MRI of the first event in pediatric acquired demyelinating syndromes with antibodies to myelin oligodendrocyte glycoprotein

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Abstract

Antibodies against the myelin oligodendrocyte glycoprotein (MOG-Ab) can be detected in various pediatric acquired demyelinating syndromes (ADS). Here, we analyze the spectrum of neuroradiologic findings in children with MOG-Ab and a first demyelinating event. The cerebral and spinal MRI of 69 children with different ADS was assessed in regard to the distribution and characteristics of lesions. Children with acute disseminated encephalomyelitis ($n = 36$) or neuromyelitis optica spectrum disorder ($n = 5$) presented an imaging pattern characterized predominantly by poorly demarcated lesions with a wide supra- and infratentorial distribution. Younger children also tended to have poorly defined and widespread lesions. The majority of patients with an isolated optic neuritis ($n = 16$) only presented small non-specific brain lesions or none at all. A longitudinally extensive transverse myelitis mainly affecting the cervical, and less often so the thoracic, lumbar, and conus regions, was detected in 31 children. The three children of our cohort who were then finally diagnosed with multiple sclerosis had at onset already demarcated white matter lesions as well as transverse myelitis. In conclusion, children with MOG seropositive ADS present disparate, yet characteristic imaging patterns. These patterns have been seen to correlate to the disease entity as well as to age of symptom onset.

Introduction

Serum myelin oligodendrocyte glycoprotein antibodies (MOG-Ab) can be detected in different pediatric acquired demyelinating syndromes (ADS) such as acute disseminated encephalomyelitis (ADEM), aquaporin-4 antibody negative neuromyelitis optica spectrum disorders (NMOSD), ADEM followed by optic neuritis (ADEMON), multiphasic disseminated encephalomyelitis (MDEM), and optic neuritis (ON) [1–9]. In contrast, the presence of MOG-Ab is rare in children with multiple sclerosis (MS) [10–13]. Several studies have addressed the clinical and prognostic relevance of MOG-Ab. High-titer and transient serum MOG-Ab are predominantly found in young children with ADEM. Children with high and persisting MOG-Ab are at risk of developing further attacks, in particular episodes of ON. Until recently, MOG-Ab related diseases were thought to have a more benign outcome compared to other recurrent demyelinating diseases including MS or NMOSD with aquaporin-4 antibodies. Nevertheless, recent findings from adult cohorts indicate that patients with MOG-Ab may also develop relevant neurological deficits over time, suggesting the need for immunomodulatory treatment in particular in relapsing cases [14].

So far only few studies have examined the spectrum of imaging features of children with MOG-Ab related diseases. Lesions in pediatric ADEM with MOG-Ab are poorly

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demarcated and often large involving white matter and deep gray matter in addition to other anatomical regions such as the brainstem, cerebellum, and spinal cord [1]. Other investigators found that MOG-Ab positive pediatric patients with ADS are less likely to have lesions involving the corpus callosum or periventricular white matter [7, 10]. To date, no study has addressed the wide range of radiological findings in the context of all clinical subtypes of MOG seropositive diseases.

In this study, we analyzed the spectrum of neuroradiological findings in children presenting with a first ADS in a large cohort of children with MOG-Ab.

Methods

Patients

As described recently [12], we included pediatric patients with ADS in an ongoing prospective study investigating the presence of serum MOG and aquaporin-4 antibodies. Approval for this study was obtained from the institution's review board. All included patients or caregivers provided written informed consent. Between 2009 and 2015, serum samples of 339 children with a suspected ADS were sent to us. From this cohort, which included children from Austria, Canada, Germany, Italy, Switzerland, and Turkey, we initially identified 81 patients with MOG-Ab, who had their first event between January 2010 and December 2015. Twelve patients who had the first MOG-Ab analysis more than 3 months after onset or in which the magnetic resonance imaging (MRI) of the first event was not available were subsequently excluded (Fig. 1). From 69 children clinical data, MRI of the brain and spine at disease onset, and serum MOG-Ab status were reviewed. Serial clinical and MRI visits were offered to all participants, but adherence to protocol was variable. Of the 69 participants, all patients were at least seen annually, and 42 at least 6 monthly during the first year. Not all parents agreed to an MRI follow-up. Serial imaging was nevertheless performed in 58/69 patients. Of the 11 patients without serial imaging all showed a monophasic disease course during clinical follow-up. The clinical characteristics in addition to radiological findings in selected cases of 52 patients were previously described [1, 2, 4, 8, 12]. We included these patients, since detailed analysis of imaging studies concerning the whole spectrum of disease entities was not performed nor published before.

