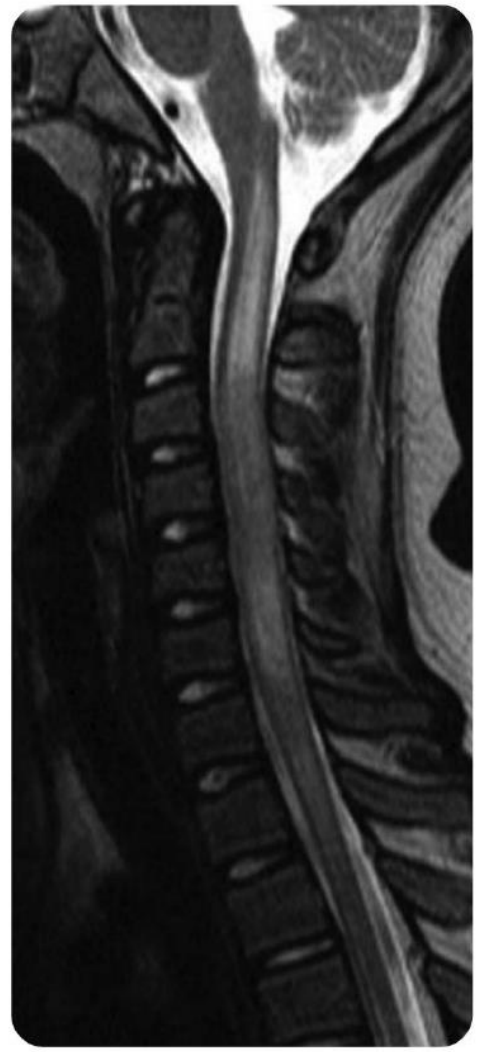
Twelve-year-old girl presenting with intractable vomiting, further developing optic neuritis and longitudinally extensive transverse myelitis (positive aquaporin-4 immunoglobulin G). (A) Axial fluid-attenuated inversion recovery imaging shows typical diencephalic signal changes (black arrows). (B) Sagittal T2-weighted brain MRI with hyperintense lesion in brainstem involving dorsal medulla (area postrema) (white arrow).

Figure 2 Optic chiasm MRI pattern in pediatric neuromyelitis optica spectrum disorder (NMOSD)



Thirteen-year-old girl presenting with bilateral visual loss due to optic neuritis. Axial fluid-attenuated inversion recovery brain imaging showed optic chiasm involvement (white arrow). Aquaporin-4 immunoglobulin G seropositivity confirmed NMOSD diagnosis.

Figure 4 Spinal cord MRI pattern in pediatric neuromyelitis optica spectrum disorder



Aquaporin-4 antibody–positive 13-year-old girl with an acute severe myelopathy. Sagittal T2-weighted spinal cord MRI shows a longitudinally extensive lesion extending over more than 3 vertebral segments involving the central spinal cord.

Anti-myelin oligodendrocyte glycoprotein antibodies in pediatric patients with optic neuritis.

Rostasy K. et al. Arch. Neurol. 2012, 69:752-6.

- 37 patients 18 years or younger with single or recurrent episodes of ON
- *High titers of MOG-IgG antibodies were more frequently observed in 12 of the 15 patients with recurrent episodes of ON*
- *High-titer MOG-IgG antibodies are predominantly detected in pediatric patients with recurrent ON, indicating that anti-MOG-specific antibodies may exert a direct role in the pathogenesis of ON in this subgroup*

Acute disseminated encephalomyelitis followed by recurrent or monophasic optic neuritis in pediatric patients.

Rostasy K. et al. Mult. Scler. 2012

- 7 patients with a *with monophasic or recurrent ADEM followed by ON*
- Cranial magnetic resonance imaging (MRI) was typical for ADEM with complete or almost complete resolution of lesions on follow-up.
- Cerebrospinal (CSF) studies were negative for oligoclonal bands (OCBs) in all.
- In all patients high titers for serum anti-MOG antibodies were detected.
- ADEM followed by ON is a rare but distinct clinical phenotype among pediatric patients?

Children with multiphasic disseminated encephalomyelitis and antibodies to the myelin oligodendrocyte glycoprotein (MOG): Extending the spectrum of MOG antibody positive diseases

Matthias Baumann, Eva-Maria Hennes, Kathrin Schanda, Michael Karenfort, Barbara Kornek, Rainer Seidl, Katharina Diepold, Heinz Lauffer, Iris Marquardt, Jurgis Strautmanis, Steffen Syrbe, Silvia Vieker, Romana Höftberger, Markus Reindl and Kevin Rostásy

Abstract

Background: Myelin oligodendrocyte glycoprotein (MOG) antibodies have been described in children with acute disseminated encephalomyelitis (ADEM), recurrent optic neuritis, neuromyelitis optica spectrum disorders and more recently in children with multiphasic disseminated encephalomyelitis (MDEM).

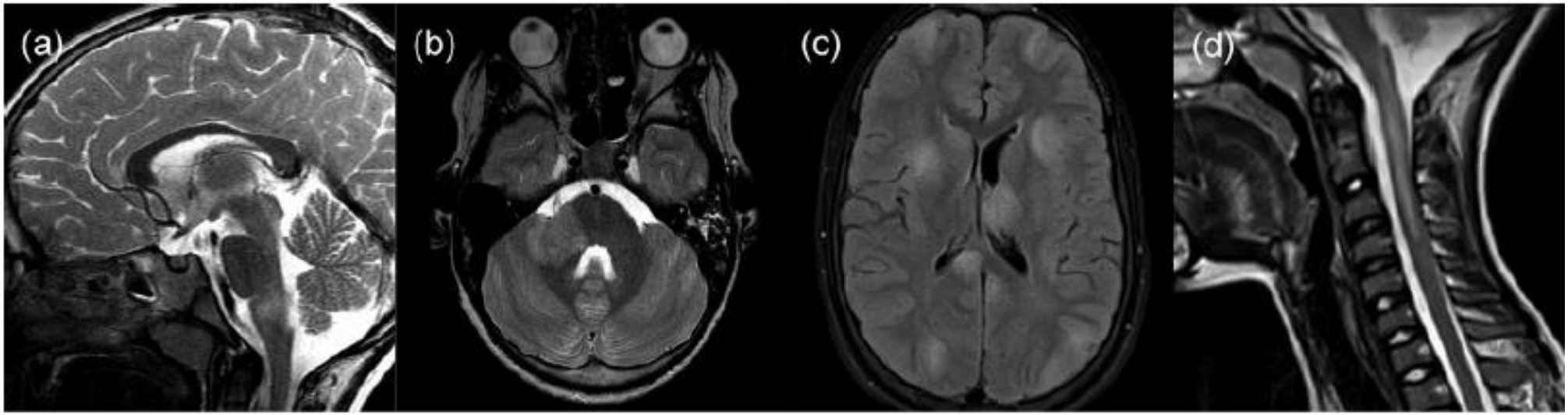
Objective: To delineate the clinical, cerebrospinal fluid (CSF) and radiological features of paediatric MDEM with MOG antibodies.

Methods: Clinical course, serum antibodies, CSF, magnetic resonance imaging (MRI) studies and outcome of paediatric MDEM patients were reviewed.

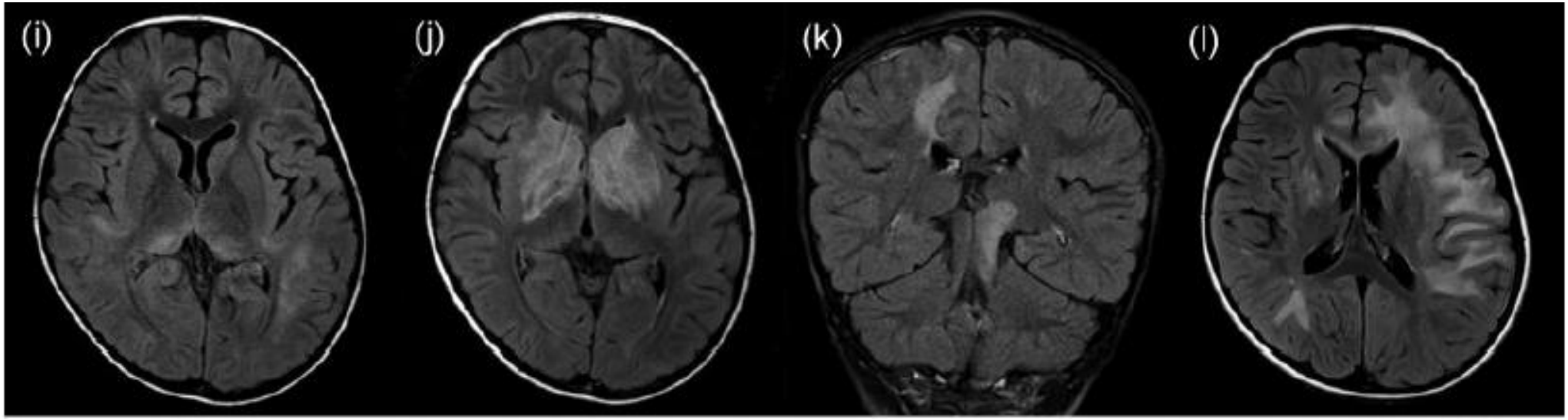
Results: A total of 8 children with two or more episodes of ADEM were identified from a cohort of 295 children with acute demyelinating events. All children had persisting MOG antibodies (median titre: 1:1280). All ADEM episodes included encephalopathy, polyfocal neurological signs and a typical MRI. Apart from ADEM episodes, three children had further clinical attacks without encephalopathy. Median age at initial presentation was 3 years (range: 1–7 years) and median follow-up 4 years (range: 1–8 years). New ADEM episodes were associated with new neurological signs and new MRI lesions. Clinical outcome did range from normal (four of the eight) to mild or moderate impairment (four of the eight). A total of four children received monthly immunoglobulin treatment during the disease course.

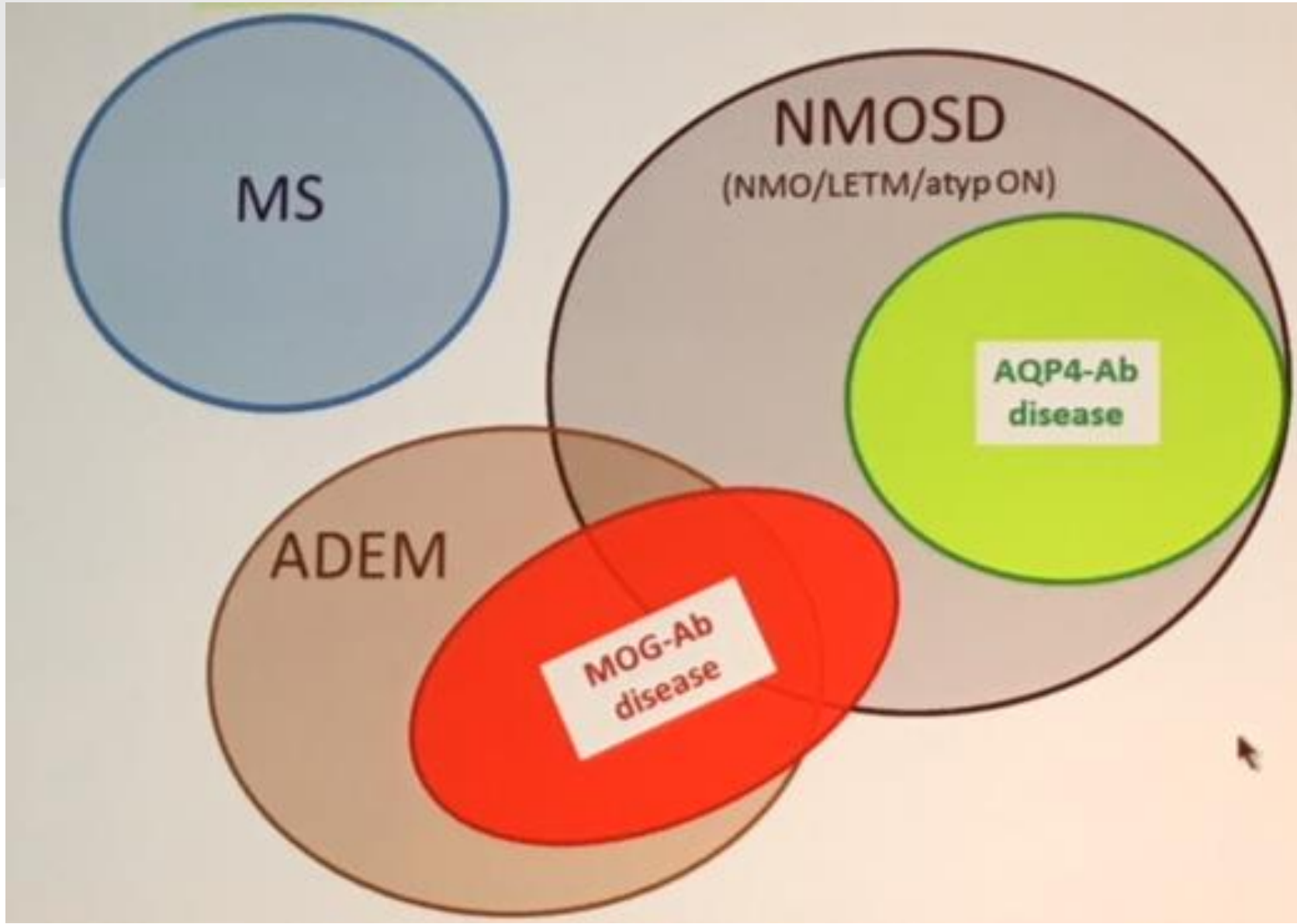
Conclusion: Children with MDEM and persisting MOG antibodies constitute a distinct entity of relapsing demyelinating events and extend the spectrum of MOG antibody–associated diseases.

ADEM episode at the age of 5 years and in total four ADEM episodes (3 months, 3 years and 7 years after the first episode).

