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ORIGINAL COMMUNICATION

MOG antibody-related disorders: common features and uncommon presentations

Álvaro Cobo-Calvo[1,2] · Anne Ruiz[2] · Hyacintha D'Indy[2] · Anne-Lise Poulat[3] · Maryline Carneiro[3] · Nicolas Philippe[1] · Françoise Durand-Dubief[1] · Kumaran Deiva[4] · Sandra Vukusic[1] · Vincent Desportes[3] · Romain Marignier[1,2]

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Abstract Myelin oligodendrocyte glycoprotein antibodies (MOG-Ab) have been reported in acute demyelinating encephalomyelitis (ADEM), optic neuritis (ON), and neuromyelitis optica spectrum disorders (NMOSD) in adults and pediatrics. We aimed to delineate the common features of MOG-Ab-related disorders in children and adults, and report uncommon presentations. Twenty-seven consecutive pediatric and adult patients testing positive for MOG-Ab, with a minimum follow-up of 6 months, were included. Comprehensive epidemiological, clinical, radiological, and laboratory data were retrospectively analyzed. Additionally, we compared radiological features between ADEM MOG-Ab-positive patients, and a group of ADEM MOG-Ab-negative ones, recruited during the same period. Among the whole cohort, 13 (48.1%) were pediatric, and 14 (51.9%) were female. MOG-Ab-related disorders comprised eight ADEM, eight ON, five isolated myelitis, four with NMOSD and two patients with multiple sclerosis, at last follow-up. After a median follow-up of 17.8 months, 11 (40.7%) patients presented a relapse. The most frequent clinical phenotype at onset was encephalopathy in pediatrics (53.9%) and myelitis in adults (50%) ($p = 0.013$). There were no other differences between both groups. When comparing ADEM MOG-Ab positive and negative patients, bilateral thalamic lesions were more often found in the positive group ($p = 0.010$). Unusual presentations were identified in three patients: patchy spinal cord gadolinium-enhancing lesions, an associated teratoma, and one presented with status epilepticus. MOG-Ab-related disorders shared common clinical and prognostic features, but encompass a spectrum wider than recently reported.

Keywords MOG antibodies · Aquaporin-4 antibodies · Neuromyelitis optica · Multiple sclerosis

Introduction

Myelin oligodendrocyte glycoprotein-auto-antibodies (MOG-Ab) have been mainly described in pediatric patients with acute demyelinating encephalomyelitis (ADEM) or optic neuritis (ON) [1–5], as well as pediatric and adults diagnosed with neuromyelitis optica spectrum disorders (NMOSD) without aquaporin-4 antibodies (AQP4-Ab) [6–8].

Patients presenting with demyelinating diseases and MOG-Ab in serum were initially characterized by a younger age at onset, lower risk to relapse and a more benign course than AQP4-Ab-positive ones [6–8]. However, recent studies with longer follow-up plead against these first described features [9, 10]. Clinical manifestations at onset are reported different between pediatric and adults patients: a higher predisposition to encephalopathy in children [11, 12], in comparison to ON or transverse myelitis in adults [13, 14]. However, most of the studies describing characteristics of

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✉ Álvaro Cobo-Calvo
alvaro.cobo-calvo@chu-lyon.fr

1 Service de Neurologie A, Hôpital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, 69677 Bron, France

2 Lyon's Neuroscience Research Center, U1028 Inserm, UMR5292 Cnrs, FLUID Team, 69008 Lyon, France

3 Hôpital Femme Mère Enfant, Neurologie pédiatrique, Hospices Civils de Lyon, 69677 Bron, France

4 Service de neuropédiatrie, Hôpital Kremlin-Bicêtre, 78, rue du Général-Leclerc, 94270 Le Kremlin-Bicêtre, France

MOG-Ab-positive patients usually mix features from adults and pediatrics, without having performed a direct comparison between both groups.

Some patients develop a different evolution with less common clinical or radiological features, or a fulminant course [9, 13, 15, 16]. Since MOG-Ab-related disorders are an emerging entity, there is a need for a deeper comprehensive description of atypical cases as the whole spectrum has likely not been fully described.

In the present study, we aimed to delineate the common features of MOG-Ab-related disorders between children and adults, and we report new uncommon presentations.

Methods

Patients

Between January 2014 and January 2016, 177 serum samples from adult and pediatric patients presenting with a suspected acquired demyelinating syndrome (ADS) admitted to Hôpital Neurologique Pierre Wertheimer and Hôpital Pédiatrique Mère Enfant of Lyon (France) were routinely analyzed for AQP4 and MOG-Ab by cell-based assay (CBA). All patients had a minimum of 6 months follow-up. We defined ADS as an acute clinical episode of the central nervous system (CNS) lasting for more than 24 h involving the optic nerve, brain, brainstem or spinal cord associated with T2 lesions on magnetic resonance imaging (MRI).

We registered epidemiological features such as age, gender, ethnicity, concomitant autoimmune diseases, infections or vaccinations 1 month prior to disease onset. We noted the topography of the first episode, neurological symptoms as well as the number and location of relapses. Relapse was defined as a new episode at any CNS structure at least 1 month after the first episode, and sustained at least 24 h in the absence of fever or infection.