Diagnosis

Clinical data at onset and follow-up were obtained in the majority of cases with a standardized questionnaire or a medical discharge summary from the referring physician. All children were centrally assigned to one of the following diagnoses based on the 2012 International Pediatric MS Study Group (IPMSSG) recommendations: ADEM (defined as a first polyfocal clinical CNS event with presumed inflammatory demyelinating cause and encephalopathy that cannot be explained by fever), NMOSD (in the absence of AQP4 antibodies: optic neuritis, longitudinally extensive transverse myelitis (LETM), and brain MRI not meeting the criteria for MS), polyfocal clinically isolated syndrome (CIS), LETM (contiguous spinal cord MRI lesion extending over three vertebral segments), uni- and bilateral ON, and short transverse myelitis for monophasic disease, and MDEM, ADEMON, multiphasic NMOSD, recurrent ON and MS for relapsing

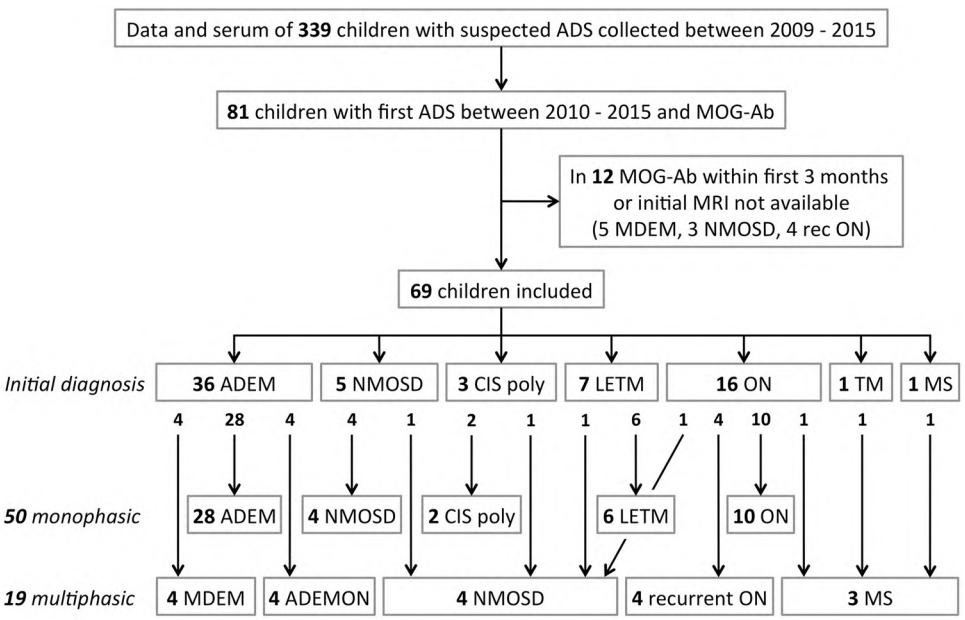

Fig. 1 Flow chart study profile showing the diagnosis at onset and last follow-up. The numbers at the base of the arrows indicate how many patients moved from one category towards another. *ADEM* acute disseminated encephalomyelitis, *ADEMON* acute disseminated encephalomyelitis followed by optic neuritis, *ADS* acquired demyelinating syndrome, *CIS poly* polyfocal clinically isolated syndrome, *LETM* longitudinally extensive transverse myelitis, *MDEM* multiphasic disseminated encephalomyelitis, *MOG* myelin oligodendrocyte glycoprotein, *MS* multiple sclerosis, *NMOSD* neuromyelitis optica spectrum disorder, *ON* optic neuritis, *TM* transverse myelitis

disease [15]. The diagnosis of MS was made in case of (1) a first, single, non-encephalopathic acute event whose MRI findings were consistent with the 2010 Revised McDonald criteria for dissemination in space (DIS) and dissemination in time (DIT), (2) one non-encephalopathic episode typical of MS associated with MRI findings consistent with criteria for DIS and a follow-up MRI consistent with DIT criteria, (3) a second non-encephalopathic event involving more than one area of the CNS, or (4) one ADEM attack followed by a non-encephalopathic clinical event three or more months after symptom onset associated with new MRI lesions that fulfill DIS criteria.

Antibodies

Serum samples were analyzed for the presence of IgG antibodies to MOG and aquaporin-4 by recombinant live cell-based immunofluorescence assays with HEK293A cells as previously described [16]. Screening was performed at dilutions of 1:20 and 1:40 by at least two independent clinically blinded investigators (MR, KS) and antibody titers of positive serum samples were determined by serial dilutions. MOG-IgG antibody titer levels of $\geq$ 1:160 were classified as seropositive.

MR imaging

MRI scans were scored independently by two experienced neuroradiologists (AG, TD) with a third rater (MB) in cases with discordant results. AG and TD were blinded for the clinical data of the patients. The minimum requirements of brain MRI sequences for inclusion were axial T2, axial FLAIR, sagittal T2, and contrast enhanced axial T1. From 66 children also diffusion-weighted images were available. In 2 out of 69 children the initial MRI was performed on scanners with field strengths of 1.0 T, in 55/69 with 1.5 T, and in 12/69 children with 3.0 T scanners. In 51/69 patients a spinal cord MRI was performed during the initial investigations including the following sequences: sagittal T2, axial T2, contrast enhanced sagittal T1.

