MOG Spectrum Disorders and Role of MOG-Antibodies in Clinical Practice

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Neuropediatrics 2018;49:3–11.

Abstract

Myelin oligodendrocyte glycoprotein (MOG) antibodies (abs) are present in one third of all children with an acute demyelinating syndrome (ADS). MOG-abs can be found in acute disseminated encephalomyelitis (ADEM), transverse myelitis, isolated optic neuritis (ON), or recurrent demyelinating diseases, such as multiphasic neuromyelitis optica spectrum disorders (NMOSD) without aquaporin-4 (AQP4) abs or multiphasic ADEM (MDEM), but rarely in children who subsequently develop multiple sclerosis (MS). The presence of MOG-abs is age dependent with the highest seropositivity rates found in young children and an episode of ADEM, whereas older children with MOG-abs present with ON, myelitis, or brainstem symptoms. MOG-abs, initially thought to be associated with a benign disease course, are found in a substantial proportion of children with relapsing episodes associated with high and persisting MOG-ab titers. This review describes, in particular, the increasing spectrum of phenotypes associated with MOG-abs with a focus on clinical characteristics, radiological features, and therapeutic aspects.

Keywords
- MOG-antibodies
- acute demyelinating syndromes
- children
- monophasic
- relapsing

Introduction

The clinical spectrum of acute demyelinating syndromes (ADS) encompasses optic neuritis (ON), transverse myelitis (TM), clinically isolated syndromes (CIS), acute disseminated encephalomyelitis (ADEM), and relapsing forms, such as neuromyelitis optica spectrum disorder (NMOSD), multiphasic ADEM (MDEM), or multiple sclerosis (MS). Identification and distinction of different subtypes of ADS can be challenging, especially at the initial episode with important implications with regard to treatment (e.g., MS) and prognosis. In recent years, substantial progress has been made in the clinical, radiological, and therapeutic aspects in children with ADS. In children with MS, several studies revealed that the clinical course is nearly exclusively relapsing–remitting and that the presence of intrathecal oligoclonal bands (OCBs) after the first attack is highly associated with further attacks, and children with demyelinating diseases show brain volume reduction at the first episode itself.[1,2]

Furthermore, the discovery of serum aquaporin-4 (AQP-4) antibodies (AQP4-abs) has led to the paradigm of autoantibody-mediated central nervous system (CNS) demyelinating diseases with the pathological hallmark of an autoimmune-mediated astrocytopathy separating it from MS pathology. In addition, the clinical manifestations of neuromyelitis optica (NMO), with common denominator of AQP4-abs, have become more variable than previously thought (e.g., area postrema syndrome, acute brainstem syndrome, narcolepsy) leading to the introduction of the term NMO spectrum disorder (NMOSD).[3,4] More recently, MOG-abs were detected in children with various forms of ADS, including monophasic ADEM, ON, longitudinally

received
June 4, 2017
accepted after revision
June 14, 2017
published online
August 31, 2017

DOI https://doi.org/10.1055/s-0037-1604404.
ISSN 0174-304X.

extensive transverse myelitis (LETM), recurrent forms of ADEM, AQP4-ab–negative NMOSD, and recurrent ON, but less frequently in adults with demyelinating diseases.[5–14] MOG-abs initially considered as biomarkers in MS are only rarely found in subjects with MS at the initial episode pleading strongly against an MS course.[10–12] MOG is a member of the immunoglobulin superfamily and constitutes only a minor component of the myelin sheath expressed exclusively in the CNS. The precise function of MOG is not known but the expression of MOG in mature oligodendrocytes suggests a role in maturation, as well as in myelin integrity and cell surface interactions.[15,16] Autoantibodies against MOG are primarily of the IgG1 subtype and directed against extracellular conformational epitopes on the outmost surface of the myelin sheath. MOG-abs induce complement-mediated cytotoxicity in vitro and appear to transiently disrupt oligodendrocytic microtubule organization.[17] MOG-abs have been shown to induce experimental autoimmune encephalomyelitis (EAE) and thus were initially suspected to play an important role in the pathogenesis of MS.[18–21] Histopathological findings in adults with fulminant episodes and MOG-abs revealed a demyelination reminiscent of MS pattern 2 with well-demarcated plaques and actively demyelinating macrophages at the lesion edge and complement deposition at the sites of ongoing demyelination.[22–24] As for AQP4-ab testing, serum MOG-abs are commonly detected using live cell-based assays (CBAs), in which native human MOG in its natural confirmation is transfected or transduced into the mammalian cell lines. All recently published studies used CBA for the measurement of MOG-abs, although with different MOG expression vectors, cell lines, and read-out systems (immunofluorescence versus flow cytometry).[5,25] In contrast to other autoantibody-mediated diseases, such as NMDA receptor (NMDAR) encephalitis, subjects with MOG-ab–associated ADS usually do not have an intrathecal synthesis of MOG-abs in cerebrospinal fluid (personal observation).[25–27] The clinical picture of MOG-abs–associated diseases is broad and partly overlapping. To better characterize the new autoantibody-associated spectrum, this review describes the increasing spectrum of phenotypes associated with MOG-abs with a focus on clinical characteristics, radiological findings, and therapeutic aspects.