Clinical disability at nadir of symptoms and last visit was measured by the Expanded Disability Status Scale (EDSS). An EDSS < 3.0 at last visit was considered as a good outcome. For ON, visual acuity (VA) was evaluated by the visual functional system, and severe visual disability was defined as VA ≤ 0.2 both at nadir and last visit.

Treatments at the acute phase and type of immunosuppressant were also registered. Analysis of brain and spinal cord MRI was performed by a specialized neuroradiologist blinded to the patient sero-status. MRI studies included axial and sagittal images of the brain and spinal cord obtained by T1-weighted (W), T2-W, FLAIR and T1-W post-contrast sequences. Brain MRI at first episode was classified based on Paty's criteria and topography of lesions was noted: juxtacortical, periventricular, corpus callosum, putamen, thalamus, cerebellar peduncles and brainstem tegmentum.

Longitudinally extensive transverse myelitis (LETM) was defined as ≥3 contiguous vertebral segments in the sagittal plane. Available brain and spinal cord MRI follow-up studies were compared to the initial MRI, and were categorized in four subgroups: complete resolution, improvement, new lesions and no change.

Cerebrospinal fluid (CSF) was analyzed for cell count (pleocytosis >5 cells/mm^3), protein content, IgG index and oligoclonal bands (OCB).

At the end of the follow-up, patients were classified as ADEM [17], NMOSD [18], MS [19] or other limited NMO-like phenotypes (i.e.; isolated monophasic or relapsing myelitis or ON).

In addition, aiming to characterize features associated with ADEM MOG-Ab positive, we compared this group to monophasic ADEM tested seronegative for AQP4 and MOG-Ab during the same period of recruitment. All data were prospectively entered in the database adapted from the EDMUS system and software (Eugène Devic European Network, EDEN), and retrospectively analyzed [20].

Autoantibody detection

Aquaporin-4 Ab was detected using a cell-based assay [21]. MOG-Ab was detected by cell-based assay using an in-house method [22]. Briefly, HEK293 cells were transfected with pEGFP-N1-hMOG plasmid (kind gift from Markus Reindl, Innsbruck, Austria) for 48 h. Transfected cells were incubated with patients serum diluted at 1:640. This cut-off was selected to avoid false-positive signal detected with healthy control in previous works [23]. Bound IgG was detected with a fluorescent secondary antibody, APC-Goat anti human IgG-Fcγ fragment-specific (1:100 dilution, Jackson ImmunoResearch). Evaluation of signal intensity was performed by flow cytometry. Titration of positive samples was performed using serial dilution until loss of positive signal (from 1:160 to 1: 20.000).

Statistical analysis

At first episode, patients were classified into two groups: pediatric [admitted at neuropediatrics department (<16 years old)] and adult groups. Categorical and continuous variables were compared with nonparametric test (Fisher exact and Mann–Whitney *U* test, respectively). Statistical significance was set at two-tailed p value <0.05. All statistical analyses were performed using STATA (64-bits) software.

Results

General cohort features

We found a positive result for MOG-Ab in the serum of 27 patients. None of them were positive for AQP4-Ab. Flow chart for patient selection is depicted in Fig. 1.

After a median follow-up of 17.8 [interquartile range (IQR) 11.5–68.3] months, eight patients were finally diagnosed with ADEM, eight with isolated ON (four monophasic and four relapsing), five with isolated monophasic myelitis (four LETM), four with NMOSD and two patients with MS (Table 1).

Among the 27 MOG-Ab-positive patients, the median age of presentation was 16.8 (IQR 6.8–33.7) years. Patients were mainly Caucasians 25 (92.6%) with a female:male ratio of 1:0.9 (Table 1).

The most frequent clinical phenotypes at onset were myelitis, encephalopathy and unilateral ON (33.3 vs 29.6 vs 25.9%, respectively). The median EDSS at nadir was four (IQR 2.5–5.0); three patients presented with a severe motor attack at onset (two paraplegic, and one tetraplegic needing intubation). Eight out of 10 (80%) patients presenting with an initial ON had severe visual impairment (VA $\leq$ 0.2). During the follow-up, 11 (40.7%) patients relapsed either in form of ON (37%) or brainstem symptoms (3.7%). All but three patients relapsed within 8 months (median 3.8; IQR 2.0–22.5 months) from disease onset. No other CNS topographies were affected at relapse (Table 1).

Median time from onset of symptoms to MOG sampling was 1.4 months (IQR 0.4–21.9) (Table 1). When analyzing only those samples taken within 3 months from onset of symptoms, encephalopathy was related to higher MOG-Ab titers in comparison to the other phenotypes at onset [median 6280 (IQR 2560–20.000) vs 640 (640–2560), $p = 0.043$]. Similarly, ADEM showed to have higher MOG-Ab titers than the remaining phenotypes at last follow-up [median 10.000 (IQR 2560–20.000) vs 640 (640–2560), $p = 0.014$ (Supplementary Fig. 1).

