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Temporal Dynamics of MOG Antibodies in Children With Acquired Demyelinating Syndrome

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Abstract

Background and Objective

The spectrum of myelin oligodendrocyte glycoprotein (MOG) antibody-associated disorder (MOGAD) comprises monophasic diseases such as acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), and transverse myelitis and relapsing courses of these presentations. Persistently high MOG antibodies (MOG immunoglobulin G [IgG]) are found in patients with a relapsing disease course. Prognostic factors to determine the clinical course of children with a first MOGAD are still lacking. The objective of the study is to assess the clinical and laboratory prognostic parameters for a risk of relapse and the temporal dynamics of MOG-IgG titers in children with MOGAD in correlation with clinical presentation and disease course.

Methods

In this prospective multicenter hospital-based study, children with a first demyelinating attack and complete data set comprising clinical and radiologic findings, MOG-IgG titer at onset, and

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BIOMARKER Study Group coinvestigators are listed in the appendix at the end of the article.

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Glossary

ADEM = acute disseminated encephalomyelitis; **ADEMON** = acute disseminated encephalomyelitis, followed by optic neuritis; **ADS** = acute/acquired demyelinating syndrome; **DMT** = disease-modifying therapy; **EDSS** = expanded disability status scale; **FU** = follow-up; **IgG** = immunoglobulin G; **IQR** = interquartile range; **IVIG** = intravenous immunoglobulin; **MDEM** = multiphasic acute disseminated encephalomyelitis; **MOG** = myelin oligodendrocyte glycoprotein; **MOGAD** = MOG-IgG associated disorder; **NMOSD** = neuromyelitis optica spectrum disorder; **OCBs** = oligoclonal bands; **ON rec** = recurrent optic neuritis; **ON** = optic neuritis; **PLEX** = plasma exchange; **TM** = transverse myelitis.

clinical and serologic follow-up data were included. Serum samples were analyzed by live cell-based assay, and a titer level of $\geq 1:160$ was classified as MOG-IgG-positive.

Results

One hundred sixteen children (f:m = 57:59) with MOGAD were included and initially diagnosed with ADEM (n = 59), unilateral ON (n = 12), bilateral ON (n = 16), myelitis (n = 6), neuromyelitis optica spectrum disorder (n = 8) or encephalitis (n = 6). The median follow-up time was 3 years in monophasic and 5 years in relapsing patients. There was no significant association between disease course and MOG-IgG titers at onset, sex, age at presentation, or clinical phenotype. Seroconversion to MOG-IgG-negative within 2 years of the initial event showed a significant risk reduction for a relapsing disease course. Forty-two/one hundred sixteen patients (monophasic n = 26, relapsing n = 16) had serial MOG-IgG testing in years 1 and 2 after the initial event. In contrast to relapsing patients, monophasic patients showed a significant decrease of MOG-IgG titers during the first and second years, often with seroconversion to negative titers. During the follow-up, MOG-IgG titers were persistently higher in relapsing than in monophasic patients. Decrease in MOG-IgG of ≥ 3 dilution steps after the first and second years was shown to be associated with a decreased risk of relapses. In our cohort, no patient experienced a relapse after seroconversion to MOG-IgG-negative.

Discussion

In this study, patients with declining MOG-IgG titers, particularly those with seroconversion to MOG-IgG-negative, are shown to have a significantly reduced relapse risk.

During the last years, myelin oligodendrocyte glycoprotein (MOG)-IgG associated disorder (MOGAD), a newly defined entity of acquired demyelinating syndromes (ADS), has gained increasing attention. MOGAD presents with different clinical phenotypes, including monophasic diseases such as acute disseminated encephalitis (ADEM), optic neuritis (ON), transverse myelitis (TM) or rarely with (brainstem) encephalitis, or with a relapsing, non-MS disease course such as multiphasic ADEM (MDEM) or recurrent ON (rec ON).¹⁻⁶ ADEM is the predominant clinical phenotype in younger children, whereas older children tend to present with ON and/or TM.^{1,7,8} MOG-IgG are directed against the myelin oligodendrocyte glycoprotein located at the outer membrane of the myelin sheath. They are mainly of the IgG1 subtype, induce complement-mediated cytotoxicity in vitro, and transiently disrupt microtubule organization of oligodendrocyte.^{9,10} Prognostic factors to determine the clinical course of children with a first MOGAD are still lacking. In adults, male patients are described to have a lower risk of relapse, whereas ON/TM at any point proved to be associated with a higher risk of relapsing disease.^{8,11} A decline of high MOG-IgG titer in children with monophasic ADEM was already described in 2011 in a small cohort of pediatric patients¹² and other studies.^{1,13} In children with relapsing forms such as MDEM and acute disseminated encephalomyelitis, followed by optic neuritis (ADEMON), high and persisting MOG-IgG titers were observed.^{2,14} The