Clinical Spectrum of Monophasic Acute Demyelinating Syndromes Associated with Serum MOG-Antibodies

Pooling the data from different studies in children with a first episode of ADS, it appears that at least one third of children harbor serum MOG-abs (►**Tables 1**, **2**).[10–12] The spectrum of monophasic ADS subtypes in children with MOG-abs is diverse and entails optic neuritis (ON), transverse myelitis (TM), and rarely other forms of a clinically isolated syndrome (CIS), ADEM, and NMOSD in addition to rare phenotypes not fitting into the aforementioned subtypes (►**Table 1**).[7,9–12]

In monophasic subtypes, MOG-abs are found most often in ADEM (►**Table 2**). In particular, children with ADEM who do fulfill the criteria of the International Pediatric Multiple Sclerosis Study Group (IPMSSG),[28] including encephalopathy, multifocal neurological signs, and who do have an MRI with hazy bilateral signal alterations in different anatomical areas including the myelon are seropositive for MOG-abs in more than half of the cases.[29] The second ADS subtype in which MOG-abs are found is in children who present with signs of ON and TM and are classified as simultaneous NMOSD. Previously, it was assumed that these children have AQP4-abs or will eventually develop them, but it was shown that MOG-abs are even more prevalent in this subtype. Furthermore, children with only one

Table 1 Key features of ADS associated with MOG-abs or MOG-spectrum diseases

Keypoints
• MOG is a target antigen in inflammatory demyelinating CNS diseases with the highest density in the outermost lamellae of myelin sheaths
• Pathogenic MOG-abs bind to conformational MOG in its original folded structure with most reliable detection by live cell-based assay (CBA)
• In pediatric patients with ADS, prevalence of serum MOG-abs is higher (one-third seropositive) than in adult patients with a peak in children younger than 5 years of age
• In MOG-ab–positive ADS, the optic nerves and myelon are frequently affected
• MRI findings are variable, often with hazy, widespread ADEM-like lesions and complete resolution on follow-up
• MOG-abs plead against a MS disease course
• MOG-ab titers that subsequently decline are detected in ADEM, AQP4-abs–negative NMOSD, ON, and TM with a monophasic disease course
• A subgroup of children with high and persisting MOG-ab titers has recurrent episodes (ON rec, MDEM, ADEMON, AQP4-neg–NMOSD) associated with a less favorable outcome
• Therapies that target B cell mechanisms seem to be more beneficial (e.g., IVIG, RTX) in the latter subgroup
• We recommend to measure serum MOG-abs on follow-up visits to help predict the course of disease

Abbreviations: abs, antibodies; ADEM, acute disseminated encephalomyelitis; ADEMON, acute disseminated encephalomyelitis followed by optic neuritis; ADS, acute demyelinating syndrome; AQP-4, aquaporin-4; AQP4-neg, aquaporin-4-negative; CBA, cell-based assay; CNS, central nervous system; IVIG, intravenous immunoglobulin; MDEM, multiphasic disseminated encephalomyelitis; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; ON rec, recurrent optic neuritis; RTX, rituximab; TM, transverse myelitis.

Table 2 Comparison of demographic, clinical, and laboratory features of pediatric patients with ADS with and without MOG-abs in recently published cohorts