Brain MRI at onset was abnormal in 16 (59%) patients. Among them, 7 (43.8%) and 5 (31.2%) patients showed bilateral thalamic or brainstem tegmental lesions, respectively. Eleven (73.3%) out of 15 patients with an available brain MRI during follow-up showed either complete resolution or improvement of the lesions. Spinal cord MRI performed at the acute phase disclosed LETM in 10 patients, and one

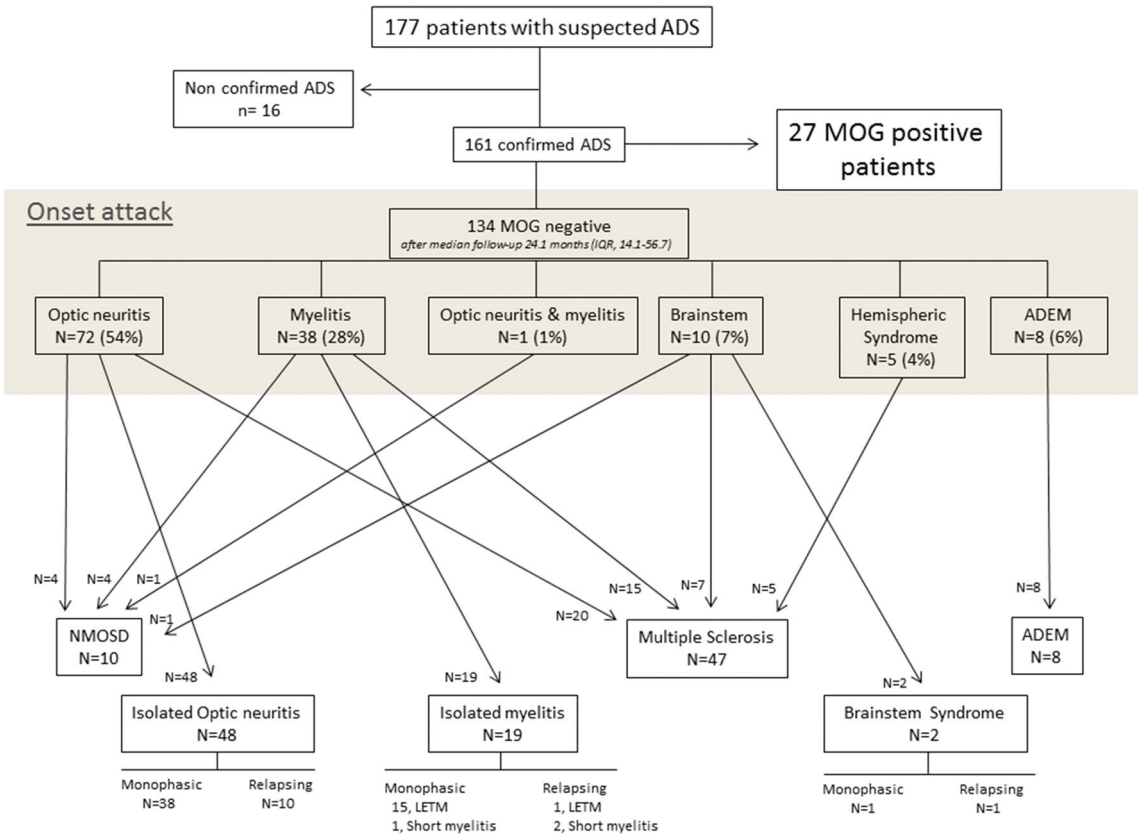

Fig. 1 Flowchart showing the clinical phenotype at onset and last follow-up in MOG seronegative patients. *ADS* acquired demyelinating syndrome, *ADEM* acute demyelinating encephalomyelitis, *NMOSD* neuromyelitis optica spectrum disorders, *LETM* longitudinal extensive transverse myelitis

Table 1 Epidemiological and clinical features in pediatric and adults MOG-Ab patients