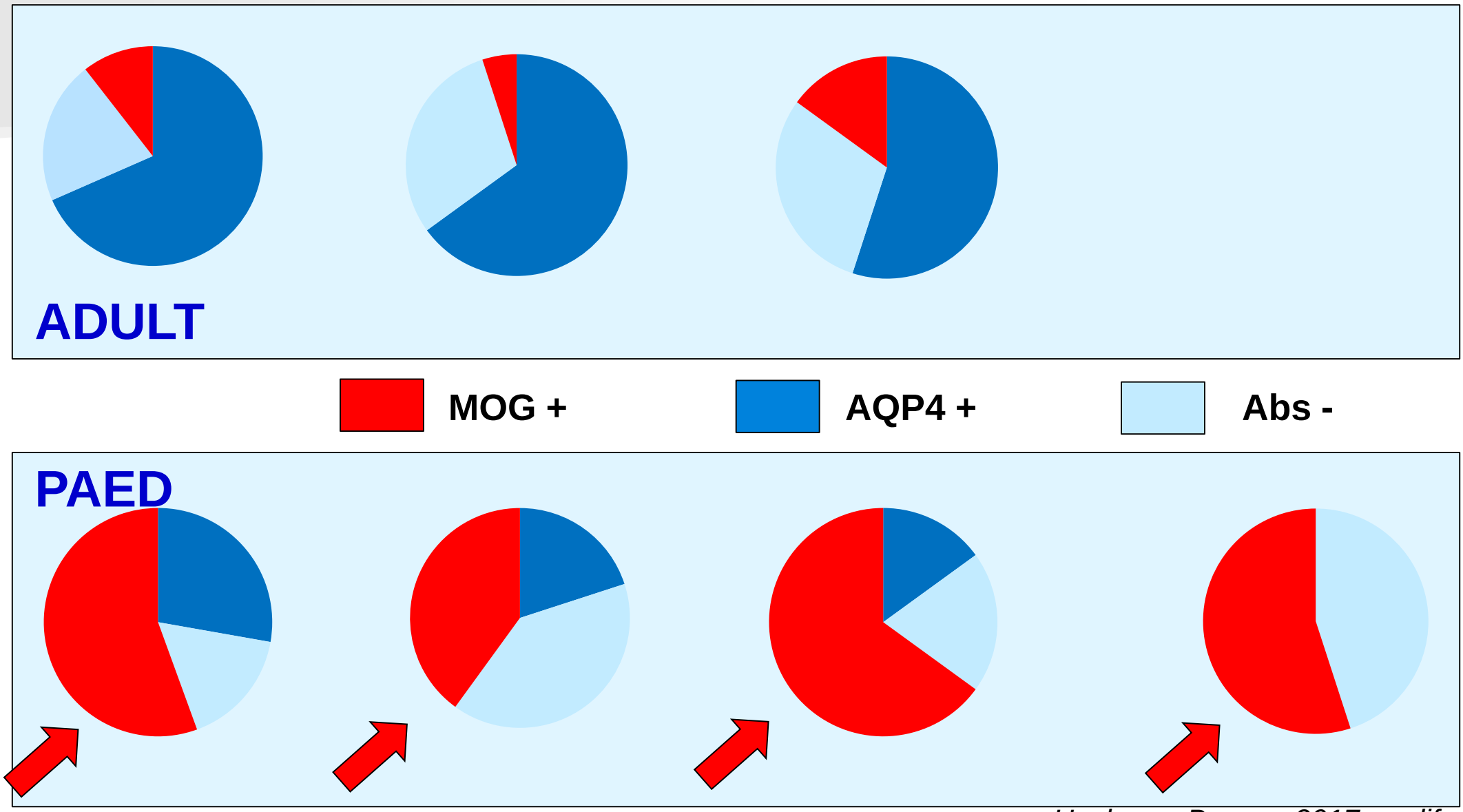


MRI of a girl (patient 5) who had the first ADEM episode at the age of 6 years and in total three episodes of ADEM (2 and 18 months after the first episode) and two further non-encephalopathic events (9 and 20 months after the first episode). The MRI of the first episode showed lesions in the supratentorial white matter





Hachoen, Baveno 2017 modif.



Hachoen, Baveno 2017 modif.

sindrome anti-MOG vs NMOSD

- Più giovani
- Minore predominanza femminile
- NO più frequentemente bilaterale rispetto a NMOSD-AQP4Abs+
- Edema papillare più frequente
- Minor rischio di ricadute e minor accumulo di disabilità
- Anormalità MRI meno frequenti
- Lesioni midollare estese da midollo toraco-lombare a cono più frequenti
- Pleiocitosi e OB rare
- Istopatologia: assenza di astrocitopatia

Jarius et al. Journal of Neuroinflammation (2016) 13:280
DOI 10.1186/s12974-016-0718-0

Journal of Neuroinflammation

RESEARCH Open Access

MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: Epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome

Sven Jarius[1*], Klemens Ruprecht[2], Ingo Kleiter[3], Nadja Borisow[4,5], Nasrin Asgari[6], Kalliopi Pitarokoili[3], Florence Pache[4,5], Oliver Stich[7], Lena-Alexandra Beume[7], Martin W. Hümmert[8], Marius Ringelstein[9], Corinna Trebst[8], Alexander Winkelmann[10], Alexander Schwarz[1], Mathias Buttmann[11], Hanna Zimmermann[2], Joseph Kuchling[2], Diego Franciotta[12], Marco Capobianco[13], Eberhard Siebert[14], Carsten Lukas[15], Mirjam Korporal-Kuhnke[1], Jürgen Haas[1], Kai Fechner[16], Alexander U. Brandt[2], Kathrin Schanda[17], Orhan Aktas[8], Friedemann Paul[4,5†], Markus Reindl[17†], and Brigitte Wildemann[1†]; in cooperation with the Neuromyelitis Optica Study Group (NEMOS)

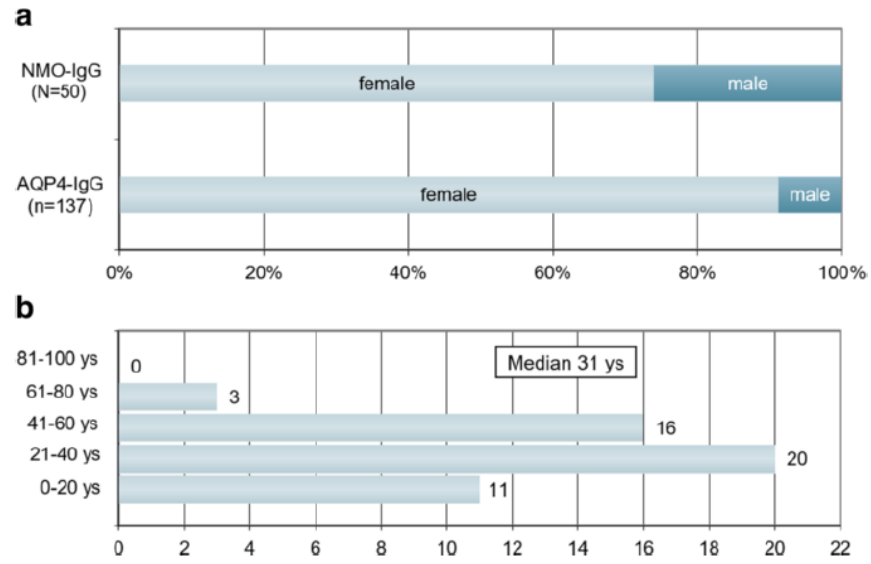
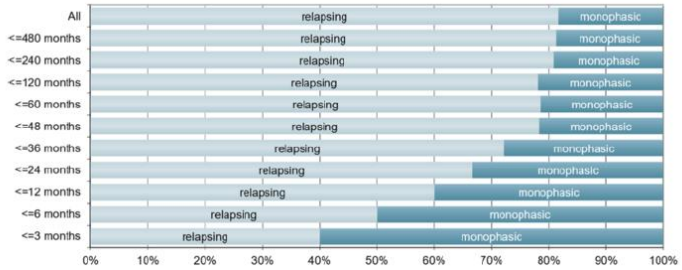


Fig. 1 Sex ratio and age distribution. **a** Sex ratio in MOG-IgG-positive patients with ON and/or LETM compared with AQP4-IgG-positive ON and/or LETM (the latter data are taken from ref. [34]). **b** Age distribution at disease onset in 50 MOG-IgG-positive patients with ON and/or myelitis



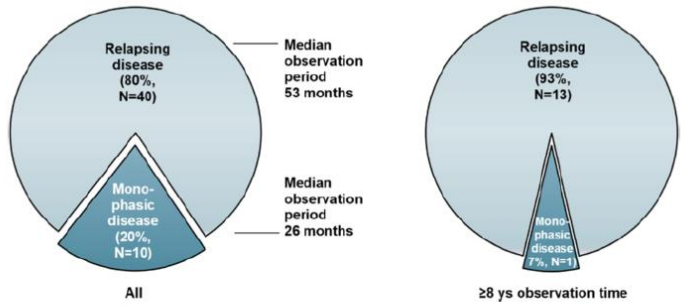


Fig. 2 Disease course in relation to observation time in 50 MOG-IgG-positive patients with ON and/or myelitis. Upper panel: Note the decrease in the proportion of monophasic cases with increasing observation time; however, in some patients no relapse has occurred more than 10 years after the initial attack. Lower panel: Note the shorter observation time in the 'monophasic' group (*left lower panel*) and the lower percentage of non-relapsing cases among patients with a long observation period (≥8 years; *right lower panel*)

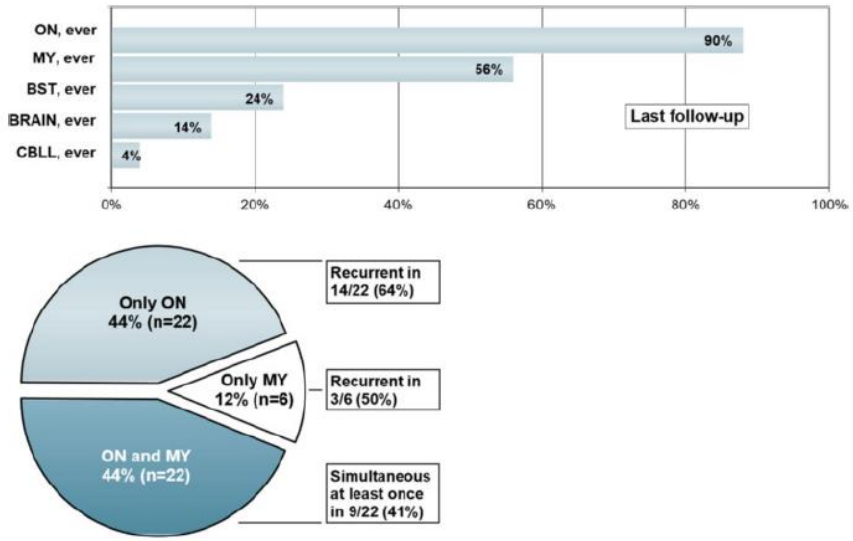
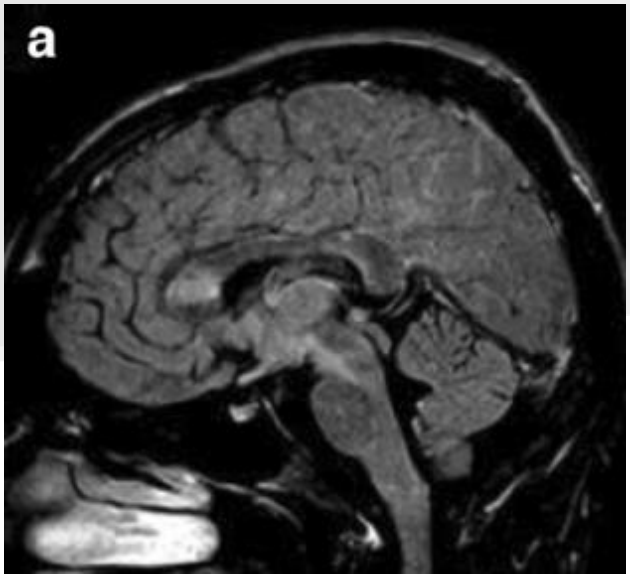