Publication	Number of ADS patients		Age at onset (y)		F:M	ON		TM		Final MS		Final ADEM		Final NMOSD		Final MDEM/ADE-MON		Recurrent		Intrathecal OCB pos		CSF cell count		MOG-ab follow-up
	MOG-ab neg	MOG-ab pos	Total cohort	MOG-ab pos	MOG-ab pos	MOG-ab neg	MOG-ab pos	MOG-ab neg	MOG-ab pos	MOG-ab neg	MOG-ab pos	MOG-ab neg	MOG-ab pos	MOG-ab neg	MOG-ab pos	MOG-ab neg	MOG-ab pos	MOG-ab neg	MOG-ab pos	MOG-ab neg	MOG-ab pos	MOG-ab neg	MOG-ab pos	
Hennes et al[12]	145	65	12	6	F: 35 M: 30	48	31	NA	NA	76	3	24	22	7	9	0	11	89	25	53%	11%	15/μL[b]	54/μL[b]	Seroneg patients remain neg over time ($n = 75$) 35/51 MOG-ab pos patients remain pos, remaining high titers in rec non-MS disease course
Fernandez-Carbonell et al[36]	61	13	15	10	F: 8 M: 5	20[a]	8[a]	25[a]	5[a]	41	4	4	3	2	2	2	1	49	8	44%	8%	16.2/μL[b]	108.8/μL[b]	NA
Hacohen et al[11]	42	23	12	10	F: 11 M: 12	12	12	14	4	16	2	8	4	3	3	NA	NA	16	3	40%	6%	Elevated in 26%	Elevated in 35%	NA
Ketelsleger et al[10]	96	21	10.7	7	F: 9 M: 12	NA	8	NA	4	46	1	28	11	NA	3	NA	5	49	9	NA	NA	NA	NA	Seroneg patients remain seroneg ($n = 9$), In 2 seropos patients, declining but still seropos titers after 3 and 7 months, resp
Dale et al[26]	42	31	8	7	F: 18 M: 13	5	10	10	5	8	7	13	11	NA	NA	NA	NA	9	10	19%	0%	NA	NA	NA
Pröbstel et al[38]	95	31	10	Mostly 3–8	F: 19 M: 12	NA	NA	NA	NA	55	10 MCF ratio > 20:1	35	19 MCF ratio >20 7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Declining titers in 15 seropos patients with ADEM and 1 seropos patient with CIS 6/8 patients with MS and fluctuating titers over time
Selter et al[c]	26	18	7	NA	NA	NA	NA	NA	NA	5	5	10	9	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: ab, antibody; ADEM, acute disseminated encephalomyelitis; ADEMON, acute disseminated encephalomyelitis followed by optic neuritis; CIS, clinically isolated syndrome; CSF, cerebrospinal fluid; F, female; M, male; MCF, geometric mean channel fluorescence; MDEM, multiphasic disseminated encephalomyelitis; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; *n*, number; neg, negative; NMOSD, neuromyelitis optica spectrum disorder; OCB, oligoclonal bands; ON, optic neuritis; pos, positive; rec, recurrent; resp, respectively; seroneg; seronegative; seropos, seropositive; TM, transverse myelitis.

[a]At first presentation.

[b]Mean value.

[c]Selter RC, Brilot F, Grummel V, et al. Antibody responses to EBV and native MOG in pediatric inflammatory demyelinating CNS diseases. Neurology 2010;74(21):1711–1715.

core clinical characteristic for NMOSD and MOG-abs, thus not fulfilling the diagnostic criteria for NMOSD without AQP4-abs, are thought to be at a higher risk for further events and developing NMOSD (see below).[9,30] The third group with monophasic ADS and MOG-abs consists of children who are commonly classified as CIS characterized by focal or polyfocal symptoms, absence of encephalopathy and white matter changes on MRI that are more reminiscent of MS, if present. Importantly, children with CIS and MOG-abs in the large majority have ON or TM but rarely other subtypes of CIS (e.g., CIS/brainstem) and do not have risk factors for further MS-like episodes such as positive OCB or MS-like lesions.[10,12] In addition, children with MOG-abs and CIS/ON often have bilateral involvement and children with CIS/TM present with LETM. Optic neuritis associated with MOG-abs has distinct features, such as bilateral involvement and rapid visual impairment combined with good recovery after steroid treatment, in addition to optic disc swelling separating it from other diseases such as MS.[13,25,30,31] The preferential involvement of the optic nerves and myelon is a hallmark of children with MOG-ab–positive diseases.[7,12,29] Frequent involvement of these structures is thought to be the result of higher MOG expression in the areas affected.[32,33] MOG-abs can also be detected in children with ADS that do not belong to the typical phenotypes. Several cases are on record that were classified as brainstem encephalitis or isolated cerebellitis (personal observation) extending the spectrum of MOG-ab–positive diseases. The simultaneous presence of MOG-abs with other autoantibodies has been described in few adults—but not in children so far—with AQP4-ab–positive NMOSD or NMDAR encephalitis.[34,35] MOG-abs are not detected in healthy controls but can be rarely found in children with MS. According to our observations,