	Total $N = 27$	Pediatrics $N = 13$	Adults $N = 14$	p value
Age, y median (range)	16.8 (1.7–64.9)	6.8 (1.7–13.8)	33.72 (16.8–64.9)	–
Female, *n* (%)	14 (51.9)	6 (46.2)	8 (57.1)	0.427
Caucasian, *n* (%)	25 (92.6)	12 (92.1)	13 (92.9)	0.741
Previous infection, *n* (%)	10 (37.0)	5 (38.5)	5 (35.7)	0.598
Other autoimmune diseases, *n* (%)	1 (3.7)	0	1 (7.1)	1.0
Follow-up, m (range)	17.8 (6.1–122.7)	14.7 (6.1–122.7)	22.9 (6.5–87.3)	0.438
Phenotype at onset				
Myelitis	9 (33.3)	3 (23.1)	6 (42.9)	**0.039**
Encephalopathy	8 (29.6)	7 (53.9)[b]	[c]1 (7.1)	
Unilateral ON	7 (25.9)	2 (15.4)	5 (35.7)	
Bilateral ON	2 (7.4)	1 (7.7)	1 (7.1)	
ON + myelitis	1 (3.7)	0	1 (7.1)	
Initial EDSS, median (range)	4 (1.0–9.0)	3.5 (2.0–6.5)	4 (1.0–9.0)	0.252
Final EDSS, median (range)	1 (0–5.5)	1 (0–5.5)	1.5 (0–4.0)	0.258
VA $\leq$ 0.2 at onset[a]	8/10 (80)	3/3 (100)	5/7 (70)	0.467
VA $\leq$ 0.2 at last visit[a]	1/10 (10)	0	1/7 (70)	0.700
Time to relapse, m median (range)	3.8 (1–33)	5.2 (1.2–33)	2.1 (1–22.5)	0.361
Relapses, *n* (%)	11 (40.7)	6 (46.2)	5 (35.7)	0.704
Relapse type				
ON	10 (37.0)	5 (38.5)	5 (35.7)	0.839
Brainstem	1 (3.7)	1 (7.7)	0	
Final diagnosis				0.237
mON	4 (14.8)	2 (15.3)	2 (14.2)	
rON	4 (14.8)	1 (7.7)	3 (21.4)	
ADEM	8 (29.6)	6 (46.2)	2 (14.2)	
mLETM	4 (14.8)	–	4 (28.5)	
m-non-LETM	1 (3.7)	1 (7.7)	–	
NMOSD	4 (14.8)	2 (15.3)	2 (14.3)	
MS	2 (7.4)	1 (7.7)	1 (7.1)	
Interval between disease onset-MOG sampling, median (range)	1.4 (0.2–112.2)	0.7 (0.2–112.16)	2.5 (0.2–63.0)	0.959
Baseline titers of MOG-Ab, median (IQR)[d]	2560 (640–6280)	2560 (2560–15.000)	40 (640–1600)	**0.020**
Acute phase treatment, *n* (%)				
i.v. MTP	26/27 (96.3)	13/13 (100)	13/14 (92.7)	0.519
i.v. IG	5/27 (18.5)	1/13 (7.7)	4/14 (28.6)	0.186
PLEX	3/27 (11.1)	1/13 (7.7)	2/14 (14.3)	0.529
Chronic therapies, *n* (%)	12/27 (44.4)	3/13 (23.08)	9/14 (64.3)	**0.054**

The values are given in bold when there are differences between adults and pediatrics ($p < 0.05$) or when there is a trend differences between both groups ($p < 0.060$)

y years, *m* months, *ON* optic neuritis, *mON* monophasic optic neuritis, *rON* relapsing ON, *ADEM* acute demyelinating encephalomyelitis, *mLETM* monophasic longitudinal extensive transverse myelitis, *m-non-LETM* monophasic non-longitudinal extensive transverse myelitis, *NMOSD* neuromyelitis optica spectrum disorder, *MS* multiple sclerosis, *EDSS* Kurtzke Expanded Disability Status Scale, *VA* visual acuity, *i.v. MTP* intravenous methylprednisolone, *i.v. IG* intravenous immunoglobulins, *PLEX* plasma exchange, *IQR* interquartile range

[a] Visual acuity is only shown in those patients presenting with an initial ON

[b] One ADEM and one MS patient presented with seizures and brainstem symptoms (ataxia + diplopia), respectively. Both patients had encephalopathy at onset

[c] The adult patient presenting with encephalopathy needed intubation. An LETM was retained in the first spinal cord MRI

[d] Only samples taken within 3 months from onset of symptoms (pediatrics, $n = 8$ and adults, $n = 8$) were used for statistical analysis

Table 2 Radiological and laboratory features in pediatric and adult patients

	Total $N = 27$	Pediatrics $N = 13$	Adults $N = 14$	p value
First brain MRI, *n* (%)				
Normal	11 (44.7)	4 (30.7)	7 (50)	0.695
Nonspecific WM lesions	9 (33.3)	5 (38.5)	4 (28.6)	
Paty's criteria	7 (25.9)	4 (30.7)	3 (21.4)	
Gad+, *n* (%)	2/15 (13.1)	0/8	2/7 (28.6)	0.200
Lesion topography, *n* (%)[a]				
Juxtacortical	8 (50)	5(55.6)	3 (42.9)	1.0
Periventricular	4 (25)	2 (22.2)	2 (28.6)	1.0
Corpus callosum	2 (12.5)	2 (22.2)	0 (0)	0.475
Putamen	4 (25)	4 (44.4)	0 (0)	0.088
Bilateral thalamic lesions	7 (43.8)	6 (66.7)	1 (14.3)	**0.060**
Cerebellar peduncle	6 (37.5)	4 (44.4)	2 (28.6)	0.633
Brainstem tegmentum	5 (31.2)	4 (44.4)	1 (14.3)	0.308
First spinal cord MRI, *n* (%)				
Normal	10/21 (47.6)	8/11 (72.7)	2/10 (20.0)	**0.015**
LETM	10/21 (47.6)	2/11 (18.2)	8/10 (80.0)	
Myelitis	1/21 (4.8)	1/11 (9.1)	0/10	
Brain ($n = 15$)/spinal cord ($n = 10$) MRI at follow-up				
Complete resolution	8 (53.3)/4 (40)	6 (66.7)/1 (33.3)	2 (33.3)/3 (42.9)	0.650
Improvement	3 (20)/2 (20)	2 (22.2)/0	1 (16.7)/2 (28.6)	
New lesions	3 (20)/3 (30)	1 (11.1)/2 (66.7)	2 (33.3)/1 (14.3)	
No change	1 (6.7)/1 (10)	0/0	1 (16.7)/1 (14.3)	
Pleocytosis (>5 cells/mm^3)	18/27 (66.7)	11/13 (84.6)	7/14 (50.0)	0.103
IgG index (>0.7)	1/22 (4.6)	1/10 (10.0)	0/12 (0)	0.455
Proteins mg/L mean (SD)	0.5 (0.31)	0.43 (0.35)	0.56 (0.26)	**0.036**
OCB, *n* (%)	3/25 (12.0)	2/12 (16.7)	1/13 (7.7)	0.593