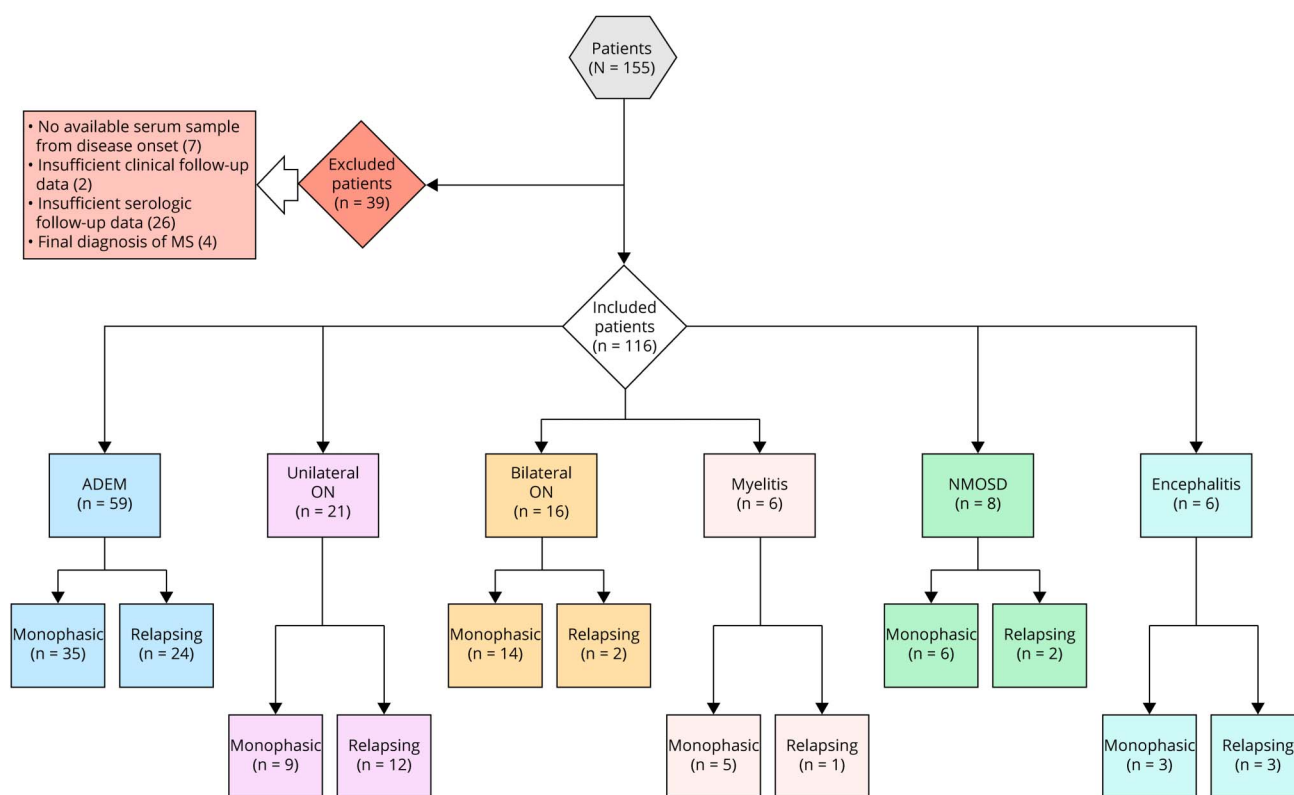
titer of MOG-IgG at the initial event has no prognostic value for the subsequent clinical course, but persisting high MOG-IgG titers are associated with a high risk of clinical relapses.^{1,2,14} In this study, we analyzed demographic and clinical features and the temporal dynamics of MOG-IgG titers in a large cohort of children with monophasic or relapsing ADS to determine the prognostic factors for relapsing disease.