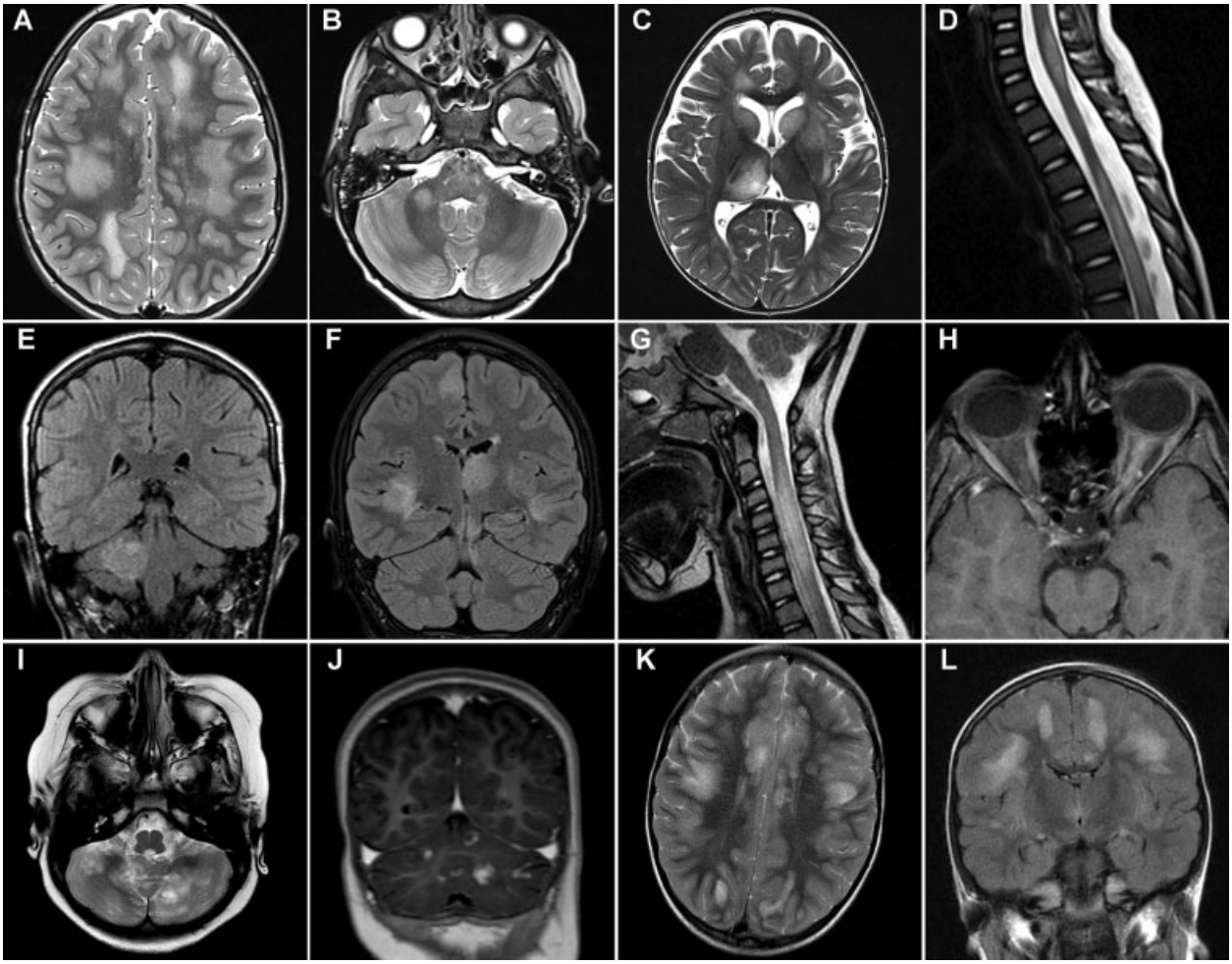

Fig. 1 Children with ADEM and MOG-abs usually show an MRI with fluffy, poorly-demarcated bilateral lesions and a widespread distribution of lesions. The spinal cord is often affected with lesions spanning more than three segments. (A, B) (axial-T2) Cerebral MRI of a 7-year-old boy with MOG-ab seropositive ADEM showing widespread poorly-demarcated lesions. (C, D) Cerebral and spinal MRI (axial-T2, sagittal-T2) of a 1-year-old boy with MOG-ab seropositive ADEM showing prominent involvement of thalamus and basal ganglia and spinal lesions spanning more than three segments (LETM). (E, F) Cerebral MRI (coronar-FLAIR) of a 5-year-old boy with MOG-ab seropositive MDEM showing a cerebellar lesion in the third episode (39 months after first episode) and new deep gray matter, cortical and juxtacortical white matter lesions in the fourth episode (87 months after first episode). (G) Spinal MRI (sagittal-T2) of a 5-year-old girl showing a MOG-ab seropositive LETM. (H) Cerebral MRI (Gd-enhanced axial-T1) of a 12-year-old boy with unilateral MOG-ab seropositive ON. (I, J) Cerebral MRI (axial-T2, Gd-enhanced coronar-T1) of a 4-year-old girl with MOG-ab seropositive MDEM showing in the sixth episode atypical features with ring enhancing cerebellar lesions. (K, L) Cerebral MRI (axial-T2, coronar-FLAIR) of a 5-year-old girl with ADEM and widespread large lesions but without MOG-abs suggesting that other autoantibodies are instrumental in the disease process. MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging.

MOG-abs are present in a small subgroup of children with MS but decline to undetectable levels over the course of the disease.[12] Although the spectrum of clinical manifestations associated with MOG-abs is broad, occasionally with overlapping features (e.g., wide spread bilateral supratentorial lesion pattern in children with simultaneous MOG-ab–positive NMOSD), several aspects are notable distinguishing the different clinical presentations from each other and separating them from other autoimmune-mediated diseases of the CNS. Children who present with ADEM and MOG-abs are often younger than 5 years and usually present with a fulminant disease course characterized by marked encephalopathy, multifocal symptoms, and a very typical MRI (►**Fig. 1 A**, **B**, see also below). Children with an ADS and MOG-abs between 5 years and puberty often have a NMOSD-like phenotype with ON and/or LETM. Older children often present with an isolated or bilateral ON.