The values are given in bold when there are differences between adults and pediatrics ($p < 0.05$) or when there is a trend differences between both groups ($p < 0.060$)

WM white matter, *Gad+* gadolinium enhancement, *MRI* magnetic resonance imaging, *LETM* longitudinally extensive transverse myelitis, *OCB* oligoclonal bands

[a] Among the 16 patients (9 pediatrics and 7 adults) presenting with an initial abnormal brain MRI

patient showed T2-W patchy non-extensive lesions with gadolinium enhancement. Complete resolution or improvement of the spinal cord lesions was observed in 6 (60%) of these patients (Table 2).

All but one patient were under intravenous (i.v.) methylprednisolone (MTP) at the acute phase of disease, and steroids were further gradually tapered over next months. Immunosuppressive or immunomodulatory therapies were started in 12 patients (44.4%): mycophenolate mofetil in seven, azathioprine in two and rituximab in one patient. One MS patient was under teriflunomide, and the other received glatiramer acetate being further switched to natalizumab due to lack of efficacy (clinical and radiological features of MS patients are depicted in Table 3 and Fig. 2; case description in the supplementary material).

We were able to test MOG-Ab during the follow-up in eight patients [median 7.1 months (IQR 2.2–11.3)]. Seven patients tested positive (three patients with relapsing ON, two NMOSD, one monophasic LETM and one ADEM) and one was negative (monophasic non-LETM).

At last visit, 23 (85.2%) had a good clinical outcome with a median EDSS of 1 (IQR 0–2.0), and only one patient with an initial clinical phenotype of unilateral ON persisted with severe visual sequelae, after 45 months of follow-up.

Comparison between MOG-Ab-positive pediatric and adult groups

No differences regarding gender and previous infections or vaccinations were observed between pediatric and adults. One adult had a previous myasthenia gravis.

Clinical phenotype at onset was more frequently characterized by encephalopathy in pediatrics than in adults [7/13 (53.9%) vs 1/14 (7.1%), $p = 0.013$]. On the contrary, myelitis

Table 3 Clinical features of multiple sclerosis patients

ID	Gender/age (y)	Disease duration (y)	Clinical phenotype at onset	Relapse type (number of relapses)	First brain MRI	Second brain MRI	CSF cells/mm^3 OCB	Final EDSS	Acute/chronic therapy	MOG-Ab serum titer
MS. 1	Female, 21	1.5	Unilateral ON (VA = 0.1)	ON (×3, before TR)	Juxtacortical and periventricular WM lesions	New WM periventricular lesions	9 cells OCB+	2.0	i.v MTP/TR	1:640
MS. 2[a]	Male, 5	7	Brainstem syndrome Encephalopathy	Brainstem syndrome (×2, after GA)	Mesencephalic lesion, juxtacortical WM and putaminal left lesions	New juxtacortical and periventricular WM lesions	19 cells OCB+	2.0	i.v MTP/GA NTZ	1:20.000

y years, *MRI* magnetic resonance imaging, *CSF* cerebrospinal fluid, *EDSS* Kurtzke Expanded Disability Status Scale, *ON* optic neuritis, *VA* visual acuity, *MS* multiple sclerosis, *OCB+* presence of oligoclonal bands, *WM* white matter, *i.v. MTP* intravenous methylprednisolone, *TR* teriflunomide, *GA* glatiramer acetate, *NTZ* natalizumab, *MOG* myelin oligodendrocyte glycoprotein

[a] Patient MS. 2 was switched to NTZ after two brainstem syndrome relapses under GA, and remained free from further MS clinical or radiological activity

was the initial phenotype in only three pediatrics (23.1%) and seven (50%) adults (Table 1).

When performing MOG-Ab titers, titers were significantly higher in the pediatric group [2560 (IQR 2560–20.000)] compared to adults [640 (IQR 640–2560)], $p = 0.020$ (Table 1; supplementary Fig. 1).

There were no differences with respect to the proportion of patients with an abnormal brain MRI at onset between both groups. However, six out of nine (66.7%) children disclosed bilateral thalamic lesions compared to only one (14.3%) adult, among patients with an initial abnormal brain MRI ($p = 0.060$) (Table 2).

In terms of severity at last follow-up, there were no differences, and both groups evolved with a general good outcome.

Comparison between ADEM MOG-Ab-positive and ADEM MOG-Ab negatives

We noted that among the ADEM MOG-Ab-positive patients ($n = 8$), 7 (87.5%) disclosed bilateral thalamic lesions in the first brain MRI in comparison with only one patient in the ADEM MOG-Ab-negative group ($p = 0.010$). We did not find other epidemiological or clinical differences between these two groups (Table 4).