Fig. 3 Attack history at last follow-up. *Upper panel:* Frequencies of MOG-IgG-positive patients ($N = 50$) with a history of clinically manifest acute optic neuritis (ON), myelitis (MY), brainstem encephalitis (BST), supratentorial encephalitis (BRAIN), and cerebellitis (CBLL) at last follow-up. *Lower panel:* Frequencies of MOG-IgG patients with a history of optic neuritis (ON) and myelitis, ON but not myelitis, and myelitis (LETM in all cases) but not ON, respectively, at last follow-up ($n = 50$)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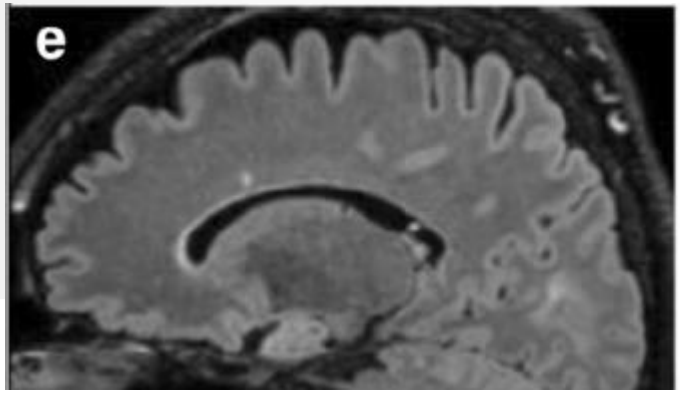
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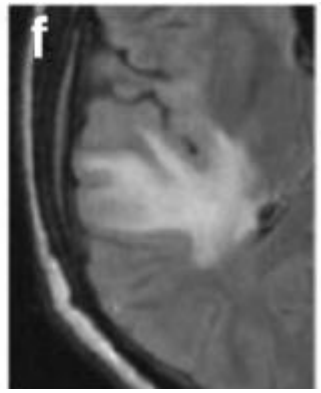
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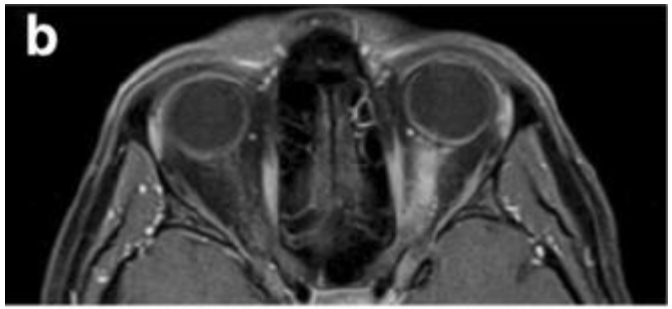
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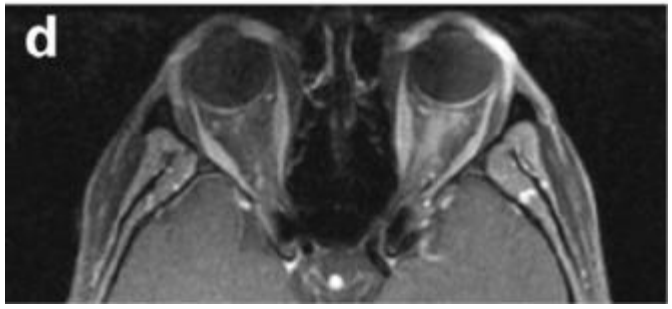
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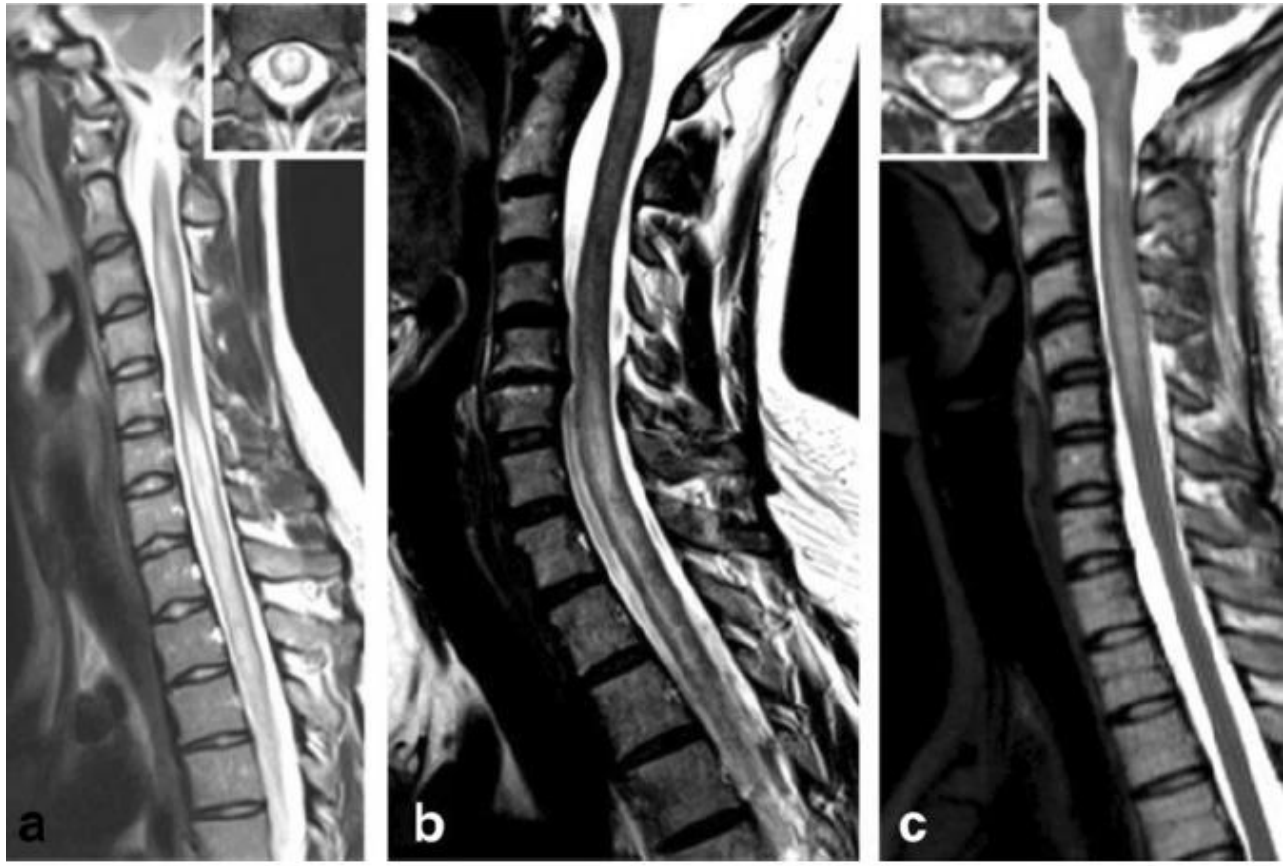
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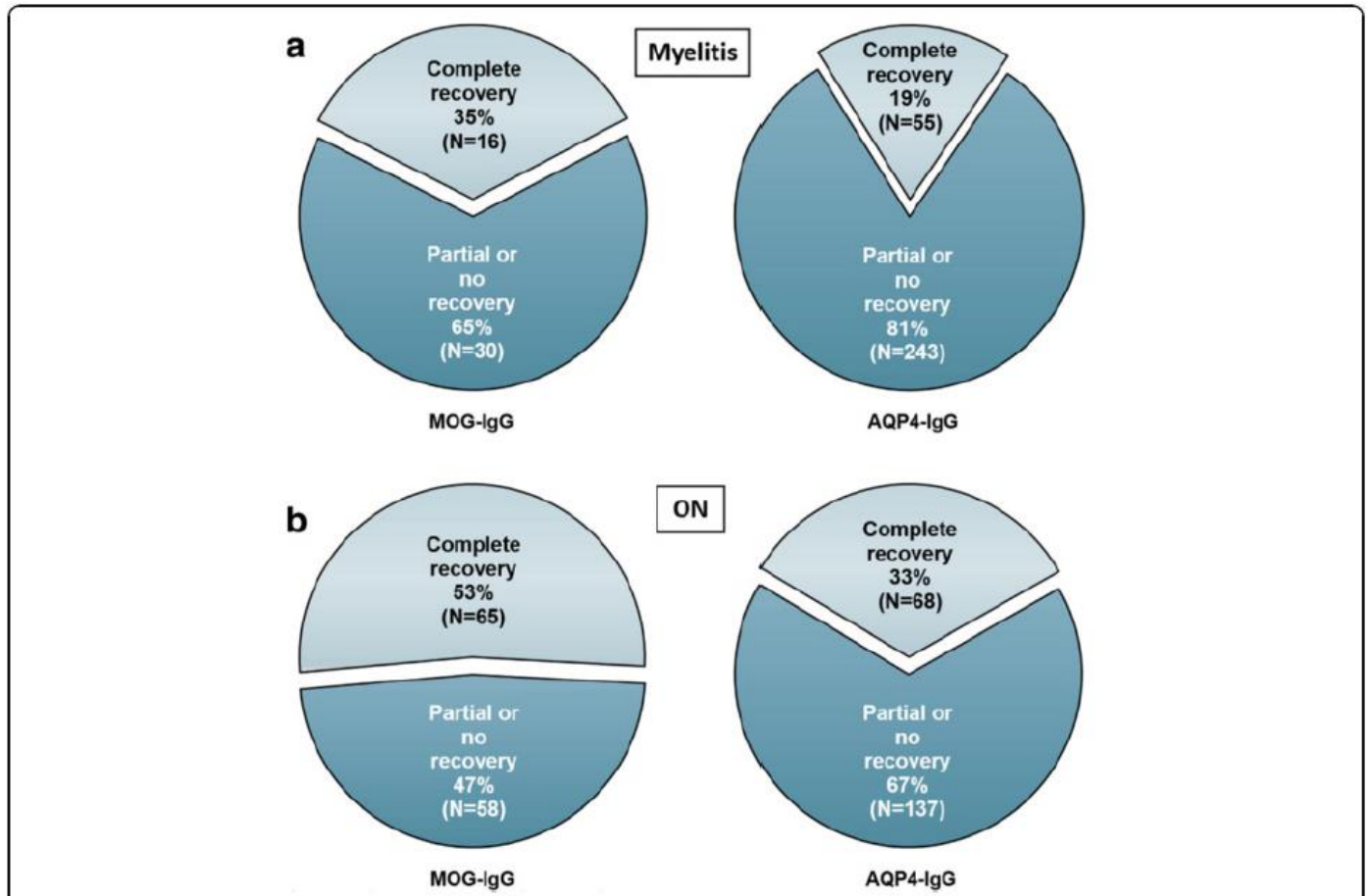


Fig. 11 Outcome after acute attacks in MOG-IgG-positive patients compared with a previously published AQP4-IgG-positive cohort. **a** Outcome after acute myelitis in MOG-IgG-positive (46 evaluable attacks) and in AQP4-IgG-positive patients (298 evaluable attacks [34]). **b** Outcome after acute ON in MOG-IgG-positive (134 evaluable attacks) and in AQP4-IgG-positive patients (205 evaluable attacks; see ref. [34]). Note that 'complete recovery' includes 'almost complete recovery' in the *left graph* (no such distinction was made in the AQP4-IgG-positive cohort)

Brain lesion distribution criteria distinguish MS from AQP4-antibody NMOSD and MOG-antibody disease

Juryńczyk M, *et al. J Neurol Neurosurg Psychiatry* 2017;**88**:132–136. doi:10.1136/jnnp-2016-314005

Table 2 Number of patients fulfilling the criteria and the sensitivity and specificity of each criterion or of combination of criteria for the discrimination between RRMS and AQP4-ab NMOSD

	Number of participants	Criterion (a): lesion adjacent to the body of a LV and inferior temporal lobe lesion	Criterion (b): U-fibre lesions	Criterion (c): Dawson's fingers	Full criteria (a, b or c)
AQP4-ab NMOSD, n	31	1	2	2	4
RRMS, n	44	32	13	36	40
Sensitivity, %	–	72.7	29.6	81.8	90.9
Specificity, %	–	96.8	93.6	93.6	87.1
PPV, %	–	97	86.7	94.7	90.9
NPV, %	–	71.4	48.3	78.4	87.1

Table 3 Number of patients fulfilling the criteria and the sensitivity and specificity of each criterion or of combination of criteria for the discrimination between RRMS and MOG-ab NMOSD

MOG-ab NMOSD, n	21	0	1	0	1
RRMS, n	44	32	13	36	40
Sensitivity, %	–	72.7	29.6	81.8	90.9
Specificity, %	–	100	95.2	100	95.2
PPV, %	–	100	92.9	100	97.6
NPV, %	–	63.6	39.2	72.4	83.3

The criteria were fulfilled by 90.9% RRMS, 12.9% AQP4-ab NMOSD, 4.8% MOG-ab NMOSD and 12.5% ab-negative NMOSD/MS overlap patients.

anti-MOG + vs anti-MOG-

Clinical and MRI phenotype of children with MOG antibodies

Multiple Sclerosis Journal

2016, Vol. 22(2) 174–184

Cristina Fernandez-Carbonell, David Vargas-Lowy, Alexander Musallam, Brian Healy, Katherine McLaughlin, Kai W Wucherpfennig and Tanuja Chitnis

Objective: To investigate the clinical and magnetic resonance imaging (MRI) features of anti-myelin oligodendrocyte glycoprotein (MOG) antibody-seropositive pediatric demyelinating syndromes.

Methods: Serum samples collected from 74 children with suspected demyelinating disorders whom were being followed at Massachusetts General Hospital were incubated with control green fluorescent protein (GFP)- and MOG-GFP-transfected Jurkat cell clones. The binding ratios were calculated using flow cytometry. Using statistical analyses, we compared the demographic, clinical and radiological features in our seropositive and seronegative patients.

Results: We found that 13 out of 74 (17.5%) patients were seropositive for MOG. The MOG-seropositive patients were younger than the seronegative patients ($p = 0.049$). No single disease category predominated among the seropositive patients, nor was one group more likely to have a polyphasic course. There were two out of four neuromyelitis optica (NMO) patients who had MOG antibodies; both were seronegative for aquaporin –4 (AQP4) antibodies. One had monophasic disease and the other had frequent relapses. There was a bimodal distribution of the MOG-seropositive patients by age at onset, with a distinct younger group (4–8 years) having a high prevalence of encephalopathy and an older group (13–18 years), whom presented almost exclusively with optic neuritis. MRI analysis demonstrated the absence of corpus callosum lesions in the seropositive patients ($p = 0.012$). The annualized relapse rate (ARR) and the Expanded Disability Status Scale (EDSS) results at 2 years did not differ between the seropositive and seronegative patients.

Conclusion: MOG antibodies are found across a variety of pediatric demyelinating syndromes having some distinct clinical and MRI features.

	MOG positive	MOG negative	*P*-value
N	13	61	
Female, *N* (%)	8 (61.5)	44 (72.1)	0.510
Ethnicity, *N* (%)			0.719
Hispanic	2 (15.4)	15 (24.6)	
Non-hispanic	11 (84.6)	46 (75.4)	
Race, *N* (%)			1
White	9 (69.2)	45 (73.8)	
Black/African American	2 (15.4)	8 (13.1)	
Other	2 (15.4)	8 (13.1)	
Age at blood sample, mean (SD)	12.1 (5.1)	15.7 (2.4)	**0.020**
Disease duration at blood sample	2.15 (3.02)	1.89 (2.43)	0.81
Duration of follow-up from disease onset	4.53 (3.88)	4.86 (3.06)	0.500
Disease Category, *N* (%)			
MS	4 (30.77)	41 (67.21)	**0.026**
CIS	2 (15.38)	10 (16.39)	1
ADEM	3 (23.1)	4 (6.56)	0.099
NMO	2 (15.38)	2 (3.28)	0.14
RIS	0		

Labs[a]	MOG Seropositive	MOG Seronegative	*P*-value
CSF WBC, Mean (SD)	108.8 (126.5)	16.2 (32.1)	**0.0004**
Oligoclonal bands in CSI	1 (14.29)	20 (52.6)	0.101

	MOG seropositive	MOG seronegative	*P*-value
Brain			
N	6	45	
Cortical, *N* (%)	0	3 (6.7)	1.00
Subcortical, *N* (%)	5 (83.3)	34 (75.6)	1.00
Periventricular, *N* (%)	2 (33.3)	31 (68.9)	0.17
Corpus callosum, *N* (%)	0	25 (55.5)	**0.023**
Optic chiasm, *N* (%)	0	1 (2.2)	1.00
Thalamus, *N* (%)	1 (16.7)	7 (15.6)	1.00
Brainstem, *N* (%)	2 (33.3)	20 (44.4)	0.69
Area postrema, *N* (%)	0	2 (4.4)	1.00
Cerebellum, *N* (%)	1 (16.7)	11 (24.4)	1.00
Spine			
N	3	23	
Cervical spine, *N* (%)	2 (66.7)	12 (52.2)	1.00
Thoracic spine, *N* (%)	0	8 (34.8)	0.53

Radiological differentiation of optic neuritis with myelin oligodendrocyte glycoprotein antibodies, aquaporin-4 antibodies, and multiple sclerosis