[12] Fernandez-Carbonell et al also observed a bimodal distribution in 13 MOG-ab–seropositive pediatric patients of their study, with the younger patients presenting with ADEM, while the older patients presented with ON, and suggested that this may reflect different and changing levels of regional expression of MOG antigen in different age groups.[36] The manifestation and range of MRI findings are also influenced by age. Younger children with MOG-ab–positive ADS have a cerebral MRI characterized by poorly demarcated and widespread lesions (►**Fig. 1A**, **B**). In addition, children with ADEM and MOG-abs often have extensive involvement of myelon including the conus (►**Fig. 1C**, **D**, **G**). Children with MOG-ab–associated diseases often do not have lesions that enhance after contrast-medium application. In some patients, lesions can also be found in the corpus callosum (personal observation).[29] Interestingly, despite the widespread involvement of different anatomical areas, most children show resolution of signal changes over time. Older children with ON often have no or only small unspecific cerebral lesions (►**Fig. 1H**). Children with a clinical phenotype of NMOSD can occasionally have—apart from involvement of spine and optic nerves—an MRI lesion pattern reminiscent of ADEM (see ►**Fig. 1A**) but without signs of encephalopathy or focal symptoms indicative of supratentorial involvement.[9,37] The reason why children present with different clinical and radiological phenotypes remains unresolved but most likely variables, such as genetic susceptibility, differences in patients' autoimmune response, environmental factors, and the myelination process during childhood play an important role.[27] Several demographic and laboratory findings in children with MOG-abs and a monophasic disease course are notable. Children with MOG-abs rarely have OCB in contrast to children with MS, and the CSF cell count is reported to be significantly higher (►**Table 2**).[12] Also, male patients are preferentially affected in children with a monophasic ADS and MOG-abs. In children with a monophasic disease course, MOG-ab titers are highest in children with ADEM and who are younger than 5 years, followed by children with NMOSD, ON, and LETM.[12] MOG-ab titers decline in children with a monophasic disease course over the following months (decline of median titer from 1:1,280 [range: 160–40,960] at onset to 1:160 [range: 0–5,120]) to undetectable levels in the majority of cases.[12,29,38]

Clinical Spectrum of Multiphasic Acute Demyelinating Syndromes Associated with Serum MOG-Antibodies

