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Association of MOG-IgG Serostatus With Relapse After Acute Disseminated Encephalomyelitis and Proposed Diagnostic Criteria for MOG-IgG–Associated Disorders

A. Sebastian López-Chiriboga, MD; Masoud Majed, MD; James Fryer, MS; Divyanshu Dubey, MD; Andrew McKeon, MD; Eoin P. Flanagan, MD; Jiraporn Jitprapaikulsan, MD; Naga Kothapalli, MBBS; Jan-Mendelt Tillema, MD; John Chen, MD, PhD; Brian Weinshenker, MD; Dean Wingerchuk, MD; Jessica Sagen, MA; Avi Gadoth, MD; Vanda A. Lennon, MD, PhD; B. Mark Keegan, MD; Claudia Lucchinetti, MD; Sean J. Pittock, MD

IMPORTANCE Recent studies have reported a higher relapse rate following an initial inflammatory demyelinating disorder in pediatric patients with persistent seropositivity of antibodies targeting myelin oligodendrocyte glycoprotein (MOG-IgG1). To date, the clinical implications of longitudinal MOG-IgG1 seropositivity using live cell assays with IgG1 secondary antibodies in adults after acute disseminated encephalomyelitis (ADEM) are unknown.

OBJECTIVE To determine whether MOG-IgG1 serostatus (transient vs persistent) and titer change over time provide clinical utility in predicting the likelihood of relapse after ADEM.

DESIGN, SETTING, AND PARTICIPANTS This cohort study identified patients with an initial diagnosis of ADEM evaluated at a single referral center between January 1, 1990, and October 1, 2017. Fifty-one patients were included, including 31 children and 20 adults. Longitudinal serologic testing was performed detecting autoantibodies targeting aquaporin 4 (AQP4-IgG) and MOG-IgG1 with clinically validated fluorescence-activated cell sorting assays. Patients were divided into 3 cohorts: persistent seropositivity, transient seropositivity, and seronegativity.

MAIN OUTCOMES AND MEASURES Clinical demographic characteristics, longitudinal AQP4-IgG and MOG-IgG1 serostatus, titers, relapses, use of immunotherapy, and Expanded Disability Status Scale score at follow-up.

RESULTS Of 51 patients presenting with an initial diagnosis of ADEM, 20 (39%) were adult, 24 (47%) were female, and ages ranged from 12 months to 57 years. Seventeen patients fulfilled criteria for persistent seropositivity; of those, 8 of 9 children (89%) and 7 of 8 adults (88%) had at least 1 relapse after median (range) follow-up periods of 75 (15-236) months and 39 (9-161) months, respectively. Eight patients (16%), including 4 adults, fulfilled criteria for transient seropositivity; of those, no children and 1 of 4 adults (25%) relapsed after median (range) follow-up periods of 32 (24-114) months and 16 (13-27) months, respectively. Of 24 patients with AQP4-IgG and MOG-IgG seronegativity, 6 of 17 children (35%) and 2 of 7 adults (29%) had at least 1 relapse after median (range) follow-up periods of 36 (3-203) months and 34 (15-217) months, respectively. There were only 2 patients, including 1 adult, with AQP4-IgG seropositivity, and both relapsed. The hazard ratio for relapses in those with persistent MOG-IgG1 positivity compared with AQP4-IgG and MOG-IgG1 seronegativity was 3.1 (95% CI, 1.1-8.9; $P = .04$) in children and 5.5 (95% CI, 1.4-22.5; $P = .02$) in adults. Immunotherapy was used in 5 of 9 children (56%) and 6 of 8 adults (75%) with persistent seropositivity and in 3 of 17 children (18%) and 1 of 7 adults (14%) with AQP4-IgG and MOG-IgG seronegativity.

CONCLUSIONS AND RELEVANCE Relapse occurred in 15 of 17 patients (88%) with persistent MOG-IgG1 seropositivity after ADEM; only 1 patient with transient seropositivity experienced relapse. Our data extend the clinical utility of MOG-IgG1 serological testing to adult patients and highlights that longitudinal serologic evaluation of MOG-IgG1 could help predict disease course and consideration of immunotherapy.

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Supplemental content

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Sean J. Pittock, MD, Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (pittock.sean@mayo.edu).