The cerebral MRI of the initial event was assigned to one of four predefined MRI patterns: (1) predominantly poorly demarcated lesions involving gray and/or white matter, (2) extensive confluent white matter changes, (3) predominantly well-demarcated white matter lesions, (4) no or only small (< 0.3 cm) nonspecific lesions. The distribution of lesions was assessed in regard to the involvement of certain regions such as cortical gray matter, juxtacortical, deep and periventricular white matter, corpus callosum, thalamus, basal ganglia, brainstem and cerebellum [17].

Furthermore, the following additional features were recorded: (1) areas of restricted diffusion (high signal on diffusion weighted imaging (DWI) and low signal on apparent diffusion coefficient (ADC) maps), (2) presence of T1-hypointense lesions, (3) Gadolinium enhancing lesions, (4) large lesions with a diameter of more than 2 cm in the transversal plane, (5) curved juxtacortical lesions involving U-fibers or (6) ovoid lesions oriented perpendicular to the surface of the lateral ventricles (Dawson finger type lesions). Spinal MRI was analyzed for the presence of transverse myelitis or LETM and the distribution of lesions. MRI sequences to evaluate the optic nerves properly were not available from all children; therefore, presence of optic nerve involvement was not included in the evaluation. To assess the distribution of lesions in a patient, we counted the regions involved in the cerebral MRI (cortical gray matter, juxtacortical, deep, and periventricular white matter, corpus callosum, deep gray matter, brainstem and cerebellum) and created a cerebral score (0–8). To capture the extension of spinal lesions we formed a spinal score (0–6: transverse myelitis, LETM, cervical, thoracic, lumbar spine and conus medullaris).

Statistical analysis

Statistical analysis was performed using IBM SPSS, release V.24.0 (IBM Corporation). We compared clinical, demographic, neuroradiological, and serological data using the Kruskal–Wallis test and Chi-square test. Corrected Fisher's exact contingency table analysis was calculated using an online calculator (http://www.physics.csbsju.edu/stats/exact_NROW_NCOLUMN_form.html). Statistical significance was defined as a two-sided p value of < 0.05. Inter-rater agreement was assessed by kappa statistics (Table S-2).

Results

Diagnosis

Thirty-six children (52%) had an initial diagnosis of ADEM, five (7%) NMOSD, three (4%) polyfocal CIS, seven (10%) LETM, sixteen (23%) ON, one (1%) isolated short transverse myelitis, and one (1%) MS (Table 1, Fig. 1). The mean follow-up period was 33 months (median 24 months, range 12–84 months). Fifty (72%) children had a monophasic disease course and 19 (28%) children had more than one event (Fig. 1, Table S-1). In the monophasic disease group 28 had ADEM, four NMOSD, six LETM, ten uni- or bilateral ON, and two polyfocal CIS. Of the children with relapsing disease four had MDEM, four ADEMON, four NMOSD, four recurrent ON, and three MS. All three patients finally diagnosed with MS fulfilled in the initial MRI the McDonald criteria for dissemination in space, but only one of them fulfilled the MRI criteria for dissemination in time with enhancing and non-enhancing lesions [18]. Our cohort included 36 boys and 33 girls. Median age at disease onset

Table 1 Clinical and MRI findings of the first episode in 69 children with MOG-Ab seropositive ADS