Methods

Patients

Between 2009 and 2020, more than 1,000 pediatric patients with a suspected ADS were recruited for the testing of MOG and aquaporin-4 antibodies as part of our BIOMARKER study. Serum samples were sent to us from different medical centers in Germany, Austria, Switzerland, Lithuania, Turkey, Canada, Sweden, Egypt, Croatia, Argentina, Great Britain, Ukraine, and Italy and analyzed in the neurologic research laboratory of the University of Innsbruck, Austria. One hundred seventy-two patients presenting with a first ADS were tested positive for MOG-IgG at disease onset. In 155 patients, clinical and serologic follow-up was available. One hundred sixteen children were finally included fulfilling the following inclusion criteria for this study (Figure 1): (i) a complete data set of the first manifestation including clinical presentation, cerebral MRI scan, and CSF studies (oligoclonal bands [OCBs] and cell count) at

Figure 1 MOG-IgG-Positive Pediatric Patients With Clinical Presentation at the First Event and After at Least 24 Months



116/155 MOG-IgG-positive pediatric patients were included in the study. Fifty-nine patients presented with ADEM, 21 patients with unilateral ON, 16 patients with bilateral ON, 6 patients with myelitis, 8 patients with NMOSD, and 6 patients with encephalitis. After at least 24 months of a clinical follow-up, further relapses have occurred in 24 patients with ADEM, 12 patients with unilateral ON, 2 patients with bilateral ON, 1 patient with myelitis, 2 patients with NMOSD, and 3 patients with encephalitis. Thirty-nine/155 patients had to be excluded because of the following reasons: no available serum sample from disease onset ($n = 7$), insufficient clinical ($n = 2$) or serologic ($n = 26$) follow-up data, or a final diagnosis of MS ($n = 4$). ADEM = acute disseminated encephalomyelitis; IgG = immunoglobulin G; MOG = myelin oligodendrocyte glycoprotein; NMOSD = neuromyelitis optica spectrum disorder; ON = optic neuritis.

onset, (ii) serial MOG-IgG testing more than 3 months after the initial event, and (iii) a clinical follow-up of at least 24 months with final diagnosis, clinical outcome assessed using expanded disability status scale (EDSS), and treatment information. Visual impairments during the follow-up were indicated by pathologic visual evoked potential, color vision/saturation disorder, and/or visual acuity disorder. In a second step, we assessed the temporal dynamics of MOG-IgG abs. Therefore, a subgroup of 42 patients with serial MOG-IgG testing in both years 1 (months 6–12) and 2 (months 18–24) were further analyzed.

Clinical data at onset and clinical follow-up data were obtained using a standardized questionnaire or the medical discharge summary from the referring physician. In patients with relapsing disease course, interval to first relapse and the number of relapses were reported. According to the revised International Pediatric Multiple Sclerosis Study Group criteria,¹⁵ clinical or MRI changes within 3 months of the initial event were not considered as relapses. Hence, serial samples taken within 3 months of the initial event were not included in our analysis. Thirty-nine/one hundred fifty-five patients (20 females and 19 males) had to be excluded because of the following reasons: no available serum sample from disease onset ($n = 7$),

insufficient clinical ($n = 2$) or serologic ($n = 26$) follow-up data, or a final diagnosis of MS ($n = 4$). Excluded patients had a median age of 5 years (interquartile range [IQR]: 3–10 years).

Demographic, clinical, and MRI findings of 72 children from this cohort were reported already in 6 studies.^{1–3,16–18} We decided to include these children because of new available clinical data and additional serum samples (e.g., further relapses).

Serum MOG-IgG Status and CSF Studies

Serum samples from all patients included in the study were analyzed for the presence of MOG-IgG by live cell-based immunofluorescence assays. MOG-IgG were tested using full-length MOG (alpha-1 isoform) and IgG (heavy and light chains, Dianova)-specific secondary antibodies. Screening was performed at dilutions of 1:20 and 1:40 by at least 2 independent clinically blinded investigators, and positive serum samples were further diluted in 2-fold increments to determine the endpoint titers. Titer levels of $\geq 1:160$ were classified as MOG-IgG-positive and confirmed using a second assay with an IgG(Fc)-specific secondary antibody (Dianova), as previously described.¹⁹ Seronegativity was

Table 1 Demographic, Clinical, and Laboratory Findings at First Presentation

	ADEM	ON uni	ON bil	Myelitis	NMOSD	Encephalitis	<i>p</i> Value
No. of children	59 (51%)	21 (18%)	16 (14%)	6 (5%)	8 (7%)	6 (5%)	
Females:males	26:33	15:6	7:9	2:4	5:3	2:4	0.241 ^c
Age (y)^a	4 (3–8)	11 (8–12)	8 (6–12)	7 (5–9)	7 (5–13)	9 (4–13)	<0.001 ^d
Onset mono: poly symptomatic	0: 59	19:2	11:5	1:5	0:8	0:6	<0.001 ^c
MOG-IgG titer^a	1,280 (640–5,120)	1,280 (640–2,560)	2,560 (640–2,560)	2,560 (640–5,120)	640 (160–1,280)	640 (320–1,280)	0.143 ^d
CSF cells/μL^{a,b}	47 (12–93)	1 (0–7)	5 (1–29)	65 (27–109)	46 (31–77)	49 (21–136)	<0.001 ^d
CSF OCB^b	9/53 (17%)	3/20 (15%)	2/15 (13%)	1/6 (17%)	1/7 (14%)	2/6 (33%)	0.926 ^c

Abbreviations: ADEM = acute disseminated encephalomyelitis; IgG = immunoglobulin G; MOG = myelin oligodendrocyte glycoprotein; NMOSD = neuro-myelitis optica spectrum disorder; ON bil = bilateral optic neuritis; ON uni = unilateral optic neuritis.