MOG-Ab-positive patients with uncommon presentations

Unusual presentations were observed in three MOG-Ab-positive patients: (1) one presented with patchy gadolinium-enhancing lesions along the whole spinal cord; (2) one had an underlying ovarian teratoma associated with ADEM; (3) one presented with status epilepticus at onset of symptoms (Table 5; Fig. 2; supplementary data for case description).

Discussion

The present study encompassed a cohort of 27 MOG-Ab-positive patients presenting with an initial CNS demyelinating episode. Patients developed general features of MOG-Ab spectrum diseases characterized by young age at onset, ON and a general good outcome.

Although the MOG-Ab clinical spectrum seems to be highly restricted to ADEM or limited NMO-like phenotypes, two patients were diagnosed with MS: one adult developed a relapsing severe ON with typical MS-like brain lesions, and one pediatric patient presented with a relapsing brainstem syndrome. Despite that the latter relapsed under glatiramer acetate, both showed a good response to natalizumab and teriflunomide. The diagnostic classification in the pediatric MS may be a matter of discussion since the patient would

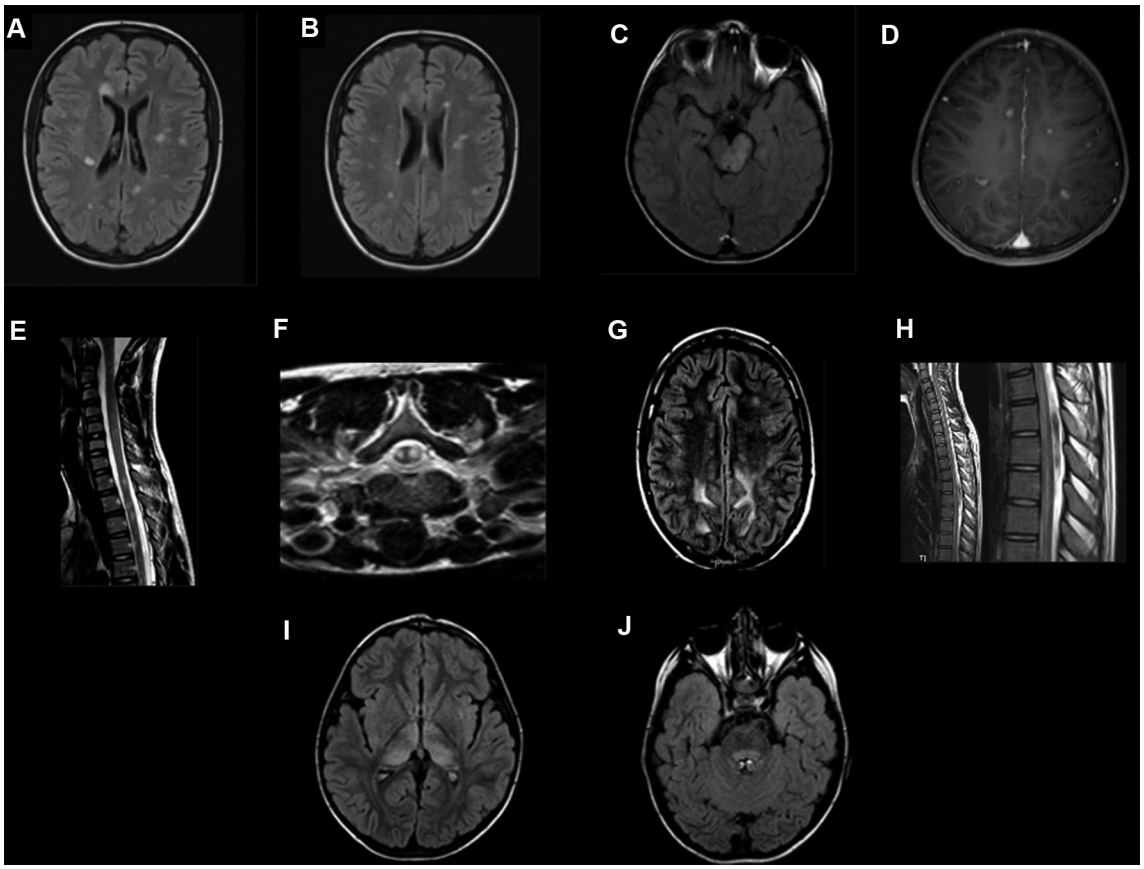

Fig. 2 Radiological features of MOG antibodies-positive patients with MS and uncommon features. Patient MS 1 **a**, **b** showed typical MS-like lesions; patient MS 2, **c** showing mesencephalic and **d** gadolinium-enhancing MS-like lesions; patient ID 1 **e** patchy T2-W spinal cord hyperintensities and **f** gadolinium-enhancing lesions; patient ID 2 with underlying teratoma, **g** diffuse occipital white matter brain FLAIR hyperintensities and **h** extensive T2-W spinal cord lesion; patient ID 3 **i**, symmetric bilateral thalamic lesions and **j** tegmental FLAIR hyperintensities

have been diagnosed by others as multiphasic ADEM [4]. One recent study has found that up to 13% of MOG-Ab-positive patients may have OCB in CSF and up to 33% fulfill 2010 McDonald criteria [9]. Whether MOG-Ab-positive patients fulfilling the current McDonald criteria should be classified as MS is still under debate. Moreover, it has been suggested that MS patients with MOG-Ab share distinctive clinical features, characterized by severe or recurrent ON, brainstem syndrome and myelitis [24]. Patients also presented with a high relapse rate and did not properly response to disease-modifying therapies. Overall, MOG-Ab-related disorders are newly described, and further studies are needed to clarify classification, prevalence, phenotypical features and therapeutic options in MS patients with MOG-Ab.