Diagnosis at onset	ADEM	NMOSD	Polyfocal CIS	LETM	ON	TM	MS	*p* value
n (%)	36 (52)	5 (7)	3 (4)	7 (10)	16 (23)	1 (1)	1 (1)	
Female, *n* (%)	13 (36)	3 (60)	2 (67)	4 (57)	9 (56)	1 (100)	1 (100)	0.42[1]
Age at first symptoms, years[a, b]	5 (1–18)	7 (3–15)	10 (9–13)	7 (2–16)	11 (4–17)	15	11	0.001[2]
MOG-IgG titer (1:)[a]	2560 (160–81,920)	640 (320–1280)	10,240 (2560–20,480)	2560 (160–5120)	640 (160–5120)	160	640	0.07[2]
Cerebral lesions, quality								
No or < 0.3 cm non-specific, *n* (%)	0 (0)	0 (0)	0 (0)	4 (57)	11 (69)	0 (0)	0 (0)	< 0.001[1]
Poorly demarcated, *n* (%)	34 (94)	5 (100)	3 (100)	3 (43)	4 (25)	0 (0)	0 (0)	< 0.001[1]
Extensive confluent, *n* (%)	2 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.92[1]
Well-demarcated, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (6)	1 (100)	1 (100)	0.001[1]
Restricted diffusion, *n* (%)	4 (11)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.69[1]
T1-hypointense, *n* (%)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	< 0.001[1]
Gd-enhancement, *n* (%)	4 (11)	1 (20)	2 (67)	0 (0)	0 (0)	1 (100)	1 (100)	< 0.001[1]
Small (0.3–2 cm), *n* (%)	7 (19)	4 (80)	1 (33)	3 (43)	3 (19)	1 (100)	0 (0)	0.05[1]
Large (> 2 cm), *n* (%)	29 (81)	1 (20)	2 (67)	0 (0)	2 (13)	0 (0)	1 (100)	< 0.001[1]
Curved U-fiber lesions, *n* (%)	3 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0.005[1]
Dawson finger type, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	< 0.001[1]
Cerebral lesions, distribution								
Cortical gray matter, *n* (%)	19 (53)	2 (40)	1 (33)	1 (14)	1 (6)	0 (0)	0 (0)	0.04[1]
Juxtacortical WM, *n* (%)	31 (86)	4 (80)	3 (100)	1 (14)	1 (6)	0 (0)	1 (100)	< 0.001[1]
Deep WM, *n* (%)	23 (64)	2 (40)	3 (100)	1 (14)	0 (0)	0 (0)	1 (100)	< 0.001[1]
Periventricular WM, *n* (%)	13 (36)	0 (0)	1 (33)	0 (0)	1 (6)	1 (100)	1 (100)	0.02[1]
Callosal, *n* (%)	11 (31)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	1 (100)	0.02[1]
Deep gray matter, *n* (%)	30 (83)	2 (40)	3 (100)	2 (29)	3 (19)	0 (0)	0 (0)	< 0.001[1]
Thalamus, *n* (%)	26 (72)	2 (40)	3 (100)	2 (29)	3 (19)	0 (0)	0 (0)	< 0.001[1]
Basal ganglia, *n* (%)	22 (61)	1 (20)	2 (67)	1 (14)	1 (6)	0 (0)	0 (0)	< 0.001[1]
Brainstem, *n* (%)	22 (61)	1 (20)	2 (67)	1 (14)	1 (6)	0 (0)	1 (100)	< 0.001[1]
Cerebellar, *n* (%)	19 (53)	0 (0)	2 (67)	0 (0)	0 (0)	0 (0)	1 (100)	< 0.001[1]
Cerebral score[a,c]	5 (1–7)	3 (1–3)	5 (5–6)	0 (0–4)	0 (0–2)	1	6	< 0.001[2]
Spinal MRI								
Available from, *n* (%)	26 (72)	5 (100)	2 (67)	7 (100)	9 (56)	1 (100)	1 (100)	
No spinal lesion, *n* (%)	7 (27)	0 (0)	1 (50)	0 (0)	8 (89)	0 (0)	0 (0)	< 0.001[1]

Table 1 (continued)

Diagnosis at onset	ADEM	NMOSD	Polyfocal CIS	LETM	ON	TM	MS	*p* value
LETM, *n* (%)	19 (73)	5 (100)	1 (50)	7 (100)	0 (0)	0 (0)	0 (0)	< 0.001[1]
TM, *n (%)*	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	1 (100)	1 (100)	< 0.001[1]
Cervical involvement, *n* (%)	19 (73)	5 (100)	1 (50)	7 (100)	0 (0)	1 (100)	1 (100)	< 0.001[1]
Thoracic involvement, *n* (%)	14 (54)	3 (60)	1 (50)	7 (100)	0 (0)	1 (100)	1 (100)	< 0.001[1]
Lumbar involvement, *n* (%)	9 (35)	3 (60)	1 (50)	4 (57)	1 (11)	0 (0)	0 (0)	0.38[1]
Conus involvement, *n* (%)	7 (27)	3 (60)	0 (0)	3 (43)	0 (0)	0 (0)	0 (0)	0.19[1]
Spinal score[a,d]	3 (0–5)	5 (2–5)	0, 4	4 (2–5)	0 (0–1)	2	2	0.002[2]

ADEM acute disseminated encephalomyelitis, *ADS* acquired demyelinating syndrome, *CIS* clinically isolated syndrome, *MOG* myelin oligodendrocyte glycoprotein, *LETM* longitudinally extensive transverse myelitis, *NMOSD* neuromyelitis optica spectrum disorder, *ON* optic neuritis, *TM* transverse myelitis

[a]Median (range)

[b]Patients ages were rounded to the nearest year

[c]Cerebral score (0–8; cortical gray, juxtacortical, deep, and periventricular white matter, corpus callosum, deep gray matter, brainstem and cerebellum)

[d]Spinal score (0–6, transverse myelitis, LETM, cervical, thoracic, lumbar spine and conus)

Groups were statistically compared with [1]corrected Fisher's exact contingency table analysis or [2]Kruskal–Wallis test

was higher in patients with polyfocal CIS, ON, transverse myelitis or MS (10, 11, 15 and 11 years, respectively) compared to patients with ADEM, NMOSD or LETM (5, 7 and 7 years, respectively).