In 2 patients with unilateral and 5 patients with bilateral ON, additional minor neurologic or vegetative symptoms (e.g., headache, neuasea) were reported. In 5 patients with myelitis, different neurologic symptoms such as limb weakness, paresthesia, or bladder dysfunction were reported.

^a Median (interquartile range).

^b CSF data were available from 107 children.

^c Statistically compared using the χ^2 test.

^d Statistically compared using the Kruskal-Wallis test.

defined as an MOG-IgG titer of less than 1:160. In MOG-IgG–positive patients, the difference of more than 1 step in antibody titers was classified as significant.

MOG-IgG status was assessed in 592 serum samples. MOG-IgG titers from samples obtained within 1 month from clinical onset were used to determine the serologic status at presentation. Serial MOG-IgG testing was performed at least 4 months after disease onset. If possible, serum samples were accompanied by information whether taken during a relapse or a routine follow-up. At initial presentation, the presence of OCBs was assessed by isoelectric focusing as part of diagnostic evaluation in most patients ($n = 106/116$). Positive OCBs were defined by ≥ 2 bands.

Standard Protocol Approvals, Registrations, and Patient Consents

The study has been approved by the Ethics Committee of the University Witten/Herdecke, Germany, and the Ethics Committee of the University of Innsbruck, Austria. All patients and parents gave informed written consent.

Statistical Analysis

Demographic, clinical, and laboratory findings at onset were compared by univariate statistical tests (the χ^2 and Kruskal-Wallis tests). The predictive role of clinical and immunologic parameters at onset with the disease course at follow-up (monophasic vs relapsing) was analyzed through Cox regression analysis using the enter model with all parameters entered at the first step. The association of serial MOG-IgG titers with the disease course at the last follow-up was analyzed with univariate statistical tests (the χ^2 test, the Fisher exact test, and the Friedman test with Dunn multiple comparisons). Ninety-five percentage CIs of proportions were calculated using the Wilson/Brown method and differences between

proportion (attributable risk) using the Newcombe/Wilson score. Significance was defined as 2-sided p value < 0.05 , and p values were corrected for multiple comparisons if necessary. Statistical analyses were performed using IBM SPSS software (IBM SPSS Statistics; Version 27.0. Armonk, NY: IBM Corp.) or GraphPad Prism 9 (GraphPad Software, La Jolla, CA).

Data Availability

The data set used and analyzed during this study is included in the main text and the supplementary files.

Results

Demographic Data and Diagnoses at Onset

One hundred sixteen children with a clinical follow-up of more than 2 years were included in the study (57 females and 59 males) with a median age at onset of 7 years (IQR 4–12 years). All demographic, clinical, and laboratory findings at first presentation are summarized in Table 1.

Clinical Course of Children With MOGAD During Follow-Up

The overall median clinical follow-up was 3.6 years, IQR 2.3–5.8. The median clinical follow-up of the 72 children with a monophasic course was significantly shorter (median 3 years, IQR 2–5) compared with 44 children with a relapsing course (median 5 years, IQR 3–7; $p < 0.001$). Twenty-nine (66%) of the 44 children with a relapsing course had a first relapse within the first year after a median of 0.5 years (IQR 0.4–1.1 years). In most of the children ($n = 28$, 64%), recurrent ON was the most frequent type of relapse. In relapsing patients, 75% (18/24) of female and 55% (11/20) of male patients experienced their first relapse in the first year