Multiple Sclerosis Journal
2016, Vol. 22(4) 470–482
DOI: 10.1177/1352458515593406

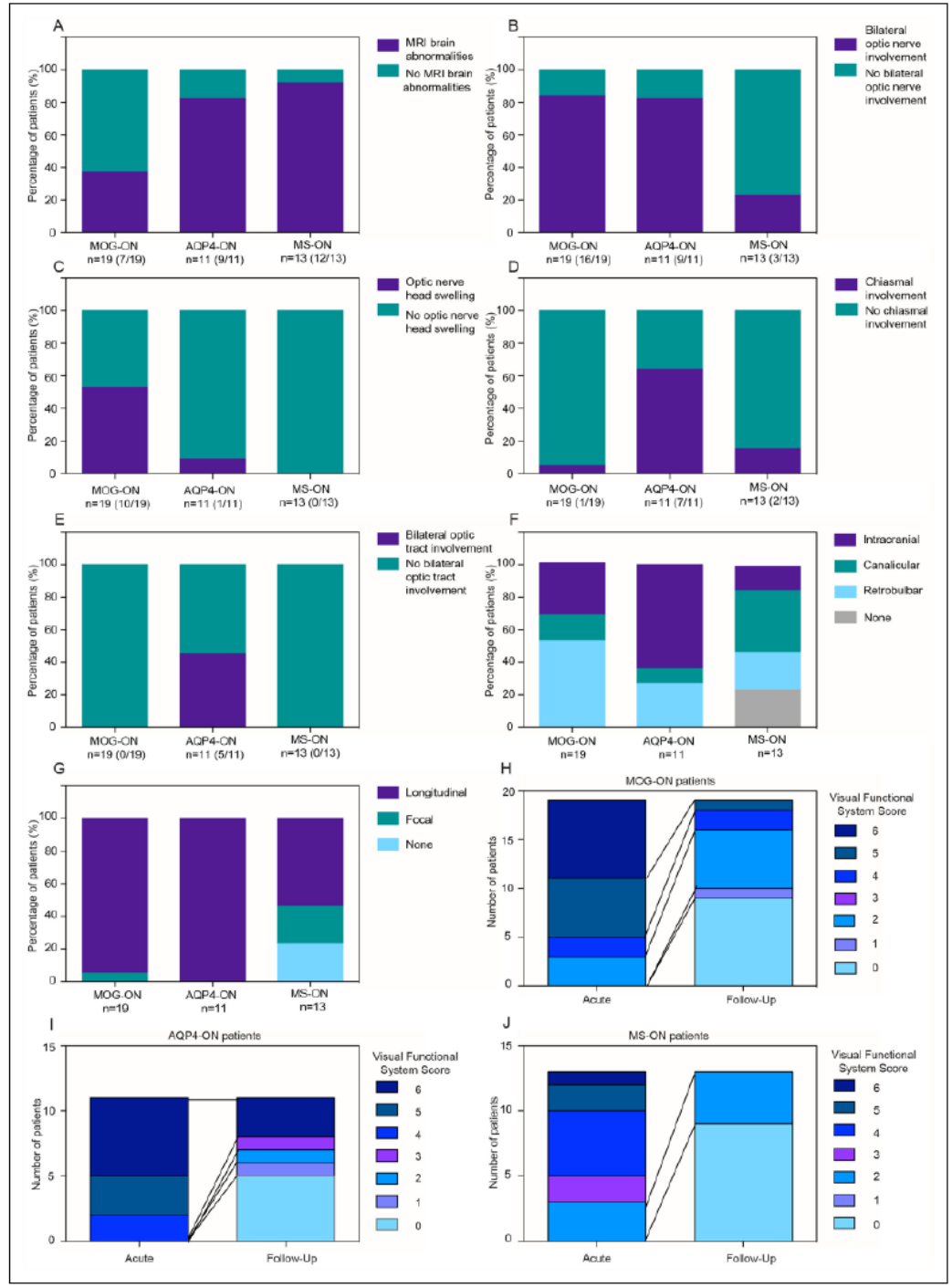
Sudarshini Ramanathan, Kristina Prelog, Elizabeth H Barnes, Stephen W Reddel, Andrew PD Henderson, Steve Vucic, Mar, Leslie A Benson, Gulay Alper, Catherine J Riney, Michael Ba, Todd A Hardy, Richard J Leventer, Vera Merheb, Margherit, Fabienne Brilot and Russell C Dale

Methods: We performed blinded radiological assessment of 50 patients presenting with first-episode myelin oligodendrocyte glycoprotein (MOG) antibody-associated ON (MOG-ON; *n*=19), aquaporin-4 (AQP4) antibody-associated ON (AQP4-ON; *n*=11), multiple sclerosis (MS)-associated ON (MS-ON; *n*=13), and unclassified ON (*n*=7).

Table 1. The clinical comparison of ON acutely and at follow-up in patients with MOG-ON, AQP4-ON, and MS-ON.

Clinical variable assessed	MOG-ON (*n*=19)	AQP4-ON (*n*=11)	MS-ON (*n*=13)	*p*-value[a]
Gender	15/19 (79%)	9/11 (82%)	12/13 (92%)	*p*=0.59
number of females (%)	*(57–91%)*[b]	*(52–95%)*	*(67–99%)*	
Age at onset	20; 14 (3–55)	23; 14 (8–58)	29; 29 (12–45)	*p*=0.11
mean; median (range) in years	*(13–28)*	*(11–35)*	*(21–37)*	
Number of patients for whom the ON episode was the first demyelinating event	18/19 (95%)	6/11 (55%)	10/13 (77%)	*p*=0.033
number (%)	*(75–99%)*	*(28–79%)*	*(50–92%)*	
Worst VFSS during acute episode of ON	4.8; 5 (2–6)	5.4; 6 (4–6)	3.7; 4 (2–6)	*p*=0.0054
mean; median (range)	*(4.2–5.5)*	*(4.8–5.9)*	*(2.9–4.5)*	
Presence of optic nerve head swelling on fundoscopy	15/19 (79%)	3/11 (27%)	2/13 (15%)	*p*=0.0006
number (%)	*(57–91%)*	*(10–57%)*	*(4–42%)*	
Presence of intrathecal oligoclonal bands when CSF analyzed	1/15 (7%)	3/8 (38%)	6/8 (75%)	*p*=0.018
number (%)	*(1–30%)*	*(14–69%)*	*(41–93%)*	
Clinical follow-up duration (months)	30; 18 (0.17–75)	37; 32 (5–102)	51; 44 (13–156)	*p*=0.13
mean; median (range)	*(18–42)*	*(19–56)*	*(29–72)*	
Presence of any clinical demyelinating relapses	6/19 (32%)	11/11 (100%)	9/13 (69%)	*p*=0.0008
number (%)	*(15–54%)*	*(74–100%)*	*(42–87%)*	
Total number of clinical demyelinating episodes	1.8; 1 (1–5)	5; 4 (3–10)	2.6; 2 (1–6)	*p*=0.0002
mean; median (range)	*(1.1–2.4)*	*(3.5–6.7)*	*(1.6–3.6)*	
Subsequent number of ON episodes	0.68; 0 (0–4)	1.45; 1 (0–3)	0.69; 0 (0–3)	*p*=0.042
mean; median (range)	*(0.04–1.33)*	*(0.76–2.15)*	*(0–1.41)*	

Conclusion: MOG-ON and AQP4-ON are more commonly bilateral and longitudinally extensive. MOG-ON tends to involve the anterior optic pathway, whereas AQP4-ON the posterior optic pathway.


A
MRI brain abnormalities
No MRI brain abnormalities
Percentage of patients (%)
MOG-ON n=19 (7/19)
AQP4-ON n=11 (9/11)
MS-ON n=13 (12/13)
B
Bilateral optic nerve involvement
No bilateral optic nerve involvement
MOG-ON n=19 (16/19)
AQP4-ON n=11 (9/11)
MS-ON n=13 (3/13)
C
Optic nerve head swelling
No optic nerve head swelling
MOG-ON n=19 (10/19)
AQP4-ON n=11 (1/11)
MS-ON n=13 (0/13)
D
Chiasmal involvement
No chiasmal involvement
MOG-ON n=19 (1/19)
AQP4-ON n=11 (7/11)
MS-ON n=13 (2/13)
E
Bilateral optic tract involvement
No bilateral optic tract involvement
MOG-ON n=19 (0/19)
AQP4-ON n=11 (5/11)
MS-ON n=13 (0/13)
F
Intracranial
Canalicular
Retrobulbar
None
MOG-ON n=19
AQP4-ON n=11
MS-ON n=13
G
Longitudinal
Focal
None
MOG-ON n=19
AQP4-ON n=11
MS-ON n=13
H
MOG-ON patients
Number of patients
Acute
Follow-Up
Visual Functional System Score
6
5
4
3
2
1
0
I
AQP4-ON patients
J
MS-ON patients

Myelin oligodendrocyte glycoprotein antibodies are associated with a non-MS course in children

Yael Hacohen, et. al

OPEN

ABSTRACT

Objective: To determine whether myelin oligodendrocyte glycoprotein antibodies (MOG-Abs) were predictive of a demyelination phenotype in children presenting with acquired demyelinating syndrome (ADS).

Method: Sixty-five children with a first episode of ADS (12 acute disseminated encephalomyelitis, 24 optic neuritis, 18 transverse myelitis, 11 other clinically isolated syndrome) were identified from 2 national demyelination programs in the United Kingdom and France. Acute serum samples were tested for MOG-Abs by cell-based assay. Antibodies were used to predict diagnosis of multiple sclerosis (MS) at 1 year.

Results: Twenty-three of 65 (35%) children had MOG-Abs. Antibody-positive and antibody-negative patients were not clinically different at presentation, but identification of MOG-Abs predicted a non-MS course at 1-year follow-up: only 2/23 (9%) MOG-Ab–positive patients were diagnosed with MS compared to 16/42 (38%) MOG-Ab–negative patients ($p = 0.019$, Fisher exact test). Antibody positivity at outset was a useful predictor for a non-MS disease course, with a positive predictive value of 91% (95% confidence interval [CI] 72–99), negative predictive value of 38% (95% CI 24–54), positive likelihood ratio of 4.02 (CI 1.0–15.4), and odds ratio of 6.5 (CI 1.3–31.3).

Conclusions: MOG-Abs are found at presentation in 35% of patients with childhood ADS, across a range of demyelinating disorders. Antibody positivity can be useful in predicting a non-MS disease course at onset.

Neurol Neuroimmunol Neuroinflamm 2015;2:e81; doi: 10.1212/NXI.0000000000000081

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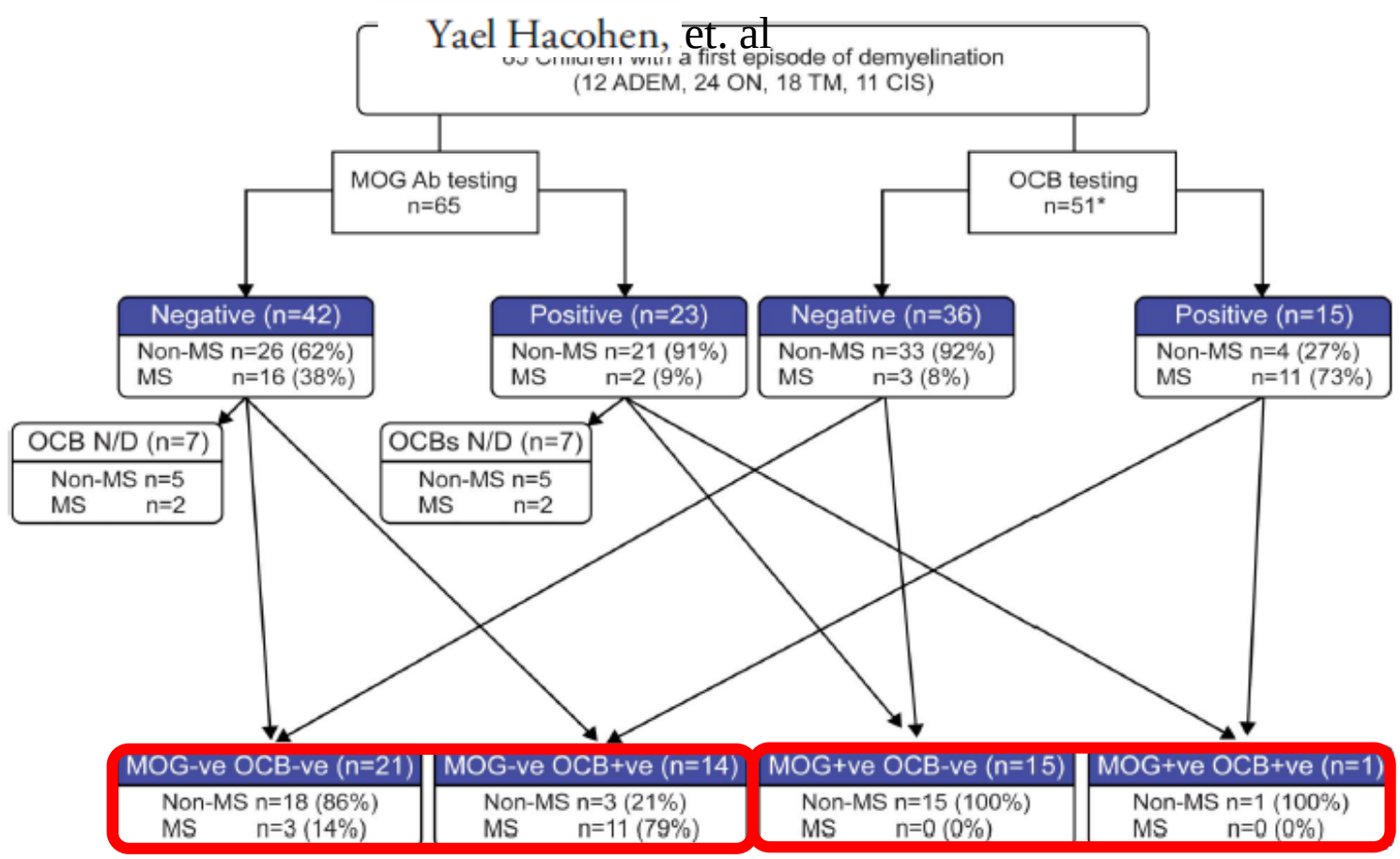
Figure 2 Summary of the utility of MOG-Abs and OCB testing in predicting pediatric disease course at onset compared to clinical follow-up at 1 year