In contrast to earlier studies that linked MOG-abs to a monophasic and more benign disease course, recent studies suggest that a substantial proportion of children with ADS develop further relapses in the context of high and persisting MOG-abs. Different relapsing subtypes, such as multiphasic ADEM (MDEM), ADEMON, recurrent ON, and NMOSD, can be delineated, which are linked to age and sex in addition to clinical phenotypes that do not fit into one of these categories (►**Table 2**).[6–9,12,39] One group of children with an initial episode of ADEM associated with MOG-abs continued to develop further demyelinating episodes characterized by ADEM-like episodes. These children developed new clinical symptoms each time, including encephalopathy, focal neurological signs, and new MRI lesions, and were assigned the final diagnosis of MDEM.[8] In our studies, the majority of children with this clinical pattern and MRI features characterized by hazy, large, and bilateral widespread lesions (►**Fig. 1E**, **F**, **I**, **J**) had high and persisting MOG-abs. All children with ADEM and further relapses in our cohorts with an absence of MOG-abs were diagnosed with other neurological diseases (ONDs).[12,29] The time interval between the attacks varies and ranges from 1 month up to 4 years (personal observation).[8,12] In the majority of children, the second demyelinating event occurs in the first year.[12] The number of attacks during the first 24 months after the onset range from one up to six episodes.[12] Another observation is that not all episodes that occur in a single child fulfill all the mandatory clinical aspects for ADEM. Children can present, for example, only with severe headache in addition to widespread new lesions on cerebral MRI.[8,12] A second subtype is characterized by an initial episode of ADEM followed by frequent episodes of ON, delineating a further small but distinct phenotype of recurrent demyelinating diseases in MOG-ab–positive pediatric patients with the acronym ADEMON. These patients are reported to have frequent ON attacks ranging from one to nine episodes during a follow-up of up to 5 years, occasionally in combination with further ADEM-like attacks.[8,39] In general, children who have further events with ON are older than children with MDEM, more often females, and do not have new supra- or infratentorial lesions including the myelon.[8,39] A third group of children with recurrent demyelinating episodes and MOG-abs fulfills the diagnostic criteria of NMOSD. Children with NMOSD and MOG-abs can present with simultaneous ON and TM or sequentially show other core clinical characteristics such as brainstem syndrome or LETM. Overall, more than half of all children with MOG-ab–positive NMOSD have a relapsing disease course.[9]

In general, it appears that MOG-abs are more often found in children with NMOSD compared with AQP4-abs, which are present in up to 80% of adult NMOSD patients.[9,40] Importantly, MOG-ab–positive NMOSD patients continue to be seronegative for AQP4-abs over time.[12,25] Frequency of subsequent ON attacks in MOG-ab–positive NMOSD patients is higher than in MOG-ab–negative patients.[9] Children with MOG-abs and episodes of NMOSD show a wide range of MRI findings that can be indistinguishable from children with AQP4-abs. Children with

symptoms suggestive of TM usually have LETM on radiological imaging. LETM lesions are often widespread, occasionally with rostral extension into the medulla (►**Fig. 1C**, **D**, **G**), and often affect the conus, which is rarely involved in MS or AQP4-ab–positive NMOSD.[6,9] Children with recurrent ON as part of NMOSD can have MRI signs of isolated optic disc swelling or contrast-medium enhancement of the optic nerves. Occasionally, children with episodes of ON or LETM can also have ADEM-like, widespread supra- and infratentorial lesions without additional clinical signs corresponding to the affected areas. In general, lesions in children with MOG-ab–positive NMOSD resolve over time.[6,9] Patients with MOG-abs are younger at disease onset compared with NMOSD patients with AQP4-abs or seronegative patients.[3,6] Children with recurrent ON present a further subgroup of MOG-ab–positive patients with a relapsing disease course. Recent studies suggest that children with recurrent ON very often harbor MOG-abs at the first episode itself and continue to have high and persisting titers in contrast to children with a monophasic event or in the context of risk factors such as positive OCB in CSF or MS-like MRI lesions who eventually develop MS.[7,12] According to our experience, sole recurrent ON in children is not associated with AQP4-abs and only rarely occurs in children without MOG-abs. Children with recurrent ON are often females, older than children with other MOG-ab–related diseases, and often present with unilateral ON.[7,12] Interestingly, recurrent episodes are also characterized by rapid visual impairment usually responding to steroids. MRI findings show signs of optic nerve involvement in selected cases in combination with a usually normal cerebral MRI.[7,39] Rarely, episodes with recurrent ON reveal ADEM-like lesions and spinal involvement.[8] Interestingly, after complete resolution of MRI lesions at first presentation, no new lesions at subsequent ON attacks were observed in children with ADEMON.[7,39] Laboratory findings in children with a multiphasic disease course are comparable to children with a monophasic disease course. CSF pleocytosis is present in majority of children, and OCBs are rarely found in CSF even on repeated CSF studies performed with subsequent relapses.[11,12,26,39]

Relevance and Titer of MOG-Antibodies at the Initial Event and Long-Term Follow-Up