Table 2 Predictive Factors at Onset for a Relapsing Disease Course

	Monophasic	Relapsing	Predictor (95% CI)	p Value
No. of children	72 (62%)	44 (38%)		
Time to relapse/last follow-up (y)^a	3.0 (2.0–4.8) ^b	0.5 (0.4–1.1)		
Clinical follow-up (y)^a	3.0 (2.0–4.8) ^c	5.1 (3.0–7.2) ^c		
MOG-IgG onset^a	1,280 (640–5,120)	1,280 (640–5,120)	1.00 (1.00)	0.291
Sex				
Males	39 (66%)	20 (34%)	Reference	
Females	33 (58%)	24 (42%)	1.24 (0.67–2.32)	0.493
Age (y)^a	7 (4–12)	7 (4–10)	0.99 (0.91–1.07)	0.754
Diagnosis at onset				
ADEM	35 (59%)	24 (41%)	Reference	
Unilateral ON	9 (43%)	12 (57%)	1.88 (0.51–6.90)	0.339
Bilateral ON	14 (88%)	2 (12%)	0.31 (0.06–1.65)	0.168
Myelitis	5 (83%)	1 (17%)	0.37 (0.05–2.77)	0.330
NMOSD	6 (75%)	2 (25%)	0.53 (0.12–2.32)	0.396
Encephalitis	3 (50%)	3 (50%)	1.49 (0.43–5.10)	0.528
Presentation at onset				
Monosymptomatic	20 (61%)	13 (39%)	Reference	
Polysymptomatic	52 (63%)	31 (37%)	1.18 (0.37–3.76)	0.781

Abbreviations: ADEM = acute disseminated encephalomyelitis; IgG = immunoglobulin G; MOG = myelin oligodendrocyte glycoprotein; NMOSD = neuromyelitis optica spectrum disorder; ON = optic neuritis.

The predictive role of clinical and immunologic parameters at onset with the disease course at follow-up (monophasic vs relapsing) was analyzed through Cox regression analysis using the enter model with all parameters entered at the first step.

^a Median with interquartile range (25th–75th percentile).

^b Censored.

^c Minimal clinical follow-up, 2 y.

after the initial event. Relapsing female patients had a median of 4 (IQR 3–4) relapses throughout the course of the study, whereas male patients had a median of 2 (IQR 2–3) relapses. The median time to first relapse was also shorter in female (0.5, IQR 0.4–0.9) as in male patients (0.9, IQR 0.3–1.1).

Predictive Factors for a Relapsing Disease Course at Onset

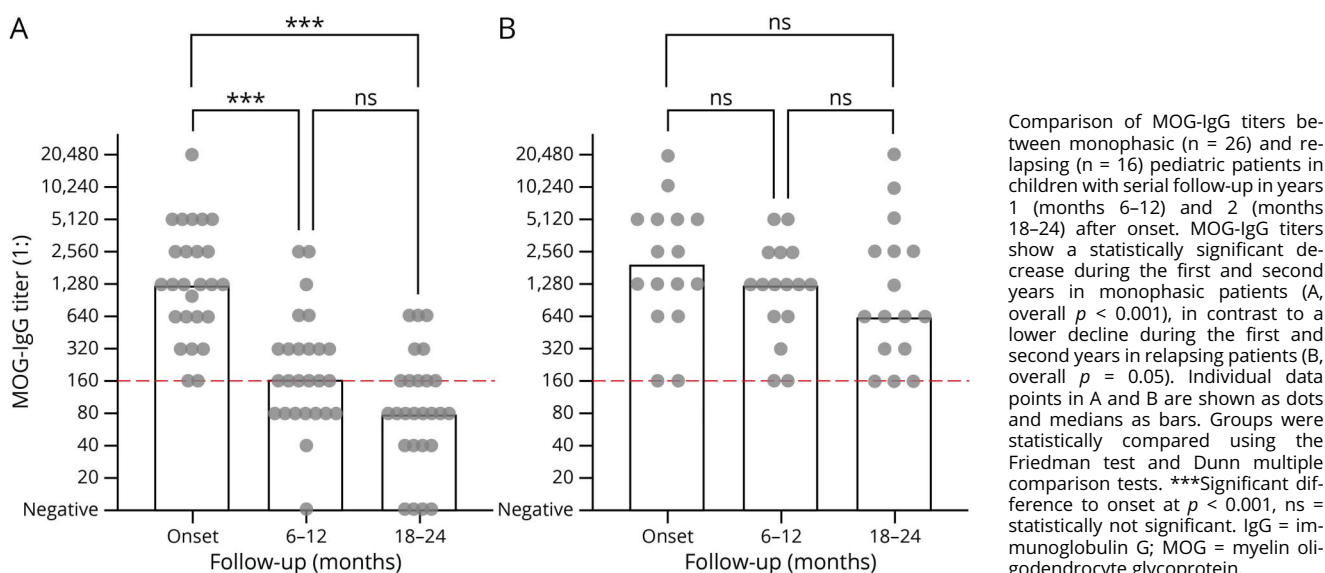
To correct the differences in the clinical follow-up between monophasic and relapsing patients, we used Cox regression analysis for time to relapse to analyze predictive factors for a relapsing disease course. Sex, age, or presentation at onset showed no significant correlation with the disease course (Table 2). A monophasic disease course was more often observed in patients who initially presented with bilateral ON (88%), myelitis (83%), or neuromyelitis optica spectrum disorder (NMOSD) (75%), whereas patients presenting with ADEM (59%), unilateral ON (43%), and encephalitis (50%) showed a rather balanced percentage of monophasic and relapsing disease courses. There was no difference in MOG-IgG

titers at onset between monophasic and relapsing patients. In a subset of 107 children with complete CSF data, CSF cell count and OCBs were also included in the model but showed no significant association with the disease course (eTable 1, links.lww.com/NXI/A744).