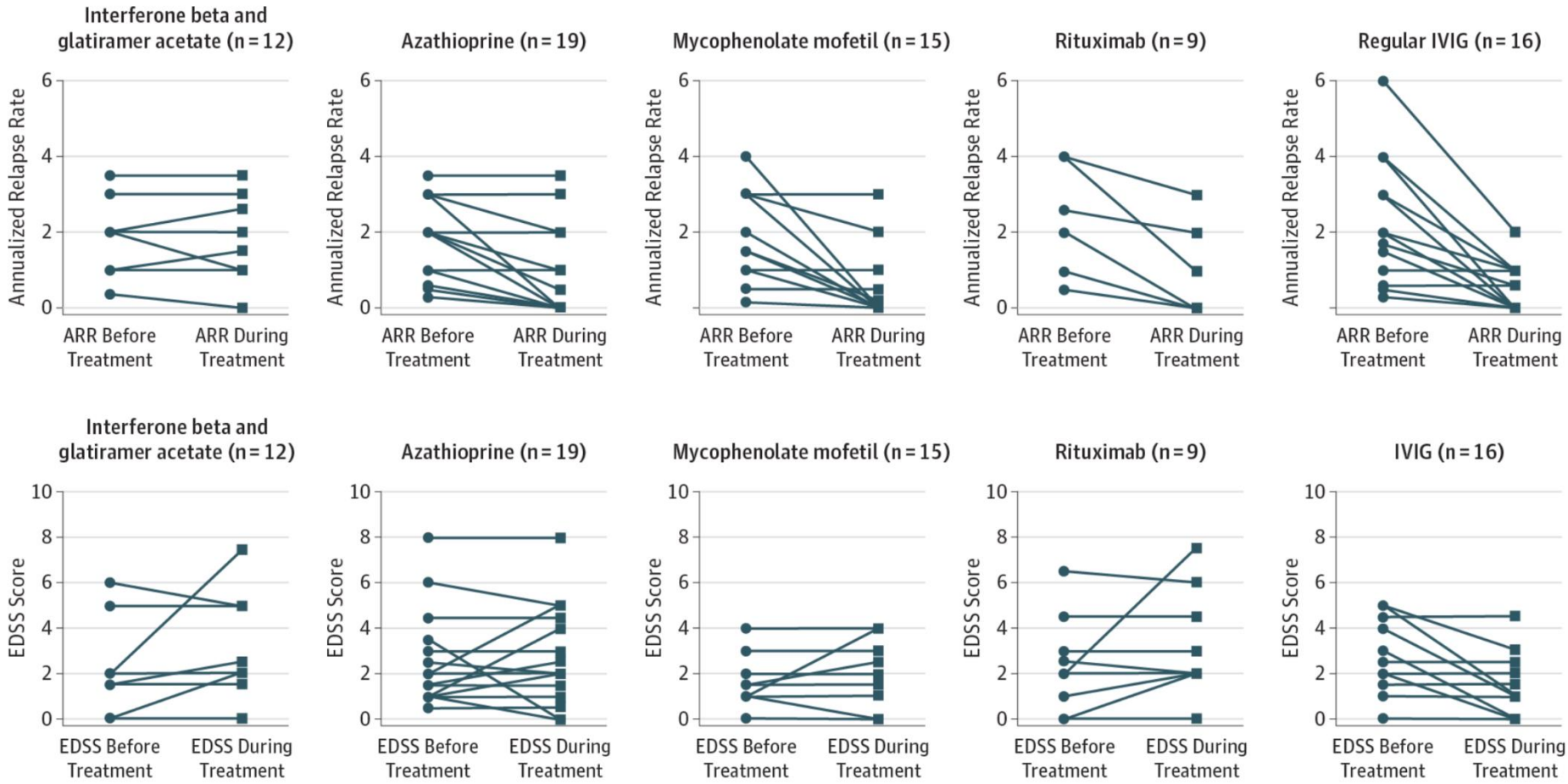


Following testing with either myelin olidgodendrocyte glycoprotein antibody (MOG-Ab) or oligoclonal blands (OCBs), the additional testing of the respective other is represented by arrows to the respective outcomes. A MOG-Ab–positive test predicted a non–multiple sclerosis (MS) diagnosis, whereas OCB positivity was highly predictive of MS. Eleven of 15 OCB- positive patients developed MS (73%), whereas 11 of 14 OCB-positive and MOG-Abs–negative patients developed MS (79%). The one MOG-Ab–positive and OCB-positive patient did not have MS, and all MOG-Ab–positive and OCB-negative cases had a non-MS course, compared to 91% if only OCB was negative. Of the 14 patients not tested for intrathecal OCBs, 7 patients tested positive for MOG-Ab; 2 patients from the antibody-positive and 2 from the antibody-negative groups had a diagnosis of MS at 1-year follow-up. ADEM = acute disseminated encephalomyelitis; CIS = clinically isolated syndrome; N/D = not done; ON = optic neuritis; TM = transverse myelitis.

Hacohen Y, Wong YY, Lechner C, et al. Disease course and treatment responses in children with relapsing myelin oligodendrocyte glycoprotein antibody–associated disease. *JAMA Neurol.* Published online January 5, 2014. doi:10.1001/jamaneurol.2014.1238

102 children :median age 7.0 ys [range 1.5-7.9] ; m/fratio, 1.0:1.8; white to other race/ethnicity ratio, 3.6:1.0.
Original diagnoses :

- neuromyelitis optica spectrum disorder: 43.1% of cases,
- acute disseminated encephalomyelitis followed by optic neuritis: 19.6% of cases,
- multiphasic disseminated encephalomyelitis: 19.6% of cases,
- relapsing optic neuritis: 18 of cases



Severe attacks and unfavorable long-term outcome are relatively frequent

Breakthrough attacks despite long-term immunotherapy

IVMP was not always effective and flare-ups were frequent

PEX treatment was often followed by full or partial recovery

AZA failure was associated with latency period and lack of cotreatment

Low relapse rate under MTX in most but not all cases

Attacks related to initial rituximab infusion and reappearance of B cells

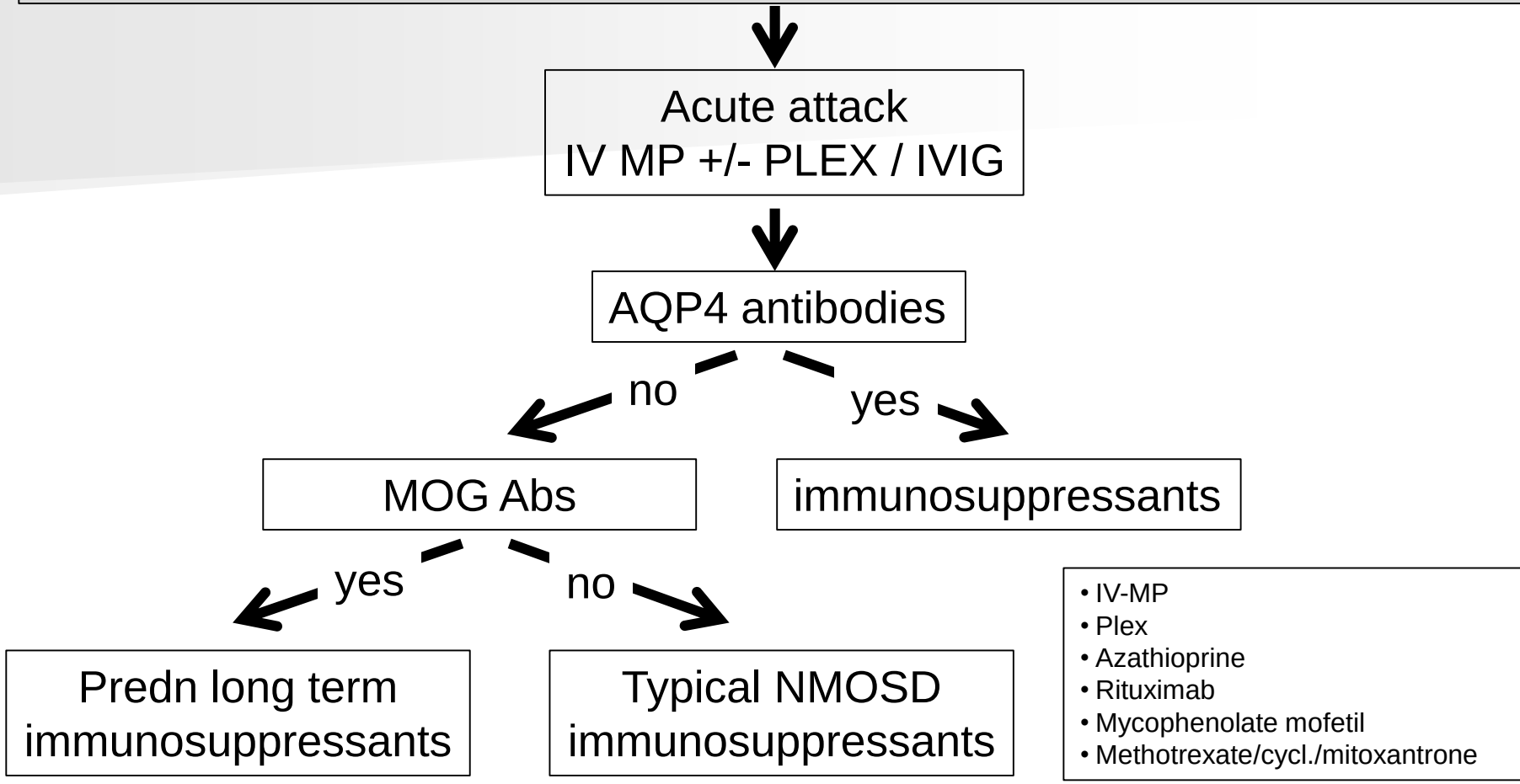
Rituximab treatment was followed by a clear reduction in relapse rate in three out of nine patients. In the six remaining patients, relapses occurred 2, 3, 4, 4, 7, 8, 8, 12 and 20 weeks after the first or second infusion (in one case despite PEX treatment 1 month earlier). This is

Ongoing or increasing disease activity under IFN-beta

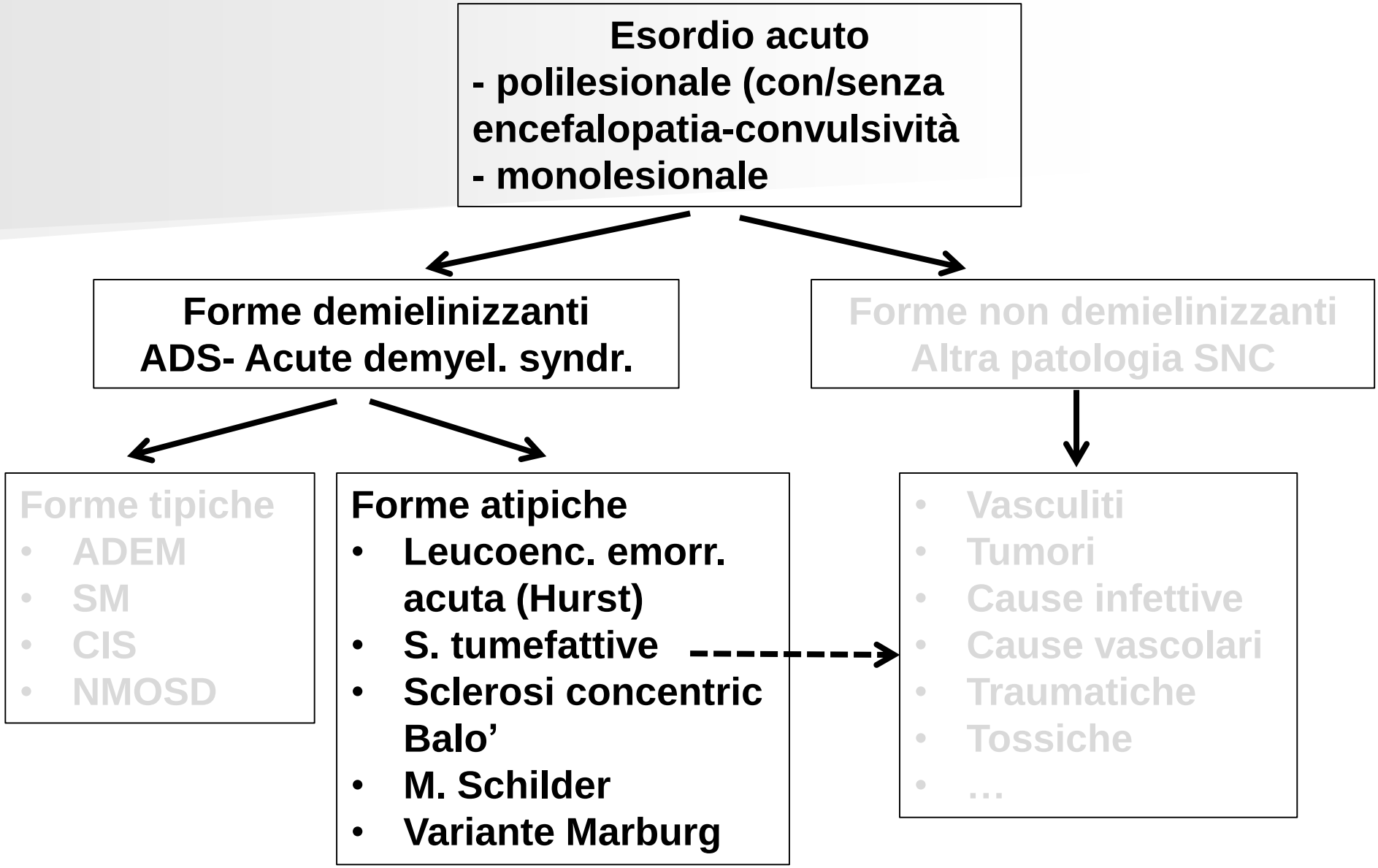
Preliminary data do not support use of GLAT or NAT

Jarius et al. J. Neuroinflammation 2016

Treatment of NMOSD/ADEM



Hachoen, Baveno 2017 modif.