As detailed above, MOG-abs can be present in children with different subtypes of ADS including monophasic and multiphasic forms. The majority of children with a monophasic disease course in our recent study with a follow-up of more than 24 months had MOG-abs levels that declined to undetectable levels in the first 2 years. A subset of children with a–so far–monophasic disease course (follow-up range: 3–69 months) continues to have elevated MOG-abs. One child in our large cohort of children who initially was diagnosed with a MOG-ab–associated ADEM had a second severe ADEM-like relapse nearly 4 years later.[41] His serum MOG-ab titer initially was 1:640 but increased to 1:2,560 with the second event. Unfortunately, no serum samples were obtained between the episodes.[12] Similar adult cases are on record who had further ADS episodes each time with MOG-abs even decades later.[42] MOG-ab levels in children with a relapsing disease course other than MS are markedly elevated at disease onset, in particular in young children with ADEM and do not decline as in children with a monophasic disease course. In our cohort, all children with MDEM or ADEMON had elevated and persisting MOG-abs, followed by the majority of children with recurrent ON and AQP4-ab–negative NMOSD patients.[6–10,12] The initial titer of serum MOG-abs is similar between children with a monophasic and relapsing disease course and therefore cannot predict the future course of the disease. On the other hand, persistence of high MOG-ab titers has been shown to be strongly associated with a recurrent non-MS disease course.[12] In the aforementioned study, it was observed that titers remained high in patients with recurrent non-MS disease course, with a median titer of 1:1,280 (range, 1:160–1:20,480) at onset and a median follow-up titer of 1:640 (range, 1:160–1:5,120) after more than 24 months.[12] The time interval between the initial episode and significantly declining MOG-abs levels can differ markedly in children with a MOG spectrum disorder, which is probably influenced by age, sex, and genetic factors.[12,38] As mentioned above, children with ADS other than MS without MOG-abs at onset have not been reported to develop MOG-abs over time. Another important point is the fact that children with declining or persisting MOG-ab titers over time were not assigned OND s such as CNS-vasculitis or encephalitis, and children with a clinical phenotype of ADEM in our cohort but absent MOG-abs were likely to be assigned an alternative diagnosis.[8,12]

Outcome of Children with Monophasic and Multiphasic Disease Course

In general, patients with MOG-abs and a monophasic disease course often have a good clinical recovery and lesion resolution in MRI in the context of declining MOG-abs. Nevertheless, cases of children with a monophasic event and MOG-abs, who suffered from severe sequelae such as tetraplegia, particularly in association with an initial episode of ADEM or LETM, are also recorded.[9] In a previous study, children with a monophasic ADEM with initially high and subsequently decreasing MOG-ab titers were also associated with a favorable outcome, compared with seronegative patients with ADEM.[29] In the largest cohort of pediatric patients with ADS and MOG-abs reported so far, including children with ADEM of the aforementioned study, seropositive patients with monophasic disease course had a good clinical outcome. Only 2 out of 40 seropositive patients with monophasic ADS had severe motor sequelae and seizures.[12] Initially, it was thought that even children with a multiphasic disease course and MOG-abs have a more benign disease course as compared with AQP4-abs. Reports from patients with MOG-abs who continued to relapse and developed progressive disabilities (e.g., visual failure, ataxia) despite maintenance treatment are challenging this view (Hacohen et al, unpublished data, 2017).[34,43] Two large cohorts of MOG-ab–positive adult patients revealed that patients with a relapsing course have ON as the most frequent symptom, particularly in females, and that recurrent attacks are associated with accumulating functional impairment.[44] Declining visual abilities despite good response to steroids were observed

in children with recurrent ON or ADEMON in addition to symptoms such as fatigue, behavioral problems, or seizures.[8,12,39] Children with NMOSD and MOG-abs have a more favorable outcome and are less often treated with a low requirement for immunosuppressive/modulatory drugs compared to patients with AQP-4-abs–positive NMOSD.[6,9]

MOG-Antibodies in Children and Adults with Multiple Sclerosis

In a small subset of pediatric MS patients, MOG-abs have been detected, although seropositivity for MOG-abs generally pleads against a MS disease course.[10–12] In recent publications, seropositivity was recorded only in few children with MS.[10–12] All three pediatric MS patients who had positive MOG-ab titer at disease onset in our cohort had undetectable MOG-ab levels over time.[12] The presence of MOG-abs has also been described in adult MS patients with a relapsing course, involving the brainstem and spinal cord, and a poor response to MS therapies. MOG-abs in this subgroup were present over a long time with fluctuation and reappearance of MOG-abs during the disease course. The authors concluded that MS patients with MOG-abs represent a distinct clinical phenotype benefiting from a different treatment strategy.[42] Although MOG-abs plead against MS, a seronegative status has no significant predictive value for a conversion to MS.[11,12] MS-like MRI and positive OCBs in CSF still have the highest predictive value for a MS course in pediatric patients with a first demyelinating syndrome.[11,12]