Temporal Dynamics of MOG-IgG Status

Forty-two of 116 patients (monophasic n = 26, relapsing n = 16) had available serial follow-up testing in both years 1 (months 6–12) and 2 (months 18–24) after onset and were therefore included in our analysis assessing MOG-IgG titer dynamics overtime. MOG-IgG titers did show a statistically significant decrease during the first and second years in monophasic patients, in contrast to a lower decline during the first and second years in relapsing patients. MOG-IgG titers remained persistently higher in relapsing (the median at last follow-up [FU] 1:80, range 0–640) than in monophasic patients (the median at last FU 1:640, range 160–20480) (Figure 2). This subgroup was representative for the entire study population (eTable 2, links.lww.com/NXI/A744).

Figure 2 Comparison of MOG-IgG Titers During Disease Course Between Monophasic and Relapsing Pediatric Patients



A significantly higher percentage of seroconversion to MOG-IgG–negative was observed in monophasic patients: 35% of monophasic patients had a seroconversion to MOG-IgG–negative in the first year and 62% in the second year. By contrast, not a single patient with a relapsing disease course converted to a seronegative status within 2 years after the initial event (Table 3). A seroconversion to MOG-IgG–negative in the first year is associated with a 48% (95% CI 7–66) risk reduction for a relapsing disease course; in the first 2 years, it is even associated with a 62% (95% CI 30–79) risk reduction. From Table 3, it is also evident that a decrease in MOG-IgG of ≥ 3 dilution steps (e.g., 1:640–1:80) after the first and second years is associated with a decreased risk of a relapsing disease course.

In relapsing patients, no further relapses occurred after seroconversion to MOG-IgG–negative until the end of the clinical follow-up. The median time of seroconversion in relapsing patients with seroconversion was 45 months (IQR 37.8–50.8 months), with a median time to last clinical follow-up in these patients with 69 months (IQR 61.8–82 months).

Outcome

The overall outcome, independent of clinical presentation of MOGAD, sex, age, titer at onset or disease course, was in most of the patients favorable with a median EDSS of 0 (IQR 0). Relapsing patients more often showed clinical residuals (18/44, 41%) compared with monophasic patients (14/72, 19%) at the last follow-up. While visual impairments are rare in monophasic patients (1/72, 1%), relapsing patients experienced visual impairments more often (10/44, 23%). All but 2 of these patients presented with ON at onset. Five/one hundred sixteen patients had lasting and severe impairments at the last follow-up with an EDSS of 3 or higher (3 ADEM:

EDSS 3, EDSS 4, EDSS 7.5; 1 NMOSD—EDSS 6; and 1 ADEM—EDSS 3.5). Four/five of them had a monophasic disease course. Twenty-five patients had mild deficits such as mild visual impairment, paresthesia, or mild motoric dysfunction (EDSS 0.5–3). Forty-two percentage (n = 16/38) of relapsing patients (median age 8 years, IQR 4.8–11.3 years) and 15% (n = 10/64) of monophasic patients (median age 9 years, IQR 8–11.5 years) received immunomodulatory treatment at the last follow-up (azathioprine, subcutaneous/IV immunoglobulin [SCIG/IVIG], mycophenolate mofetil, and rituximab).

Discussion

In our study of 116 children with MOGAD, MOG-IgG titers decreased significantly overtime in patients with a monophasic disease course compared with patients with a relapsing disease course in most of the children. Seronegativity, defined as an MOG-IgG titer of less than 1:160 during the first and second years, points against further relapses.