Antibodies

MOG-Ab titers were higher in patients with the initial diagnosis of ADEM (median 1:2560; range 1:160–81,920), polyfocal CIS (median 1:10,240; range 1:2560–1:20,480), and LETM (median 1:2560; range 1:160–1:5120). Median MOG-Ab titers were lower in patients with NMOSD (median 1:640; range 1:320–1:1280), ON (median 1:640; range 1:160–1:5120), transverse myelitis (1:160) and MS (1:640) (Table 1). All 69 included participants were tested for antibodies directed against AQP4, and all were negative.

MR imaging

Each cerebral MRI was assigned to one of the four patterns according to the morphology of the lesions (Table 1, 2). Forty-nine of 69 patients (71%) presented with a pattern of predominately poorly demarcated lesions (Fig. 2a, b) and 34 of those showed the clinical picture of ADEM. Extensive confluent white matter changes (Fig. 2c) were seen in two patients with ADEM. Well-demarcated white matter lesions (Fig. 2i, k) were seen in one patient who was diagnosed with MS at the first episode and in two further patients who were later diagnosed with MS. Small nonspecific or no cerebral lesions were seen in patients with the initial diagnosis of ON (69%) or LETM (57%).

Areas with restricted diffusion (high signal on DWI and low signal on ADC, Fig. 2d) suggestive of cytotoxic edema were seen in four of 66 patients. In these patients not all lesions, but the majority of them, and in particular larger lesions, demonstrated restricted diffusion. All children with these features initially presented with ADEM with a median age of 3 years of age (range one to 5 years). One child subsequently developed episodes of optic neuritis.

In patients with ADEM involvement of several regions including the cortical gray matter (53%), juxtacortical (86%) and deep white matter (64%), deep gray matter (83%), brainstem (61%), cerebellum (53%), and spinal cord (73%) was common. A wider distribution of lesions was seen in particular in patients younger than 5 years of age. They showed poorly demarcated and large lesions with eminent involvement of juxtacortical and deep white matter, deep gray matter (especially basal ganglia), brainstem, cerebellum and also corpus callosum (Table 2).

Table 2 Clinical and MRI findings of the first episode in 69 children with MOG-Ab seropositive ADS according to age at onset

Age at onset[b]	0–5 years	5–10 years	10–17 years	*p* value
n (%)	27 (39)	23 (33)	19 (28)	
Female, *n* (%)	7 (26)	13 (57)	13 (68)	0.010[1]
MOG-IgG titer (1:)[a]	2560 (160–81,920)	1280 (160–20,480)	640 (160–20,480)	0.05[3]
Diagnosis at onset				
ADEM, *n* (%)	22 (81)	11 (48)	3 (16)	0.006[1]
NMOSD, *n* (%)	1 (4)	2 (9)	2 (11)	
Polyfocal CIS, *n* (%)	0 (0)	1 (4)	2 (11)	
LETM, *n* (%)	2 (7)	4 (17)	1 (5)	
ON, *n* (%)	2 (7)	5 (22)	9 (47)	
TM, *n* (%)	0 (0)	0 (0)	1 (5)	
MS, *n* (%)	0 (0)	0 (0)	1 (5)	
Cerebral lesions, quality				
No or < 0.3 cm non-specific, *n* (%)	1 (4)	6 (26)	8 (42)	0.007[1]
Poorly demarcated, *n* (%)	24 (89)	17 (74)	8 (42)	0.002[1]
Extensive confluent, *n* (%)	2 (7)	0 (0)	0 (0)	0.33[2]
Well-demarcated, *n* (%)	0 (0)	0 (0)	3 (16)	0.02[2]
Restricted diffusion, *n* (%)	4 (15)	0 (0)	0 (0)	0.04[2]
T1-hypointense, *n* (%)	1 (4)	0 (0)	1 (5)	0.74[2]
Gd-enhancement, *n* (%)	5 (19)	1 (4)	3 (16)	0.29[2]
Small (0.3–2 cm), *n* (%)	6 (22)	5 (22)	8 (42)	0.25[1]
Large (> 2 cm), *n* (%)	20 (74)	12 (52)	3 (16)	< 0.001[1]
Curved U-fiber lesions, *n* (%)	3 (16)	0 (0)	1 (5)	0.30[2]
Dawson finger type, *n* (%)	0 (0)	0 (0)	1 (5)	0.28[2]
Cerebral lesions, distribution				
Cortical gray matter, *n* (%)	12 (44)	9 (39)	3 (16)	0.12[1]
Juxtacortical WM, *n* (%)	22 (81)	13 (57)	6 (32)	0.003[1]
Deep WM, *n* (%)	19 (70)	8 (35)	3 (16)	< 0.001[1]
Periventricular WM, *n* (%)	10 (37)	4 (17)	3 (16)	0.16[1]
Callosal, *n* (%)	10 (37)	1 (4)	2 (11)	0.007[1]
Deep gray matter, *n* (%)	22 (81)	11 (48)	7 (37)	0.005[1]
Thalamus, *n* (%)	18 (67)	11 (48)	7 (37)	0.12[1]
Basal ganglia, *n* (%)	20 (74)	6 (26)	1 (1)	< 0.001[1]
Brainstem, *n* (%)	17 (63)	6 (26)	5 (26)	0.010[1]
Cerebellar, *n* (%)	16 (59)	1 (4)	5 (26)	< 0.001[1]
Cerebral score[a,c]	6 (0–7)	2 (0–5)	1 (0–6)	< 0.001[3]
Spinal MRI				
Available from, *n* (%)	19 (37)	20 (39)	12 (24)	
No spinal lesion, *n* (%)	8 (42)	4 (20)	4 (33)	0.33[1]
LETM, *n* (%)	11 (58)	16 (80)	5 (42)	0.08[1]
TM, *n* (%)	0 (0)	0 (0)	3 (25)	0.01[2]
Cervical involvement, *n* (%)	10 (53)	16 (80)	7 (58)	0.18[1]
Thoracic involvement, *n* (%)	8 (42)	13 (65)	6 (50)	0.35[1]
Lumbar involvement, *n* (%)	4 (21)	10 (50)	4 (33)	0.17[1]
Conus involvement, *n* (%)	3 (16)	7 (35)	3 (25)	0.39[1]
Spinal score[a,d]	2 (0–5)	4 (0–5)	2 (0–5)	0.14[2]