MOG-Ab-related disorders were previously known for having fewer relapses in comparison to AQP4-Ab-positive patients [6–8]. We underline that up to 40% of patients relapsed in our study, despite the relatively short follow-up duration. Not unexpected, relapses involved the optic nerve in all but one patient. Moreover, we also found that most of the relapses occurred within 8 months after disease onset. In line with our observation, a recent study supports that most of MOG-Ab-positive patients will develop a relapse disease course, having the second attack only few months after the disease onset [9]. A dependency on steroids has been previously noted in MOG-Ab-related disorders [25, 26], and steroids cessation may have been related to the short time to relapse in the present study. Although controlled prospective studies evaluating the optimal therapeutic options are not available in MOG-Ab-related disorders, we believe that the prompt introduction of an immunosuppressant therapy together with an individualized steroid tapering could have a beneficial effect in reducing the number of further episodes.

In the present study, we noted that most of patients presenting with ON developed a severe initial visual impairment, and three adults presented with a fulminant motor attack. MOG-Ab-positive patients with a high degree of disability at onset have been described, leading in some cases to neurologic sequelae or even death [9, 15, 16, 25, 27]. In the present cohort, 15% of patients remained disabled at

Table 4 Epidemiological and radiological features in ADEM MOG-antibody positive and negative patients

	Total ADEM $N = 16$	ADEM MOG-positive $N = 8$	ADEM MOG-negative $N = 8$	p value
Epidemiological features				
Age, y median (range)	7.4 (1.7–59.9)	6.12 (1.7–53.1)	11.7 (4.2–59.9)	0.749
Female, *n* (%)	6 (37.5)	4 (50)	2 (25)	0.608
Caucasian, *n* (%)	16 (100)	8 (100)	8 (100)	1.0
Time onset-MOG sampling, m median (range)	0.5 (0.1–117.1)	0.5 (0.2–112.2)	0.4 (0.1–117.1)	0.600
Relapses, *n* (%)	2 (13.5)	2 (25)	0	0.467
Final EDSS, median (range)	1 (0–8.0)	1 (0–2.5)	0.5 (0–8.0)	0.652
MRI features				
First brain MRI, *n* (%)				
Nonspecific WM lesions	8 (50)	6 (75)	2 (25)	0.212
Paty's criteria	8 (50)	2 (25)	6 (75)	
Gad+, *n* (%)	2 (12.5)	0	2 (25)	0.467
Lesion topography				
Juxta cortical	8 (50.0)	3 (37.5)	5 (62.5)	0.619
Periventricular	8 (50)	3 (37.5)	5 (62.5)	0.619
Corpus callosum	3 (18.8)	2 (25)	1 (12.5)	1.0
Putamen	6 (37.5)	3 (37.5)	3 (37.5)	1.0
Bilateral thalamic lesions	8 (50)	7 (87.5)	1 (12.5)	**0.010**
Cerebellar peduncle	7 (43.8)	3 (37.5)	4 (50)	1.0
Brainstem tegmentum	4 (25)	3 (37.5)	1 (12.5)	0.294
CSF features				
Pleocytosis (>5 cells/mm^3)	12/15 (80)	8/8 (100)	4/7 (57.1)	0.077
Index IgG (>0.7)	3/10 (30)	1/5 (20)	2/5 (40)	0.524
OCB, *n* (%)	1/12 (8.3)	1/6 (16.7)	0/6 (0)	1.0

The value is given in bold when there are differences between adults and pediatrics ($p < 0.05$) or when there is a trend differences between both groups ($p < 0.060$)

y years, *m* months, *ADEM* acute demyelinating encephalomyelitis, *WM* white matter lesions; *EDSS* Kurtzke Expanded Disability Status Scale, *CSF* cerebrospinal fluid, *MRI* magnetic resonance imaging, *Gad+* gadolinium enhancement, *OCB* oligoclonal bands

last visit, reinforcing the need to identify prognostic factors at onset in order to select those individuals at high risk of disability where more aggressive acute treatments, such as plasma exchange, could be beneficial.

The encephalopathic onset of symptoms seems to be directly related to the bilateral thalamic affection observed in all but one ADEM MOG-Ab-positive. Bilateral thalamic lesions are described up to 63% of ADEM patients, occurring more frequently in pediatrics than adults [28, 29]. These patients are characterized by showing a complete resolution of the brain lesions and experiencing a good prognosis. In the only study focused on the radiological features of ADEM MOG-Ab-positive patients, up to 89.5% of patients presented with lesions either in thalamus or basal ganglia [3]. Other interesting radiological findings were the presence of brainstem lesions involving the pontine tegmentum in one-third of patients, as others have remarked [13, 25]. Whether there is a predilection for selected anatomical brain areas in MOG-Ab-related disorders is a matter of controversy. Age-related radiological differences could be the result of different myelination stages in the course of development [30].