Prognosis regarding disease course and outcome after the first clinical episode in children with MOGAD is challenging because prognostic markers are lacking. MOGAD has an increasing spectrum of described manifestations such as autoimmune encephalitis, brainstem affection, or epilepsy.^{20–22} We decided to allocate ADS and MOG-IgG into the main so far described clinical entities: most of the patients in our cohort presented with ADEM (51%), followed by unilateral (18%) or bilateral ON (14%), NMOSD (7%), myelitis (5%), and encephalitis (5%). This is in line with previous findings, showing a high percentage of ADEM-like presentation of pediatric MOGAD.¹ Furthermore,

Table 3 Changes in MOG-IgG Seropositivity or Decrease of MOG-IgG Titers ≥ 3 Dilution Steps as Predictors for a Relapsing Disease Course

	Monophasic	Relapsing	Risk for relapsing course (95% CI) ^a	P Value ^b
No. of children	26 (62%)	16 (38%)		
Time to relapse/last follow-up (y) ^c	2.6 (2.0–4.42)	0.5 (0.4–1.0)		
Clinical follow-up (y) ^c	2.6 (2.0–4.4) ^d	3.0 (2.7–6.8) ^d		
Seroconversion to MOG-IgG-negative				
After 6–12 mo	9 (35%)	0 (0%)	0.48 (0.07–0.66)	0.008
After 18–24 mo	16 (62%)	0 (0%)	0.62 (0.30–0.79)	<0.001
Decrease in MOG-IgG titer of ≥ 3 dilution steps				
After 6–12 mo	15 (58%)	0 (0%)	0.59 (0.42–0.92)	<0.001
After 18–24 mo	18 (69%)	2 (13%)	0.54 (0.34–0.86)	<0.001

Abbreviations: MOG = myelin oligodendrocyte glycoprotein; IgG = immunoglobulin G.

^a The attributable risk with 95% CI for a relapsing MOGAD course was calculated using the Newcombe/Wilson method with continuity correction.

^b Groups were statistically compared using the Fisher exact test.

^c Median with interquartile range (25th–75th percentile).

^d Minimal clinical follow-up, 2 y.

an age-dependent presentation with ADEM at younger age and a shift to an opticospinal presentation in older patients confirm previous results.^{1,7,8} Clinical subgroups did not differ in MOG-IgG titer at onset with a median MOG-IgG titer ranging from 1:1,280 to 2,560. Even so, ADEM patients tend to have occasionally very high MOG-IgG titers up to 1:40,960 in selected patients, as previously described.^{1,12,23}

The spectrum of MOGAD was believed to consist mainly of subtypes associated with a monophasic disease course. More recently, it was shown that more than 30% of children with MOGAD depending on the reported study have a relapsing disease course.^{1,6} In this study, 38% of patients developed a relapsing disease course overtime. A possible bias resulting from a high percentage of monophasic patients lost to follow-up could be excluded because percentage of monophasic and relapsing patients in the group of excluded patients was balanced (monophasic: $n = 19/39$, relapsing: $n = 20/39$). As a limiting factor, the more extensive clinical follow-up of relapsing patients (5 years) compared with that of monophasic patients (3 years) has to be mentioned, but still, the overall period of recording with a median follow-up of 3.6 years is a strength of this study. Further relapses after the last follow-up cannot be excluded, but the distribution of monophasic and polyphasic patients matches with previous studies,^{1,24} and hence, we assume results are reliable.

In this study, no demographic (age, sex) or laboratory finding (white cell count, OCB in CSF, MOG-IgG titer) at onset was shown to have a prognostic value for the disease course. Of importance, due to the comprehensive data regarding long-term follow-up, we could adjust the

assumption published in 2017 that high MOG-IgG titers $\geq 1:1,280$ are associated with a relapsing disease course.¹ The titer at onset has no predictive value for the disease course.

Although MOG-IgG titers at onset are similar in monophasic and relapsing patients, titers differ significantly in the first and second years after disease onset between these groups (Figure 2, A and B). Monophasic patients show a steep decrease of titers especially during the first year and often with seroconversion to MOG-IgG titers below 1:160 (Figure 2A). In relapsing patients, MOG-IgG titers mostly remain high, as previously described.¹ Nevertheless, a certain decline of MOG-IgG titers is also observed in relapsing MOGAD patients (Figure 2B). Whether this decline of MOG-IgG titers is associated with the applied disease-modifying therapy (DMT) needs to be studied in more detail. All the relapsing patients with seroconversion to MOG-IgG-negative in this study were treated with different DMTs during disease course.

Furthermore, our study shows that a seroconversion to MOG-IgG-negative titers in the first year after disease onset is associated with a 47% risk reduction for further relapses (95% CI 11.1–64.3); a seroconversion during the second year even with a 61% risk reduction (95% CI 31.8–77.9). In the group of monophasic patients, 37% had seronegative titers in the first year and 63% in the second year, whereas no patients with relapsing disease course had a seroconversion to MOG-IgG-negative during the first 2 years after disease onset. Seroconversion to negative MOG-IgG in relapsing patients occurred the earliest after 32 months. In 65% of all patients with monophasic MOGAD, titers decreased to negative levels