Esordio acuto
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Forme demielinizzanti
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• Cause infettive
• Cause vascolari
• Traumatiche
• Tossiche
• …

Atypical inflammatory demyelinating syndromes of the CNS

Todd A Hardy, Stephen W Reddel, Michael H Barnett, Jacqueline Palace, Claudia F Lucchinetti, Brian G Weinshenker

Leucoencefalite emorragica di HURST

Fulminant form of ADEM: rapidly progressive severe encephalopathy usually leading to death within 1 week of onset

MRI: imilar tp ADEM, except that haemorrhage is present in some or most

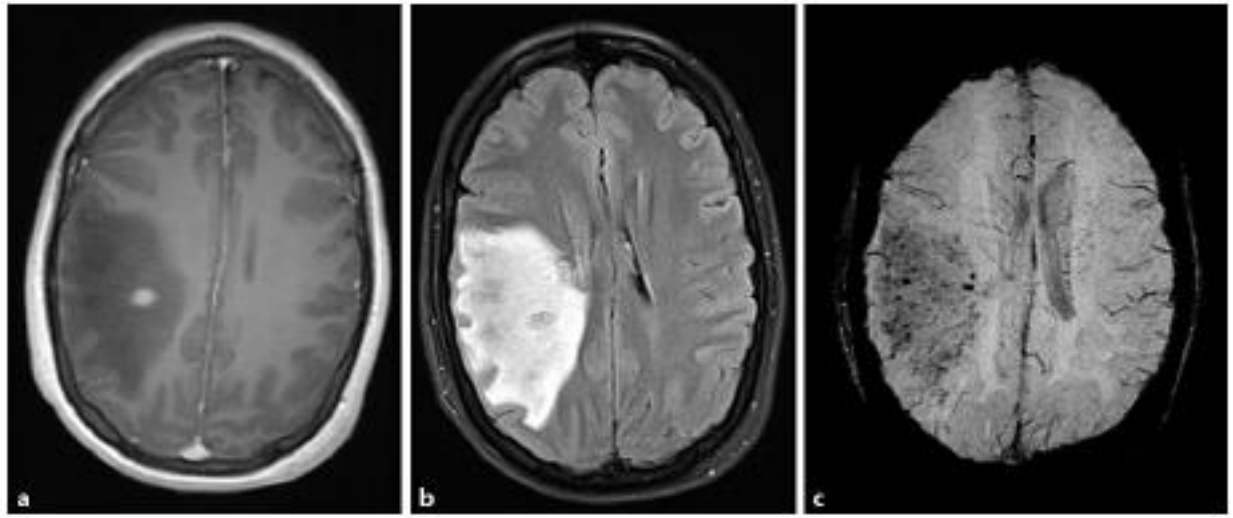

Fig. 1. Brain magnetic resonance imaging on day 1 after presentation. a T1 + gadolinium showing a discrete area of contrast enhancement. b Fluid attenuation inversion recovery consistent with significant cerebral oedema. c Susceptibility-weighted imaging demonstrates multiple petechial haemorrhages.

Solis et al. Case Rep Neurol 2017;9:106–113

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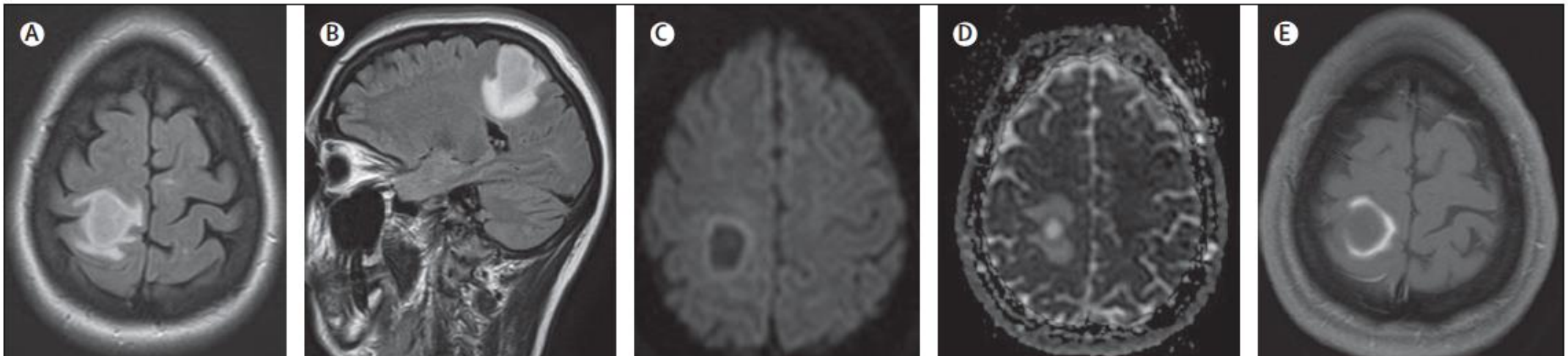
TUMEFACTIVE DEMYELINATION

symptoms include: seizures, impaired consciousness, cognitive deficits, and focal signs.

MRI
- Lesions categorised into: ring-enhancing, infiltrative, megacystic, Baló-like subtypes
- Single lesions might be mistaken for neoplasms on MRI

Diagnosis
- MRS (spectroscopy): increased glutamate-glutamine peak, increased choline/NAA ratio
- CSF. Increased proteins, OBs
- CT-PET: lower metabolic activity
- biopsy

Other differential diagnoses include: cerebral abscess, ischaemia, and infection



Atypical inflammatory demyelinating syndromes of the CNS

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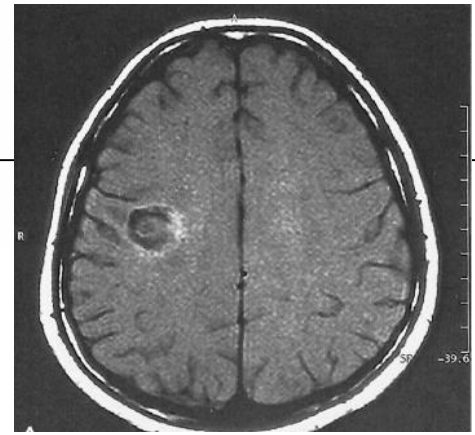
Balo' concentric sclerosis

Alternating rings of demyelination and relatively preserved myelin

Focal neurological symptoms, or symptoms of a cerebral mass

Balo'-like lesions in MS/NMOSD subjects

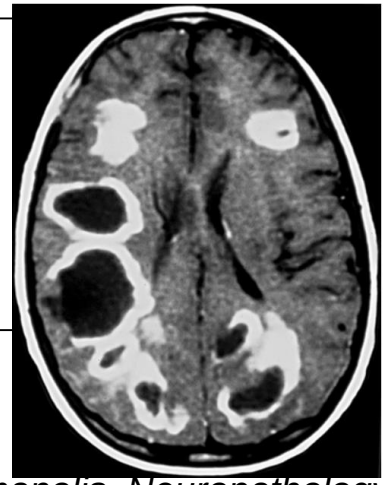


15-year-old female patient who presented with acute left hemiparesis

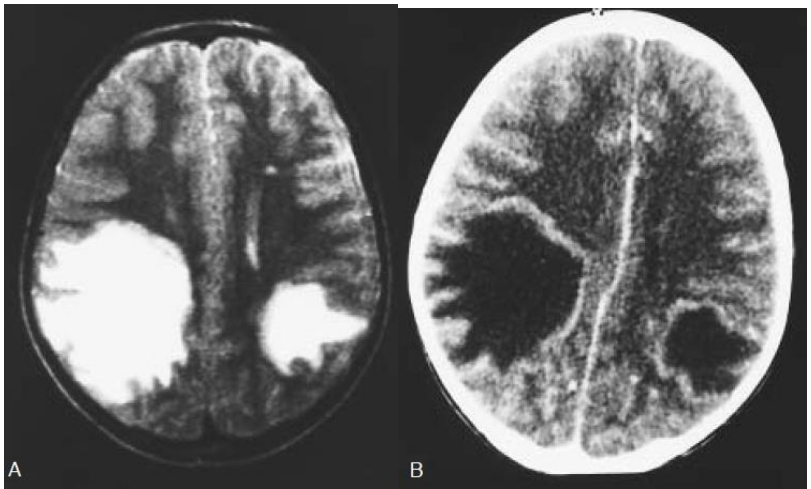
Schilder's disease

Case reports of inflammatory demyelinating condition, others recognized as due to adrenoleukodistrophy and SSPE

Not a separate atypical demyelinating syndrome



Agamanolis, Neuropathology



- 9-year-old girl who presented with left hemiparesis.
- After 2 months, right-sided visual loss.
- At 24 months of observation, the patient continued to do well without any complaints or neurologic sequelae. (Kurul et al. J Child Neurol 2003;18:58–61).

Atypical inflammatory demyelinating syndromes of the CNS

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Marburg's variant of MS

Patients typically present with seizures, headache, vomiting, bilateral optic neuritis, and gait disturbance with hemiparesis or quadriparesis.
Symptoms progress rapidly, often stepwise or continuously.

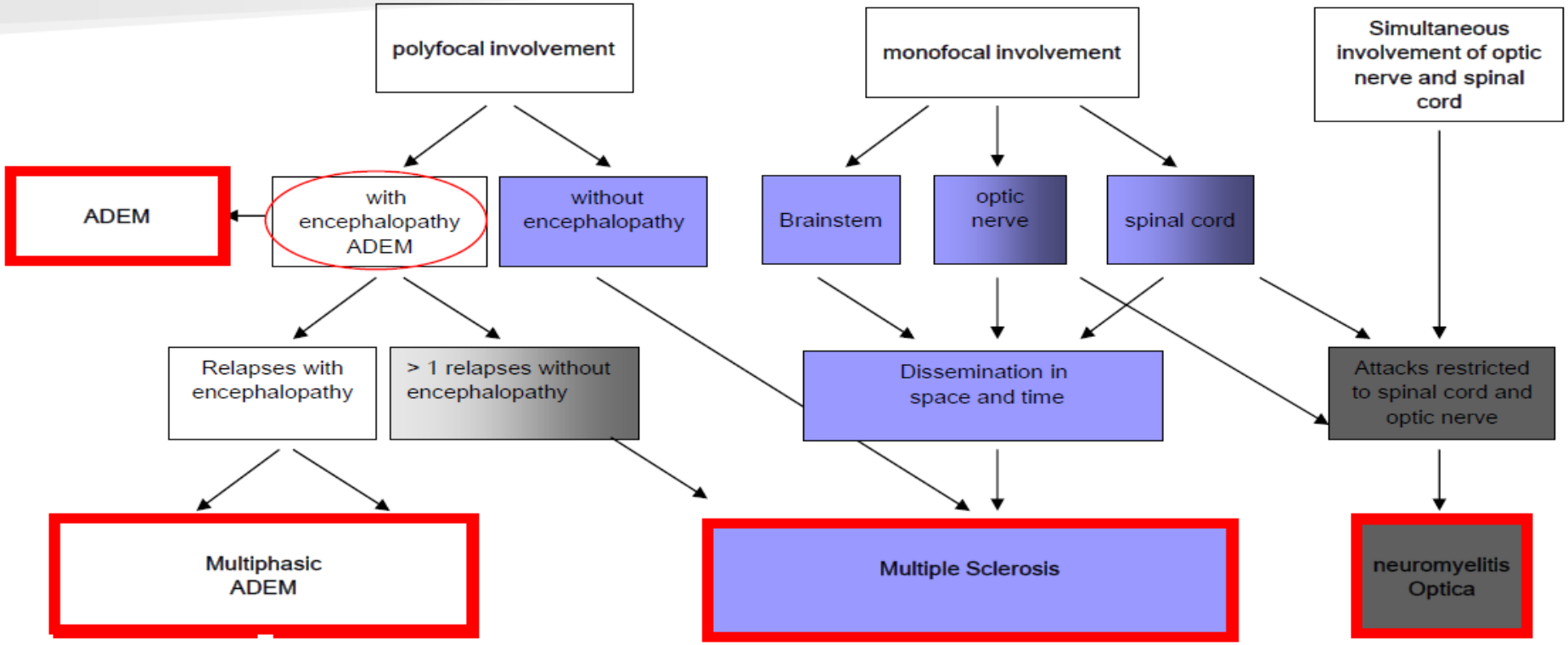
Marburg's multiple sclerosis might present with multifocal cognitive syndromes, such as aphasia and apraxia, rather than with diffuse encephalopathy.

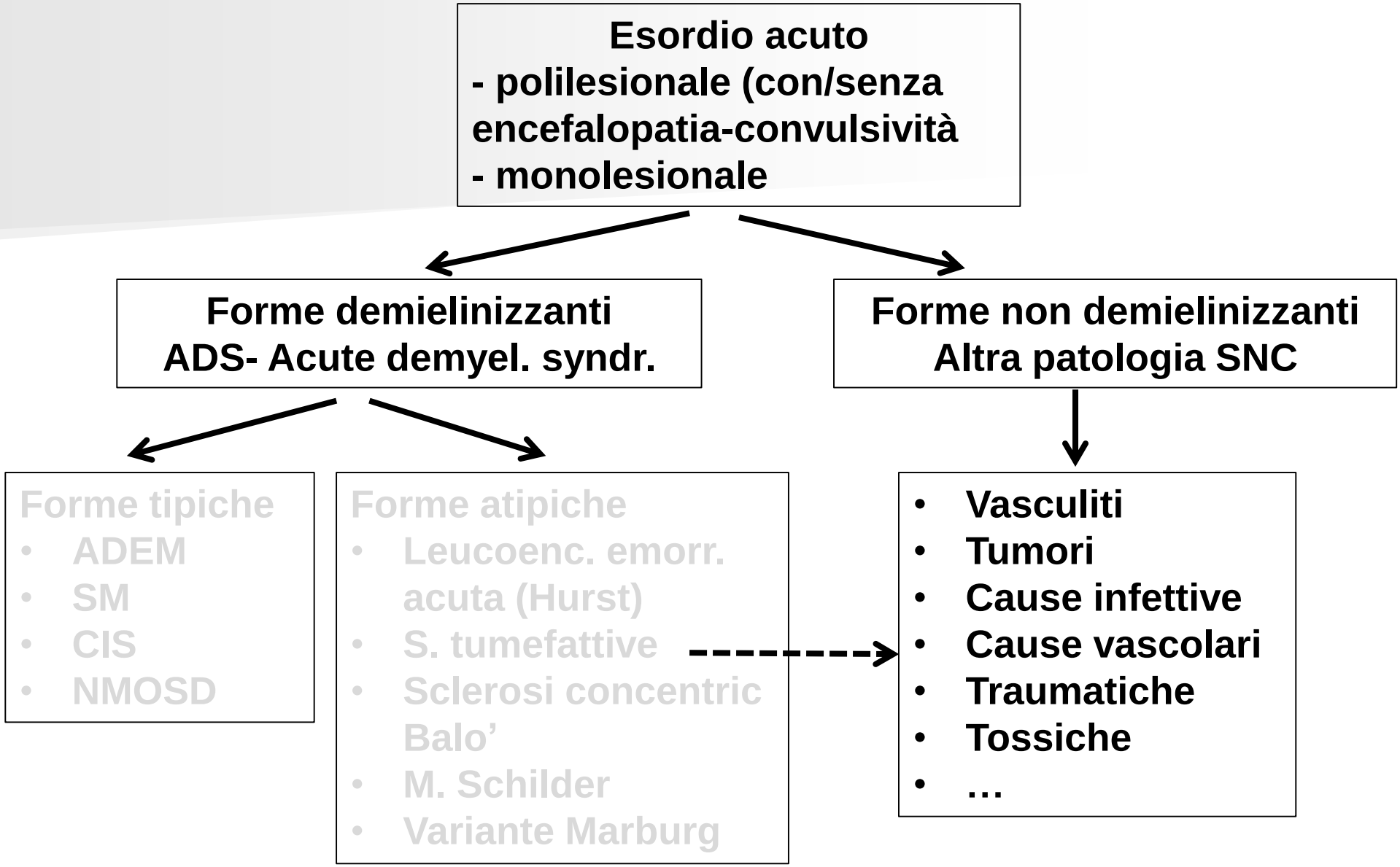
MRI
- Multifocal demyelinating lesions in the periventricular, juxtacortical, and deep white matter, and in the brainstem, cerebellum, or spinal cord,
- frequently large and show gadolinium enhancement
- Frequent severe perilesional oedema similar to that in ADEM

intermediate entity between tumefactive demyelination and ADEM, although
the pathological features suggest that it is much closer to tumefactive demyelination