Autoantibodies targeting myelin oligodendrocyte glycoprotein (MOG-IgG) detected by transfected cell-based assays using full-length human MOG as antigen[1] have been reported by several international groups to identify a subgroup of central nervous system inflammatory demyelinating disorders (IDDs). Some patients with MOG-IgG seropositivity have the phenotype of neuromyelitis optica spectrum disorder (NMOSD), including relapsing optic neuritis (ON) and transverse myelitis (TM), and others have characteristics of acute disseminated encephalomyelitis (ADEM), commonly monophasic but sometimes occurring in the context of NMOSD.[2,3] The MOG-IgG1 titer is often high at onset of monophasic ADEM in children but rapidly drops to undetectable levels (ie, seropositivity is transient).[4]

Seropositivity of autoantibodies targeting autoimmune aquaporin 4 (AQP4-IgG) in patients with ON, TM, or ADEM indicates high risk for relapse.[5,6] Since ADEM may be monophasic or herald a relapsing course, an ideal biomarker would predict relapse and the need for immunosuppressive therapy and distinguish the disorder from multiple sclerosis (MS), for which effective maintenance treatments differ. Recent studies suggest that persistent MOG-IgG1 seropositivity following an initial IDD attack is associated with a higher relapse rate in both pediatric and adult patients.[7,8] However, data from adults with ADEM are scant.[9-12] Therefore, we collected serum samples longitudinally from patients with neurological disorders reported to be associated with MOG-IgG1 to determine whether MOG-IgG1 serostatus (persistent vs transient positivity) and titer change over time is associated with the risk of relapse.

Key Points

Question What is the prognostic relevance of persistent seropositivity of antibodies targeting myelin oligodendrocyte glycoprotein (MOG-IgG1) in adults after acute disseminated encephalomyelitis (ADEM)?

Findings In this cohort study of 51 patients with an initial diagnosis of ADEM, relapse occurred in 8 of 9 children and 7 of 8 adults with persistent MOG-IgG1 seropositivity. By contrast, relapse occurred in 6 of 17 children and 2 of 7 adults with MOG-IgG1 seronegativity as well as 0 of 4 children and 1 of 4 adults with transient MOG-IgG1 seropositivity.

Meaning Persistent MOG-IgG1 positivity after recovery from ADEM in both pediatric and adult patients is useful as a longitudinal serological biomarker predicting risk for relapsing disease.

Methods

Subjects, Patients, and Ascertainment

The study was approved by the institutional review board of Mayo Clinic, Rochester, Minnesota. All included patients gave written consent for the passive use of their medical record; informed consent was signed by the patient or a parent.

We identified patients by searching medical records from January 1990 to October 2017 for all potentially relevant diagnostic codes and, after detailed medical record review, included patients fulfilling the following criteria: (1) a first polyfocal clinical central nervous system event with presumed inflammatory demyelinating cause; (2) abnormal brain magnetic resonance imaging findings during the acute phase showing widespread inflammation; (3) encephalopathy that cannot be explained by fever; and (4) stored serum available (**Figure 1**A). Patients were excluded if an initial event was consistent with isolated ON or TM.

AQP4-IgG and MOG-IgG1 were detected by clinically validated flow cytometry assays using live HEK293 cells transfected with human M1 AQP4 or full-length human MOG. Testing for MOG-IgG1 in patients with seropositivity was repeated at 3 months or later. A follow-up serum sample was requested from patients with monophasic ADEM and only a single available serum sample. Persistent seropositivity was defined as a positive result in both the initial and follow-up sample or, if no initial sample at onset was available, a positive result on a sample collected more than 1 year after ADEM episode. Medical records were reviewed to abstract demographic data, evidence and phenotype of relapses, treatment, disability, and diagnosis at last follow-up.

MOG-IgG1 Assay

An in-house, clinically validated flow cytometry assay was used for quantitative detection of MOG-IgG1 on a mixed population of transfected and nontransfected cells. Heat-inactivated patient serum (at 56°C for 35 minutes) was added to live HEK293 substrate cells transiently transfected with full-length recombinant human MOG (cloned into pIRES2-AcGFP vector, which coexpresses nonlinked green fluorescent protein [GFP]). The median fluorescence intensity-bound Alexa Fluor 647–conjugated mouse antihuman IgG1 (Fc region–specific; Catalog No. 9054-01; Southern Biotech) was determined for both nontransfected and transfected cells. The ratio of median fluorescence intensity values for GFP+ and GFP− cells is the IgG binding index (IBI). An IBI score of 2.5 or greater was considered positive. Samples were screened at 1:20 dilution and, if positive, titrated at 1:40, 1:100, and thereafter in 10-fold steps. The farthest dilution yielding a positive result (IBI ≥ 2.5) was recorded as the end point. All samples were tested additionally for AQP4-IgG using optimized flow cytometry assay.[13] Sera from 50 patients with MS and 50 healthy control patients yielded negative results by both assays.