Interestingly, MOG-Ab titers were found higher in pediatrics compared to adults, as a result of an ADEM overrepresentation within this former group. This finding suggests a more intense underlying immunity against MOG protein and reflects the more extensive affection, both clinical and radiological, observed in younger patients [3, 11].

The presence of uncommon clinical or radiological features in some MOG-Ab-positive patients must be pointed out, since MOG-Ab-related disorders is a recent entity, and the clinical spectrum is likely not to be entirely described. One patient presented with an atypical spinal image characterized by patchy gadolinium-enhancing lesions along the whole spinal cord. Thus, although LETM and less frequently partial myelitis have been related to MOG-Ab-related disorders [6, 8, 9, 13, 22], clinicians should

Table 5 Description of uncommon features in three MOG antibody-positive patients

Identification/ uncommon feature	Gender/ age (years)	Follow-up (months)	MOG-Ab serum titers	Pathological background	Clinical phenotype at onset	Other clinical remarks	New episode	Initial/ final EDSS	CSF cells/ mm^3 OCB	Initial brain MRI	Initial spinal cord MRI	Acute/ chronic therapy	Second brain/spinal cord MRI	Final diagnosis
ID. 1 Spinal cord patchy pattern	Male, 13	12	1:640	Atopic dermatitis	Myelitis	Back pain Walking troubles	No	4.5/1.0	8 cells OCB: –	Peduncular lesion Subcortical and WM lesions	Patchy gadolinium enhancement lesions C4–T11	i.v MTP/ no	Complete resolution (at day 45)	Monophasic myelitis
ID. 2[a] Ovarian teratoma	Female, 16	13	1:640	Non	Encephalopathy	Fever, vomits, urinary retention Needing intubation	No	9/2.5	62 cells OCB: n.d	Periventricular and subcortical WM lesions	LETM C2–T12	i.v Ig/no	Complete resolution (after 1 month)	Monophasic ADEM
ID. 3 Status epilepticus	Male, 3	24	1:2560	Non	Encephalopathy TC seizures with no consciousness recovery between episodes	Pharyngeal inflammation Fever	No	Glasgow 8/no symptom	55 cells OCB: n.d	Thalamic and tegmental brainstem lesions	–	No	Complete resolution (after 6 months)	Monophasic ADEM

ID identification, *CSF* cerebrospinal fluid, *EDSS* Kurtzke Expanded Disability Status Scale, *OCB* oligoclonal bands, *MRI* magnetic resonance imaging, *WM* white matter, *TC* tonic–clonic, *n.d.* not done, *IV MTP* intravenous methylprednisolone, *i.v. Ig* intravenous immunoglobulins, *ADEM* acute demyelinating encephalomyelitis

* A complete autoimmune, infectious and metabolic diagnostic workup was realized in all patients with a negative result other than serum MOG-Ab positivity

[a] *N*-Methyl-D-aspartate receptor (NMDA-R) antibodies were negative both in serum and CSF

also be aware of other spinal cord inflammatory lesions in these patients. Interestingly, an underlying teratoma was found in one ADEM MOG-Ab-positive patient presenting with severe clinical symptoms other than those typical for *N*-Methyl-D-aspartate receptor (NMDA-R) encephalitis. Contrary to the often existing overlapping observed between demyelinating syndromes and NMDA-R encephalitis [31], neither serum nor CSF NMDA-R antibodies were found. There is only a previous case reported of ovarian teratoma in patients with MOG-Ab [9]. Whether mechanisms of breakdown of immunologic tolerance or mimicry towards MOG protein expressed in the teratoma are involved in the present case are unknown, so far. Finally, we should keep in mind that in spite of their general good prognosis observed, MOG-Ab-related disorders may initiate with a live threatening picture in form of status epilepticus, requiring intubation and careful monitoring.

Altogether, we observe that MOG-Ab related disorders share common clinical and prognostic features that may differ between adults and pediatrics at onset. Since this is a recently described entity, MOG-Ab encompasses a clinical and radiological spectrum much wider than recently reported.

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Compliance with ethical standards

Conflicts of interest Cobo-Calvo, Ruiz, d'Indy, Poulat, Carneiro, Nicolas and Desportes report no disclosures. Durand-Dubief serves on scientific advisory board for Merck Serono and has received funding for travel and honoraria from Biogen Idec, Merck Serono, Novartis, Sanofi-Genzyme, Roche and Teva. Deiva received travel funding from Biogen Idec, Merck Serono, and Genzyme. Vukusic has received consulting and lecturing fees, travel grants and research support from Biogen, Geneuro, Genzyme, Novartis, Merck Serono, Roche, Sanofi Aventis and Teva Pharma. Marignier serves on scientific advisory board for MedImmune and has received funding for travel and honoraria from Biogen Idec, Merck Serono, Novartis, Sanofi-Genzyme and Teva.

Ethical standards The ethics committee of Lyon University Hospital approved this study. All samples were stored at −80 °C at Neurobiotec (Hospices Civils de Lyon, France, no. 0033-00046, AC-2013-1867, NFS96-900).

Informed consent Informed consent for storage and use of these samples for research was obtained from all patients.

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