First attack of demyelination

(modified, Banwell B, Ghezzi A, Tardieu M et al. Lancet Neurol. 2007)

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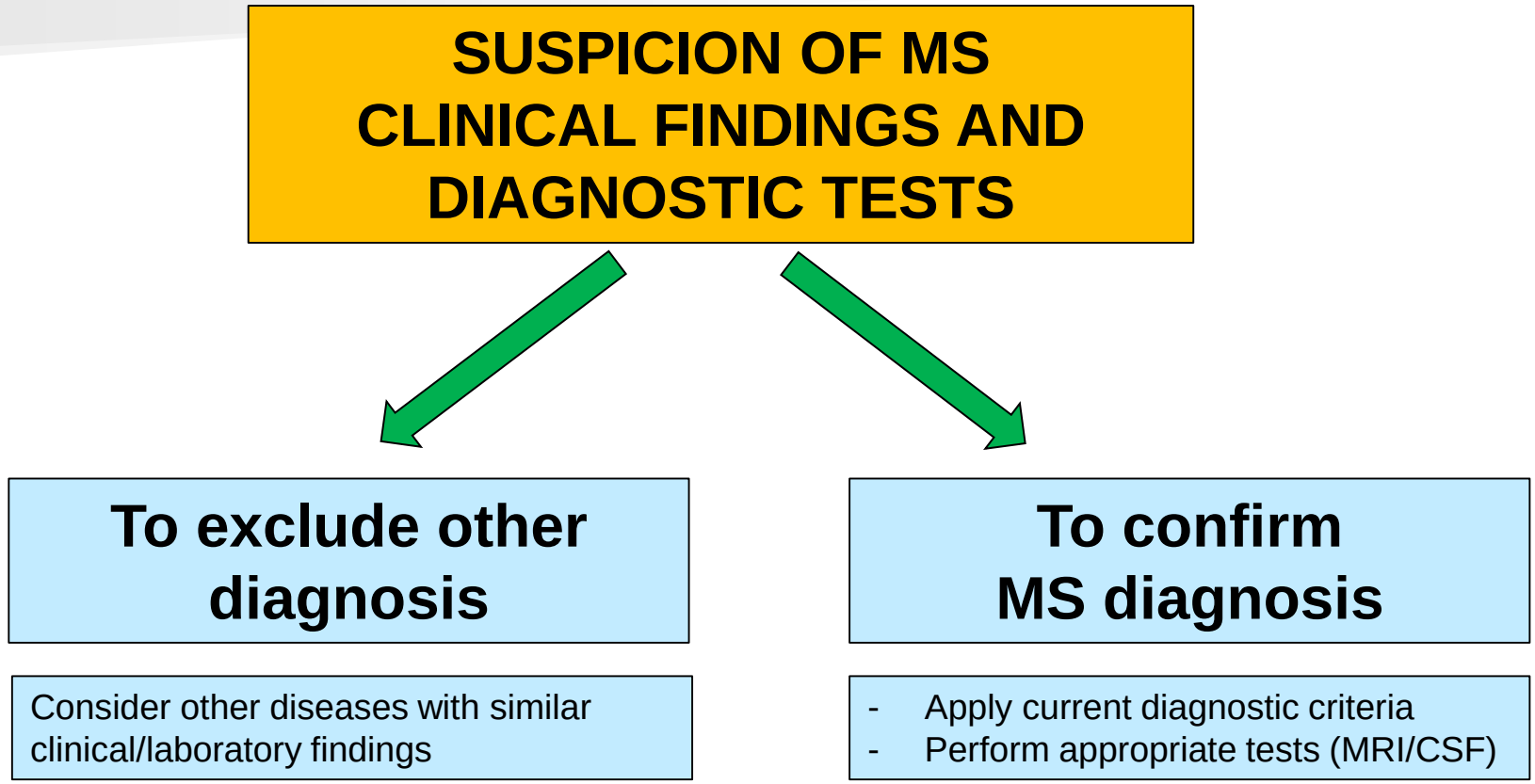
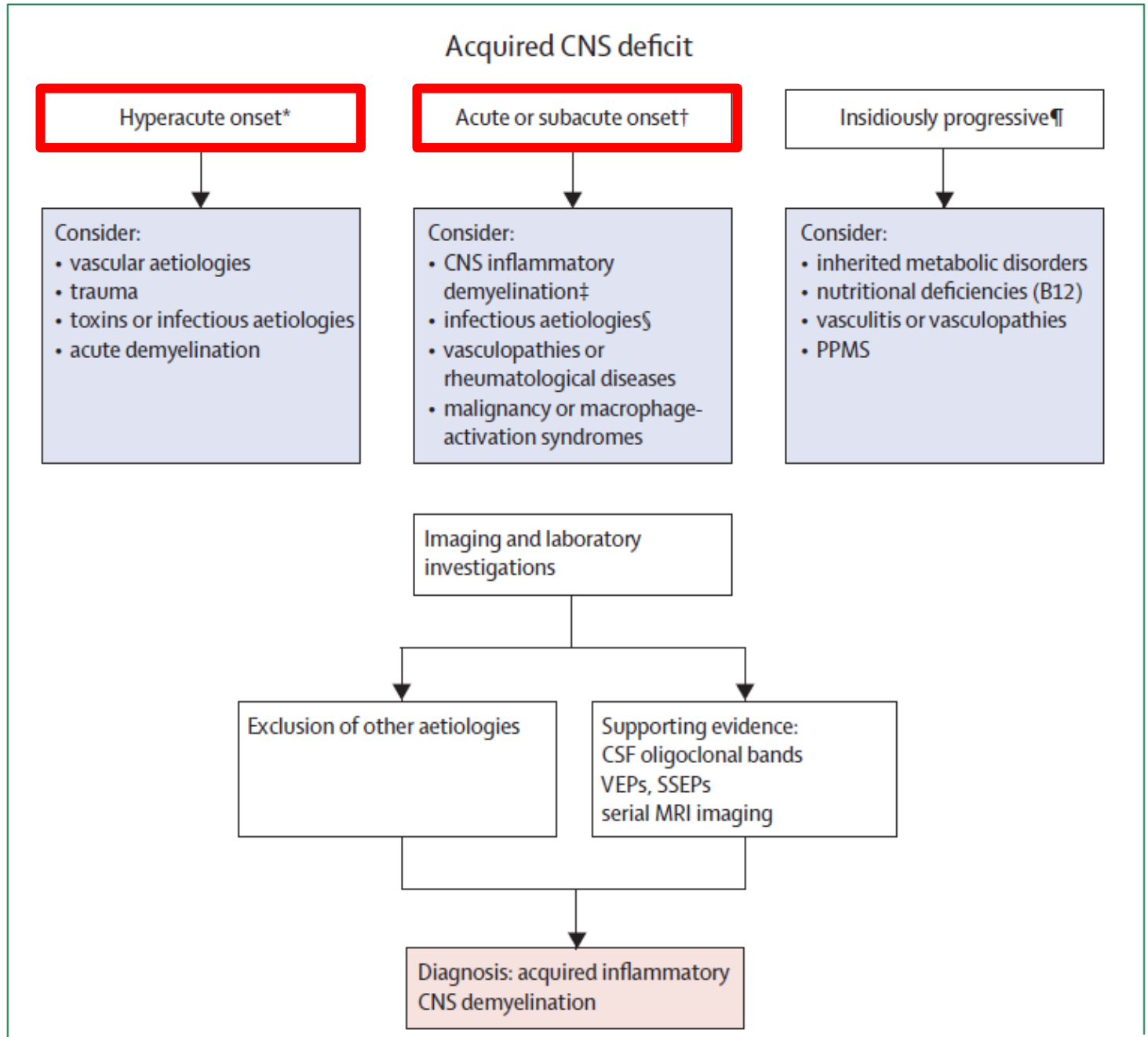
• …

Definiti i quadri sindromici, i criteri classificativi, i test e il loro apporto nella diagnosi e diagnosi differenziale, che cosa fare nella pratica clinica?





Banwell B., Ghezzi A., Tardieu M. Lancet Neurol 2007

Clinical and paraclinical findings that suggest an alternative diagnosis to initial presentation

Encephalopathy	Fever	Progressive clinical course lacking discrete attacks
Involvement of the peripheral nervous system or other organs	Elevated erythrocyte sedimentation rate or leukocyte count	Markedly elevated CSF white blood cells or protein
	Absence of CSF oligoclonal IgG	

Rubin and Kuntz. Curr Neurol Neurosci Rep. 2013;13(6):354

Differential diagnosis and evaluation in pediatric inflammatory demyelinating disorders

Kevin Rostasy, MD
Barbara Bajer-Kornek, MD
Sunita Venkateswaran, MD
Cheryl Hemingway, MD
Marc Tardieu, MD, PhD

Correspondence to Dr. Rostasy: k.rostasy@kinderklinik-datteln.de

ABSTRACT

Major advances have been made in the clinic
senting with the different forms of an acquired
as acute disseminating encephalomyelitis, neu
isolated syndromes. Nevertheless, a proportio
due to a broad spectrum of other inflammatory
tumors, or neurometabolic diseases. The clinici
of ADS, the risk factors for a chronic-relapsin
diagnosis. The goal of this article is therefore
pediatric patients with a presumed inflammato
trum of the more common differential diagnos

Table 2 Clinical red flags for conditions other than acquired demyelinating syndromes

Condition	Clinical red flags
Multisystemic involvement	HLH, Behçet disease, CNS vasculitis, SLE, mitochondrial diseases, sarcoidosis, Sjögren syndrome, LCH, infections
Spastic paraplegia	SLE, Sjögren syndrome, Lyme disease, West Nile virus, vitamin B_{12} deficiency, spinal cord tumor/ischemia/AVM/trauma, familial spastic paraplegia, AMN, Krabbe disease, Alexander disease
Protracted headache ± stroke-like episodes	SLE, MELAS, MERFF, HIV, malignancy, CADASIL, HLH, CNS vasculitis, Fabry disease, Susac syndrome
Epilepsy	Mitochondrial diseases, B_{12} metabolism disorders
Ataxia	NPC, SCA, PDH
Extrapyramidal symptoms	Anti-NMDAR encephalitis, Wilson disease, mitochondrial diseases, biotinidase deficiency, biotin-responsive basal ganglia disease, LBSL
Psychiatric symptoms	Primary CNS angiitis, anti NMDAR encephalitis, B_{12} metabolism disorders, mitochondrial disorders, SLE, Susac syndrome
Progressive disease with dementia	Leukodystrophies, mitochondrial diseases
Hypothalamic dysfunction	Sarcoidosis, LCH
Cranial nerve neuropathies	Krabbe disease, MLD, Alexander disease, Lyme disease, sarcoidosis
Peripheral neuropathy	Krabbe disease, MLD, mitochondrial disorders, ALD/AMN
Sensorineural hearing loss	Susac syndrome, mitochondrial diseases
Optic neuropathy	LHON, MELAS, MERFF, OPA-1

Abbreviations: ALD = adrenoleukodystrophy; AMN = adrenomyeloneuropathy; AVM = arteriovenous malformation; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; LBSL = leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate; HLH = hemophagocytic lymphohistiocytosis; LCH = Langerhans cell histiocytosis; LHON = Leber hereditary optic neuropathy; MELAS = mitochondrial encephalomyelopathy with lactic acidosis and stroke; MERFF = myoclonic epilepsy with ragged red fibers; MLD = metachromatic leukodystrophy; NMDAR = NMDA receptor; NPC = Niemann-Pick C; OPA = optic atrophy; PDH = pyruvate dehydrogenase deficiency; SCA = spinocerebellar ataxia; SLE = systemic lupus erythematosus.