during the follow-up, whereas 93% of all patients with polyphasic MOGAD still had elevated MOG-IgG titers at the last follow-up despite a longer follow-up of serum titers in the latter. The small group of patients in our study with recorded seroconversion to MOG-IgG-negative ($n = 63$) has to be mentioned as a limitation in this context. These patients should be further included in regular follow-up examinations to observe the further disease course. In a recent publication, an Australian research group studying a large cohort of children and adults with MOGAD also showed that MOG-IgG titers decline overtime in monophasic patients. They further found that most MOG-IgG are of low affinity targeting an extracellular epitope at Proline42 and that the MOG-ab response—confined to Proline42—remains stable overtime. On the contrary, particularly adult patients with a relapsing disease course harbor a more diverse MOG-IgG repertoire recognizing epitopes others than Proline42 in most of the cases, which could be used as a biomarker in the future.²⁴

It is of interest that no patient in our cohort experienced a relapse after the time of first seronegativity (eFigure 1, links.lww.com/NXI/A744). Only 1 patient experienced further relapses after a transient MOG-IgG-negative titer from a serum sample, which was obtained shortly after 5 courses of plasma exchange (PLEX) and most likely represents a false-negative result. Disease course in children with MOGAD after seroconversion to MOG-IgG-negative is hardly reported. In a study with 84 MOG-IgG-positive children with a first ADS, 4 children experienced a further relapse after conversion to seronegativity.⁶ In this study, a higher cutoff for seroconversion to MOG-IgG-negative was applied (1:200⁶), probably leading to a lower sensitivity compared with our cutoff for seropositivity (1:160). A further study in pediatric MOGAD, using the same cutoff of $\geq 1:160$, also showed in a cohort of 116 pediatric MOGAD patients and a serologic follow-up of 12 months that no patient with serial MOG-IgG testing ($n = 66$) had a further relapse after seroconversion to MOG-IgG-negative.²¹ Therefore, we recommend serial MOG-IgG testing as a potential monitoring tool with high prognostic value to evaluate the relapse risk if serial MOG-IgG testing with high sensitivity is applied. To date, length of treatment in relapsing MOGAD is recommended for 2 years after remission, independent of MOG-IgG status. This recommendation was the result of a pediatric MOGAD meeting of more than 20 experts in the pediatric neurology field.²⁵ Furthermore, we suggest regular testing for example every 6 months in a research setting to answer questions such as prognostic value of seroconversion to MOG-IgG-negative and relevance of fluctuating MOG-IgG titers in relation to further relapses.

Using a low cutoff with high sensitivity in the differential diagnosis of a first ADS is discussed controversially because the positive predictive value for MOGAD decreases with lower titers. Especially in patients with low-positive titers, a range of other neurologic diagnosis such as MS is

encountered.^{19,26} In this study, we used a low cut-off of $> 1:160$ in serial MOG-IgG testing to evaluate the risk of further relapses in MOGAD. An international standardized definition of seroconversion to MOG-IgG-negative titers is needed, and hereby, we suggest a definition by measurement of endpoint titers.

As described earlier, 1 patient had a negative MOG-IgG titer shortly after PLEX treatment, but positive titers reemerged in further serial testing along with new relapses. After PLEX, transient removal of antibodies in serum is described in other autoimmune diseases, for example N-methyl-D-aspartate receptor encephalitis.^{27,28} Therefore, testing of MOG-IgG after PLEX may lead to false-negative results. The effect of immunomodulating therapies such as IVIG on MOG-IgG titers has also not been studied in detail.^{10,29} MOG-IgG testing before application of these therapies and at regular intervals thereafter is needed to learn more about the changing levels of MOG-IgG over the course of the treatment regimen and the disease.

The following limitation of this study needs to be addressed: due to the multicenter approach and design of this study, regular follow-up time points for clinical and serologic testing were not performed in a standardized fashion. This led to relevant differences between monophasic and relapsing patients regarding clinical and serologic follow-up interval. Despite this limitation, we could show that MOG-IgG titers in monophasic and relapsing MOGAD reveal significant differences. A further limitation is the lack of information regarding immunomodulatory therapy in relapsing patients. In further studies, predefined time points for clinical and serologic follow-up should be included. Third, in long-term follow-up studies, additional monitoring tools are required evaluating visual and cognitive sequelae in addition to standardized tools such as modified Rankin scale or EDSS.

In this study, serial MOG-IgG titers are the only significant predictor for relapsing disease course in MOGAD. Decreasing MOG-IgG titers showed a distinct reduction of relapse risk in MOGAD, and seroconversion to MOG-IgG-negative titers ($< 1:160$) is suggestive for stable clinical remission in pediatric MOGAD. Serial MOG-IgG testing should be conducted at least every 6 months to evaluate the risk of a further relapse.

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