ADEM acute disseminated encephalomyelitis, *ADS* acquired demyelinating syndrome, *CIS* clinically isolated syndrome, *MOG* myelin oligodendrocyte glycoprotein, *LETM* longitudinally extensive transverse myelitis, *NMOSD* neuromyelitis optica spectrum disorder, *ON* optic neuritis, *TM* transverse myelitis

[a]Median (range)

[b]Patients ages were rounded to the nearest year

[c]Cerebral score (0–8, cortical gray, juxtacortical, deep, and periventricular white matter, corpus callosum, deep gray matter, brainstem and cerebellum)

[d]Spinal score (0–6, transverse myelitis, LETM, cervical, thoracic, lumbar spine and conus)

Groups were statistically compared with [1]Chi-square test, [2]corrected Fisher's exact contingency table analysis or [3]Kruskal–Wallis test

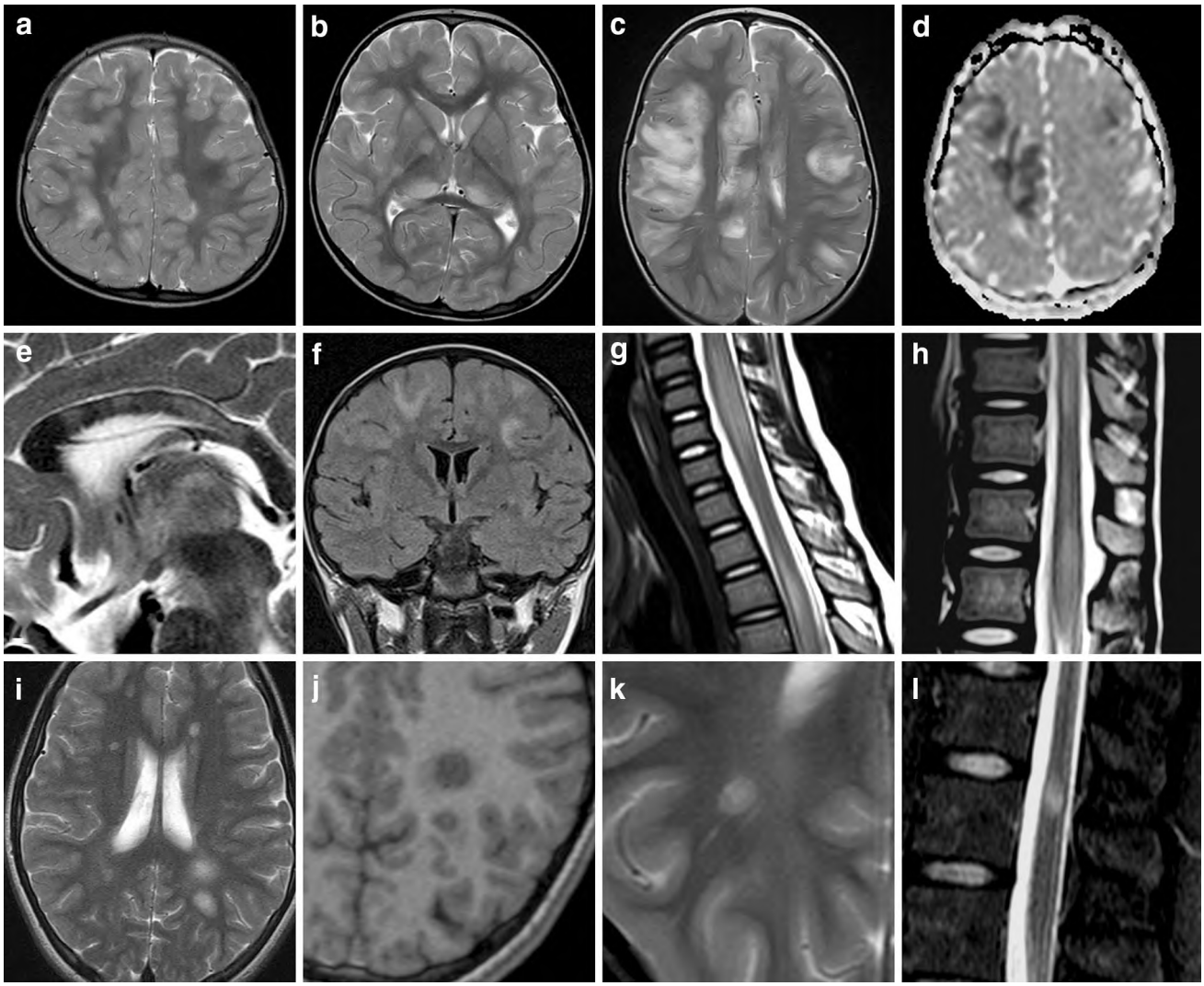

Fig. 2 MRI findings of the first episode in eight children with ADS and antibodies to MOG. Predominantly poorly marginated T2-weighted lesions in a 3-year-old boy with ADEM involving cortical gray matter, juxtacortical white matter (**a**) and deep gray matter (**b**). Extensive and confluent white matter changes on the right side (**c**) in a 4-year-old boy with ADEM, finally diagnosed as ADEMON. Lesions with diffusion restriction and low signal on ADC (**d**) in a 2-year-old boy with ADEM. Callosal lesions (**e**) in a 4-year-old boy with ADEM. Juxtacortical curved lesions involving U-fibers (**f**) in a 4-year-old boy with ADEM. LETM involving cervical, thoracic (**g**), lumbar spine and conus (**h**) in a 7-year-old girl with ADEM. Well-demarcated, ovoid (**i**) and T1-hypointense (**j**) lesions in a 11-year-old girl with MS. Single well-demarcated lesion (**k**) and short transverse myelitis (**l**) in a 17-year-old girl which presented with an ON, finally diagnosed with MS

Of the 13 patients who had callosal lesions (Fig. 2e), one was diagnosed as MS, one as polyfocal CIS and 11 as ADEM at the time of the first attack. None of these ADEM/CIS patients developed MS within the follow-up period (median 26 months, range 17–75 months). Periventricular lesions were present in all three patients who were then diagnosed with MS (Fig. 1i, Suppl. Fig S-1), but they were also present in 13 (36%) children with ADEM. Ovoid lesions perpendicular to the surface of the lateral ventricles (Dawson finger type lesions) were only seen in one patient with MS. Juxtacortical curved lesions involving U-fibers (Fig. 2f) were found in four patients, one 11-year-old patient diagnosed with MS and three children all younger than 5 years of age with ADEM.

A spinal MRI was performed in 51 patients at onset; 32 of these children had an LETM (Fig. 2g, h), three had