Therapy of Children with Acute and Relapsing MOG Spectrum Disorders

Treatment of MOG spectrum disorders has been influenced by therapy regimes used primarily for adult AQP4-ab–positive NMOSD despite the observed clinical and pathological differences in the two autoantibody-mediated diseases. In the acute phase, the majority of children with MOG-ab–positive ADS respond well to intravenous steroids such as methylprednisolone for 3 to 5 days with a dose of 20 to 30 mg/kg/day. Despite severe symptoms such as marked encephalopathy, ataxia, or paraplegia, recovery is usually prompt. To avoid a recurrence of symptoms in the initial phase, we recommend to taper the steroid treatment over the following 3 to 4 weeks starting with intravenous and followed by oral prednisolone.[7,13,31,39,45] In children with severe symptoms requiring intensive care monitoring, intravenous immunoglobulins (IVIG, 2 g/kg/course over 4–5 days) are usually added. In selected cases, the successful application of up to five cycles of plasmapheresis has been described in children with MOG-ab–positive ADEM and LETM who had not responded to steroids and IVIG.[41] The optimal treatment of children with ADS and MOG-abs who continue to have recurrent demyelinating episodes still remains controversial. At present, conclusions about optimal treatment strategies can only be drawn from recent retrospective studies in children with ADS and MOG-abs assessing relapse rate, therapies given, and clinical outcome over time (Hacohen et al, unpublished data, 2017).[12] A wide array of immunosuppressive and immunomodulatory medications has been given with diverging results usually not influencing MOG-ab seropositivity over time.[6,12–14] Drugs that have been used include mycophenolate, azathioprine, cyclophosphamide, cyclosporine, rituximab, interferons, glatiramer acetate, fingolimod, natalizumab, monthly IVIG, and monthly intravenous methylprednisolone (IVMP) or oral steroids (Hacohen et al, unpublished data, 2017).[26,46,47] Several important aspects have emerged from these studies (Hacohen et al, unpublished data, 2017).[12] First, medications used in the treatment of MS seem not to be overall beneficial, and in selected cases, have led to a dramatic aggravation of symptoms (e.g., alemtuzumab; personal observation; Hacohen et al, unpublished data, 2017).[31] Similar observations have been made in the past for children and adults with AQP4-ab–positive diseases in particular with baseline disease-modifying therapies (DMTs), such as interferons, pointing to the need that antibody-mediated diseases must be treated differently.[3,31] A recent retrospective study of more than 100 children with MOG-ab–associated relapsing diseases also found that in children who were initially started on DMTs such as interferons or escalated onto second-line MS drugs, neither improved relapse rate nor expanded disability status scale (EDSS)score. This leads to the recommendation that when faced with a child with recurrent demyelination and MOG-abs, the use of medications in MS should be strongly discouraged without initially exploring more conventional disease-modifying drugs such as rituximab or IVIG (Hacohen et al, unpublished data, 2017). This study also reported that IVIG maintenance therapy was the only drug that significantly improved relapse rate and at the same time clinical outcome as reflected in a lower EDSS score (Hacohen et al, unpublished data, 2017). A good response to regular IVIG has been described previously in smaller cohorts of children with ADEMON,[39] MDEM,[8] and MOG-ab–positive NMOSD.[6,9] As in other autoimmune-mediated diseases, such as NMDAR-encephalitis or opsoclonus–myoclonus syndrome (OMS), a treatment protocol with different steps, including steroids, IVIG, rituximab, cyclophosphamide, and others (plasma-targeting therapies), should be established and evaluated in a prospective trial, ideally on a European level due to the rarity of the disease.

Conclusion

MOG spectrum disorders include a wide range of children with monophasic and recurrent diseases. In particular, very young children with ADS harbor MOG-abs and are associated with a monophasic disease course in the context of declining antibody levels. On the other hand, a subgroup of children continues to have high and persisting MOG-abs and recurrent episodes other than MS. Collaborative studies are needed to better define this group of diseases with the common denominator, MOG-abs, to unravel the mechanisms that lead to the different clinical manifestations and find the best treatment options.

Conflict of Interest
None.

Acknowledgment
We thank Romana Höftberger for critically reviewing the manuscript.

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