Infiammatorie/infettive

Table 4 Selected diseases mimicking an acute demyelinating syndrome with clinical clues and recommended workup that should be tailored according to clinical symptoms and likelihood of an alternative diagnosis

Conditions	Clinical clues	Consider the following investigations (in addition to MRI brain/spine)
Systemic lupus erythematosus	Rash, arthralgias, headache, stroke, neuropsychiatric symptoms, cognitive changes, movement disorder, spastic paraplegia	ESR, complement (C3, C4), ANA, dsDNA, rheumatology evaluation
Behçet disease	Optic neuritis, uveitis, rash, arthralgias, oral/genital ulcers, spastic paraplegia, stroke, cerebrovenous sinus thrombosis	Examination: Oral and genital ulcers; skin pathergy test
Neurosarcoidosis	Basilar meningitis, uveoparotid fever (uveitis, parotid swelling, facial nerve swelling), cranial neuropathy, raised ICP, seizure, cognitive changes, peripheral neuropathy, spastic paraplegia	Serum/CSF ACE, calcium, ESR, IgG levels, CSF studies (flow cytometry CD4:CD8), CXR ± high-resolution CT, bronchoalveolar lavage
Isolated or primary angiitis of the CNS	Headache, stroke, seizures, encephalopathy, visual abnormalities, cognitive changes	ESR, CRP, von Willebrand factor, MRA, VZV antibodies, CSF studies, conventional angiogram, brain biopsy
Hemophagocytic lymphohistiocytosis	Fever, seizures, meningismus, motor deficit, affected sibling/consanguinity	CBC, triglycerides, ferritin, bone marrow aspiration, CSF studies, genetic testing
Immunodeficiency syndromes (e.g., XLP, NK)		
Neuroborreliosis	Early: Meningoradiculitis, cranial neuritis (e.g., facial palsy), meningitis, plexus neuritis, mononeuritis multiplex, erythema migrans	Serum antibodies against *Borrelia burgdorferi*, CSF studies with cell count (lymphocytic), AI IgG and PCR *B burgdorferi*
	Late: Encephalomyelitis, myelitis, encephalitis, vasculitis, chronic meningitis	
Progressive multifocal leukoencephalopathy	Immunosuppressed individual, hemiparesis, dysphasia, ataxia, cortical visual deficits, cognitive changes, seizures, headaches	CSF PCR for JC virus
Acute encephalopathies with autoantibodies	Seizures, neuropsychiatric symptoms, orofacial dyskinesias and sleep disturbances, autonomic dysfunction	Serum/CSF NMDA, GABA-A, glycine receptor antibodies, EEG
Steroid-responsive encephalopathy associated with autoimmune thyroiditis	Encephalopathy, seizures, focal neurologic signs, neuropsychiatric features	Antithyroid peroxidase, antithyroglobulin antibodies
Acute cerebellitis	Ataxia, headache, brainstem syndromes	CSF studies
Guillain-Barré syndrome and Bickerstaff brainstem encephalitis	Ascending sensorimotor neuropathy, ataxia, areflexia, extraocular movement abnormalities	CSF studies, GQ1 antibodies, NCS

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Table 4 Selected diseases mimicking an acute demyelinating syndrome with clinical clues and recommended workup that should be tailored according to clinical symptoms and likelihood of an alternative diagnosis

Solid tumors (astrocytoma, glioma, oligodendroglioma, ependymoma)	Typically monofocal neurologic deficits, persisting symptoms, pain	CSF analysis including cytology, lesional biopsy, tumor-specific testing
CNS lymphoma	Headache, ataxia, seizures, hemiparesis	CSF analysis including cytology, lesional biopsy, CSF immunotyping
Langerhans cell histiocytosis	Abnormalities of the hypothalamic-pituitary axis, behavior changes, seizures, visual deficits, headaches	CSF studies, lesional biopsy, CBC, liver enzymes, immunoglobulin levels, ESR, bone marrow aspiration/biopsy, *BRAF* gene mutation
Neurometabolic diseases (general)	Variable degree of acute or episodic neurologic deficits, neurologic regression	Muscle/skin biopsy, MRS, CSF/serum lactate, aminoacids, NCS, ophthalmology evaluation
Leber hereditary optic neuropathy	Unilateral or bilateral severe vision loss, abnormal retinal	Mutation in mtDNA m.3460G>A, m.11778G>A, or m.14484T>C in 90%
Kearns-Sayre syndrome, Leigh syndrome, POLG-related disorders	Kearns-Sayre syndrome: Extraocular movement abnormalities, pigmentary retinopathy, cardiac conduction abnormalities, myopathy, ataxia	Mitochondrial genetic testing, *POLG* mutation
	Leigh syndrome: Psychomotor regression, failure to thrive, hypotonia, ataxia	
	POLG: Acute encephalopathy, seizures, cognitive decline, stroke-like episodes	
Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation	Progressive spasticity, ataxia and dorsal column dysfunction	*DARS2* mutation
Acute necrotizing encephalopathy	Acute encephalopathy, seizures	Liver enzymes, CSF studies, *RANBP2* mutation
Biotin responsive basal ganglia disease	Acute encephalopathy with dystonia, seizures	*SLC19A3* mutation
Migraine	Recurrent headache meeting international headache classification	Clinical history, exclusion of other diseases

Abbreviations: ACE = angiotensin-converting enzyme; AI = antibody index; ANA = anti-nuclear antibody; CBC = complete blood count; CRP = C-reactive protein; CXR = chest X-ray; dsDNA = double-stranded DNA; ESR = erythrocyte sedimentation rate; GABA = γ-aminobutyric acid; ICP = intracranial pressure; IgG = immunoglobulin G; MRA = magnetic resonance angiography; MRS = magnetic resonance spectroscopy; NCS = nerve conduction study; NK = natural killer; POLG = polymerase γ; VZV = varicella-zoster virus; XLP = X-linked lymphoproliferative syndrome.

The clinical red flags

Seizures	Vasculitis Tumour Infection NMDA-receptor encephalitis (chorea-form movements and psychosis)
Headache	Vasculitis Susac syndrome (visual/hearing loss) Infections Venous thrombosis Cerabral oedema Idiopathic intracranial hypertension
Psychosis	Vasculitis Systemic lupus erythematosus (SLE) GM2 gangliosidosis Susac syndrome Corticosteroid therapy
Cranial neuropathy	Neuroboreilliosis Neurosarcoidosis Beçhet disease
Visual loss	Leber ON Psychogenic
Retinopathy	Susac syndrome Mitochondrial
Recurrent optic neuropathy	NMO Leber ON Chronic relapsing inflammatory ON (CRION)
Peripheral neuropathy	Charcot Marie Tooth disease Neuroboreilliosis GBS
Progressive/relapsing encephalopathy	Leukodystrophies Mitonchondrial Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy (CADASIL)
Spastic paraplegia	NMO Tumour vascular disorders SLE Sarcoidosis Hereditary spastic paraplegia (HSP)

Masquerades of Acquired Demyelination in Children: Experiences of a National Demyelinating Disease Program

Julia O'Mahony, BSc[1], Amit Bar-Or, MD[2], Douglas L. Arnold, MD[3], A. Dessa Sadovnick, PhD[4], Ruth Ann Marrie, MD[5], and Brenda Banwell, MD[1,6], Canadian Pediatric Demyelinating Disease Network

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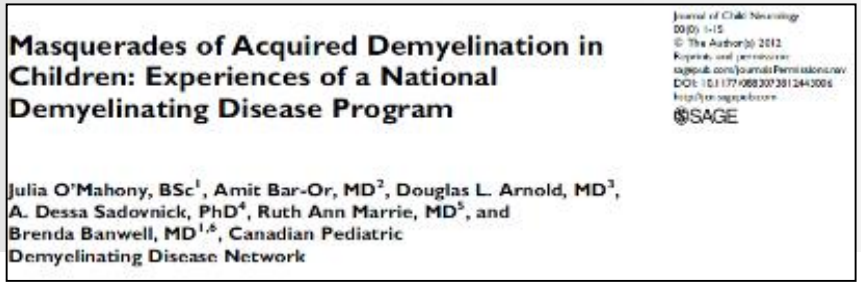

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The tests

Table 1. Diagnostic Evaluation for Children Evaluated for the Canadian Demyelination Study

The following investigations should be performed, as clinically indicated:	
MRI	Brain MRI in all children
	Spine MRI in all children with clinical spine involvement[a]
	Orbital MRI for children with visual loss
	The following MRI sequences are suggested:
	FLAIR or T2-weighted sequences in at least 2 planes
	Pregadolinium and postgadolinium T1-weighted images
	Diffusion-weighted sequences
Evoked potentials	VEPs
	SSEPs
Laboratory screening for NMO and MAS	Serum NMO IgG
	CSF NMO IgG (if serum negative)
	Ferritin
	Triglycerides
Infection screening	CBC + differential
	Serum viral serologies (EBV, mycoplasma, HSV serology)
	VDRL
	Lyme disease (seasonal)
	Cysticercosis (based on travel to endemic areas only)
	HTLV (based on travel to endemic areas only)
Endocrine	TSH, T4, anti-TPO antibodies if Hashimotos encephalopathy is a consideration

Mitochondrial lactate—serum + CSF	Pyruvate – if higher than normal lactate, calculate lactate to pyruvate ratio
	DNA studies, skin and muscle biopsy if mitochondrial disease strongly suspected
Rheumatologic Disease	ESR, CRP
	ANA, dsDNA
	Anticardiolipin and antiphospholipid antibodies
Nutritional	B_{12} (serum)
	25-hydroxy-vitamin D (25(OH)D)
CSF studies	Glucose
	Lactate
	Protein
	Cell count
	Culture and sensitivity, gram stain when appropriate
	Oligoclonal bands (compared to concurrently obtained serum)[b]
	CSF viral cultures + PCR herpes viruses
	Cytology (if indicated)

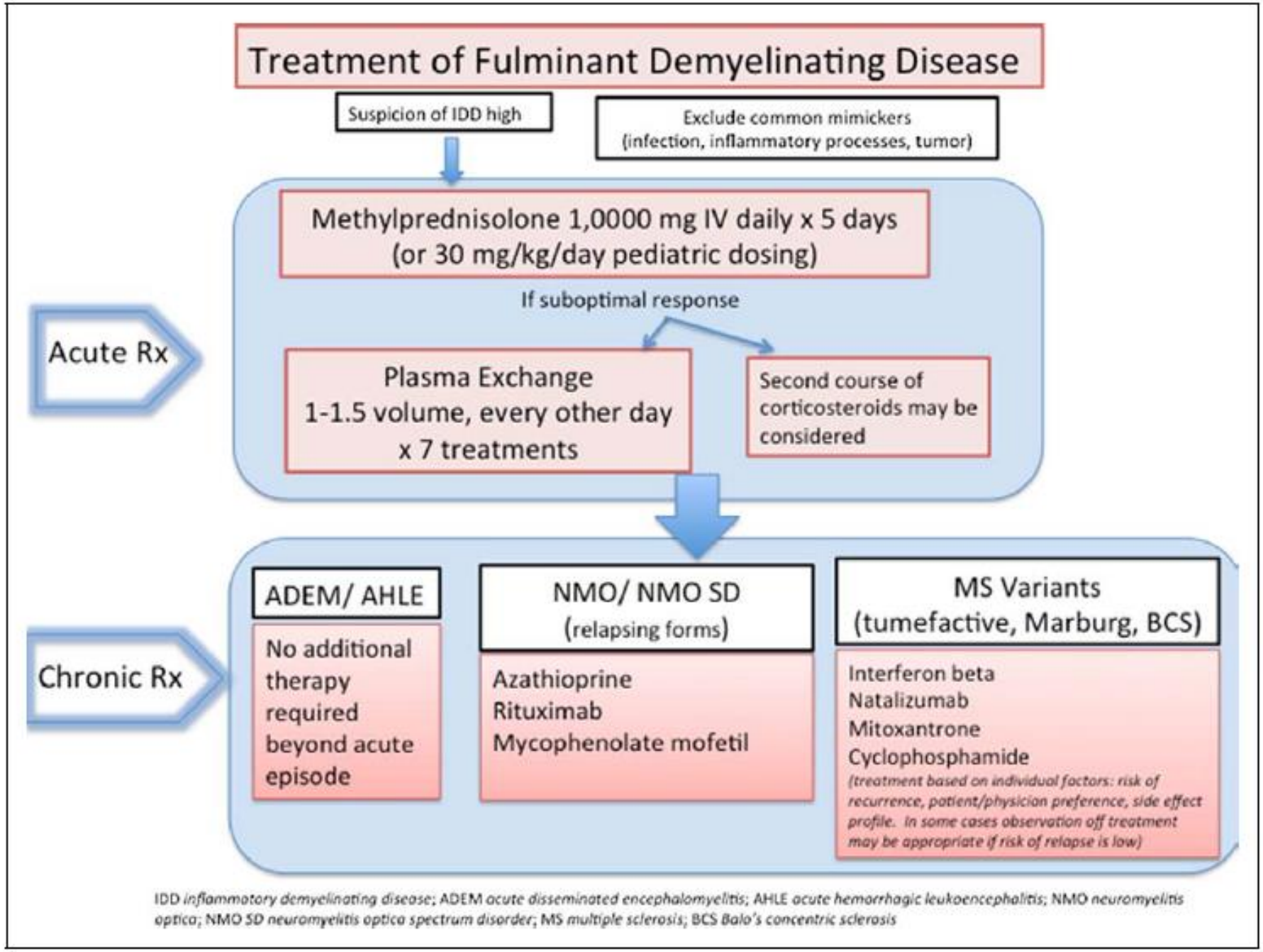
Abbreviations: ANA, antinuclear antibody; CBC, complete blood count; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computed tomography; CXR, chest x-ray; DNA, deoxyribonucleic acid; dsDNA, double-stranded deoxyribonucleic acid; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; FLAIR, fluid-attenuated inversion recovery; HSV, herpes simplex virus; HTLV, human T-lymphotrophic virus; IgG, immunoglobulin G; MAS, macrophage activation syndrome; MRI, magnetic resonance imaging; NMO, neuromyelitis optica; PCR, polymerase chain reaction; SSEP, somatosensory evoked potential; T4, thyroxine test; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; VEP, visual evoked potential; VDRL, Venereal Disease Research Laboratory.

[a]A focused MRI spine study is indicated in all children with neurologic features localized to the spine. The majority of such children experience lesions in the cervical or thoracic spine. MRI imaging of the full spine is helpful to look for evidence of demyelination extrinsic to the brain or to search for spinal root enhancement in children with features of infection or malignancy.

[b]The accuracy of OCB measurement depends on the diagnostic test used and on the experience of the laboratory performing the test. Isoelectric focusing has the highest sensitivity.

DIAGNOSIS AND DIAGNOSTIC CRITERIA: KEY POINTS AND CONCLUSIONS

- **ADS: eterogeneous group of disorders, standardised diagnostic criteria are available**
  - **Krupp's criteria**
  - **Revised Mc Donald criteria (Thompson's criteria)**
- **Diagnostic criteria applicable in PAED-MS, high sensitivity and specificity**
- **ADEM can be the first manifestation of MS**
- **MS Patients aged <10 years can have peculiar findings**
- **Clinical and MRI follow-up**
- **Anti-MOG syndrome**
- **CSF-OB and MRI: diagnostic and prognostic role**
- **Appropriate treatment of the acute/chronic phase**



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