a short transverse myelitis (Fig. 2l), and 16 had no spinal cord lesion. In 30 of 35 patients (29/32 LETM, 1/3 short transverse myelitis) spinal cord lesions were associated with clinical symptoms suggestive of transverse myelitis. Of the three patients with short transverse myelitis, one had been diagnosed with MS after the first event and the two others after a second clinical episode with new MRI lesions (Suppl Fig. S-1). Of the 35 patients presenting spinal cord lesions, the lesions could be seen in the following areas, listed according to a decreasing order: cervical (33/35), thoracic (27/35) and lumbar (18/35) region and conus medullaris (13/35) (Table 1). Patients with NMOSD or LETM presented a wider distribution of spinal cord lesions, which was expressed by a higher spinal score.

Discussion

We were able to disclose the MR imaging features of 69 children with an initial ADS and MOG-Ab. To the best of our knowledge this is the largest cohort of pediatric MOG-Ab associated ADS, which has been analyzed according to MR features. We found that children with ADEM or NMOSD often reveal a similar pattern, which is characterized by poorly demarcated, respectively, blurred and widespread lesions as described in a previous study of children with ADEM [1], despite the clinical differences between the two subtypes. Furthermore, we found that imaging features are strongly influenced by age (Table 2). As previously described patients who were initially diagnosed with ADEM, NMOSD, or LETM were of a younger age at onset compared to patients diagnosed with polyfocal CIS, ON, transverse myelitis or MS [7, 12]. Children with poorly demarcated lesions or extensive confluent lesions were often younger at symptom onset than children who had well-demarcated, no or only small non-specific lesions in their cerebral MRI. Fernandez-Carbonell et al. [7] also observed a bimodal distribution in their series of 13 MOG-seropositive pediatric patients, with younger patients presenting with ADEM, while older patients presented with ON, suggesting that this may represent differences in regional expression of MOG in the various age groups [19]. Probably myelin development and compaction has a significant influence on the neuroradiological and clinical presentation of pediatric ADS. Studies of normal white matter maturation using diffusion tensor imaging showed region-specific changes in mean diffusion diffusivity and fractional anisotropy from infancy to childhood [20, 21]. The influence of ADS on myelin maturation in non-lesional, normal appearing white matter was recently shown in a study of Longoni et al. [22] investigating diffusion properties in children with pediatric ADS and healthy children. In this study, normal-appearing white matter in children with ADS did not demonstrate age-expected maturational change. Recently, we showed in another study of 210 children with ADS that MOG-Ab seropositive children with a monophasic disease course diagnosed with ADEM were primarily younger of age than children with a relapsing course, who were not only older at onset, but also predominantly females [12].

Several imaging findings in our study are of note. Contrary to the study by Fernandez-Carbonell et al. [7] who reported the absence of corpus callosum lesions in MOG-seropositive patients, we were able to detect corpus callosum lesions in a subgroup of young children. Callosal lesions were also found in another study in 2/13 children with MOG-seropositive ADS [23]. In addition, four patients in our cohort had curved juxtacortical lesions involving U-fibers. Jurynczyk et al. identified this feature as an adequate distinguishing factor between MS, aquaporin-4-Ab positive NMOSD, and MOG-Ab disease in a cohort of mostly adult patients [24, 25]. Though three of our patients with curved U-fiber lesions were young children with ADEM, there were no curved-U-fiber lesions in older non-MS children; so that curved U-fiber lesions are most likely indicative of MS in older children, but not in younger children. Another criteria for MS in the aforementioned studies were Dawson finger type lesions. In our study, Dawson finger type lesions were only detected in one patient with MOG-Ab who was finally diagnosed with MS. Therefore, the presence of Dawson finger type lesions makes the diagnosis of a MOG spectrum disorder unlikely.

LETM can be a feature of different forms of ADS such as NMOSD, ADEM or isolated LETM. In regard to the distribution of lesions in children with ADS and MOG-Ab the following areas were predisposed to lesions, in a descending order: the cervical, thoracic, and lumbar cord, and the conus. These findings are similar to those of adults [14]. The three patients initially presenting a short transverse myelitis in the absence of LETM were diagnosed with MS, which is despite the presence of transient MOG-Ab in association with other features such as well-demarcated lesions highly suggestive of MS. According to a study by Hacohen et al. [13] blinded MRI analyses in children with relapsing ADS successfully distinguished between MS and non-MS cases already at onset.

Four patients in our cohort, all initially presenting with ADEM, had areas of restricted diffusion suggestive of cytotoxic edema in the initial cerebral MRI. Zuccoli et al. [26] identified restricted diffusion in 2/16 pediatric patients with ADEM suggesting that restricted diffusion is not a common feature in the acute stage. Due to the small number of patients in our study with diffusion restriction it was not possible to draw conclusions concerning prognosis and outcome.

Several limitations of our study need to be addressed: a referral bias not revealing the true incidence of clinical

entities or MRI patterns cannot be excluded as patients were sent from different centers. MRI studies were performed on scanners with different field strengths, leading to a different quality of images and results, and MRI sequences. As a result of this, we were not able to properly evaluate the optic nerve of all the children. The identification of cortical lesions was partly challenging, as advanced techniques such as double inversion recovery were not available. In 18 patients no spinal MRI was available. Of these patients ten had the initial diagnosis of ADEM, seven of ON, and one patient of CIS/polyfocal. Supposing that spinal imaging was preferentially obtained in the context of clinical symptoms suggestive of spinal cord involvement, the frequency of spinal lesions might have been overestimated. Finally, the influence of the time interval between onset of symptoms and MRI on lesion characteristics is an important variable and has not been assessed in our study. Wong et al. [27] showed that in children with ADEM, new or enlarging lesions occur in the first 3 months in about 50% of subsequently performed MRIs.

In conclusion, children with MOG-seropositive ADS who are younger tend to have a cerebral MRI characterized by poorly demarcated and widespread lesions that is clearly distinct from other forms of ADS such as MS. Older children with ON often have no or only small nonspecific cerebral lesions, while the few MOG-seropositive children diagnosed with relapsing–remitting MS already have a typical MS-like MRI pattern with well-demarcated lesions and short transverse myelitis at onset. Additionally, in patients with MS periventricular lesions, curved juxtacortical lesions involving U-fibers or Dawson finger type lesions can be found. Nevertheless, curved lesions involving U-fibers and periventricular lesions are not restricted to children with MS, but instead can also be found in younger patients with ADEM in addition to callosal lesions and lesions with restricted diffusion. To summarize, children with MOG seropositive ADS present disparate, but characteristic imaging patterns largely dependent on disease entity and age. Overlapping characteristic features can be seen between ADEM and NMOSD, which further supports the concept of MOG-Ab related spectrum disorders.

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Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standards Approval for this study was obtained from the institution's review board. All included patients or caregivers provided written informed consent.

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