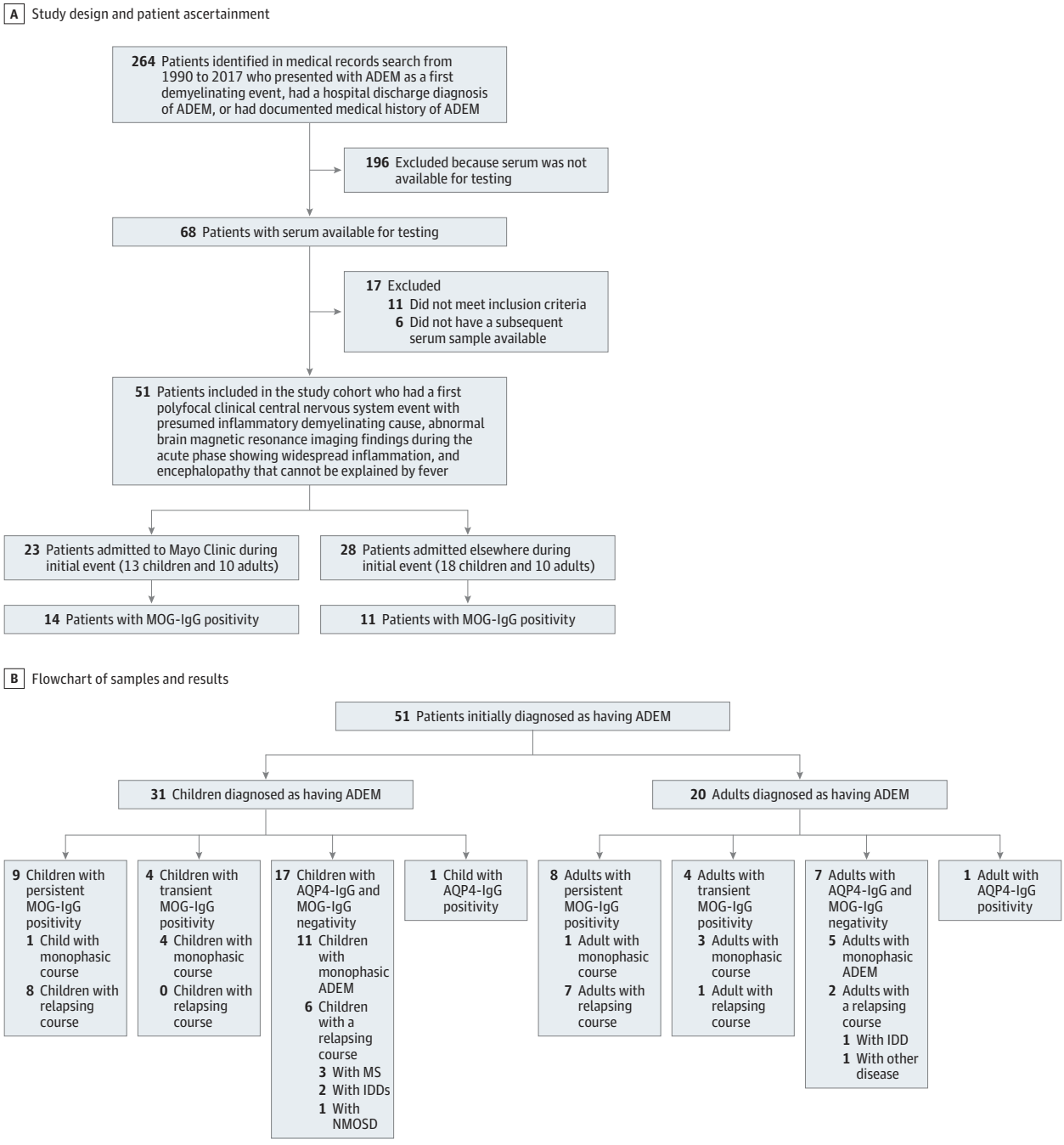
Statistical Analyses

Kruskal-Wallis and Pearson χ^2 test were used to compare continuous and nominal variables, respectively, between ADEM subgroups based on MOG-IgG status. All statistical tests were 2-sided, and a P value less than .05 was considered statistically significant. Statistical analyses were performed using SPSS version 23.0 (IBM).

Results

The clinical and serological characteristics of all 51 patients are summarized in the **Table**. The flowchart of samples and

Figure 1. Study Design



ADEM indicates acute disseminated encephalomyelitis; AQP4, aquaporin 4; IDD, inflammatory demyelinating disorder; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

results are shown in Figure 1B. Serostatus, clinical course, and Kaplan-Meier curves for pediatric and adult patients are shown in **Figure 2**.

MOG-IgG1 vs AQP4-IgG Seropositivity

MOG-IgG1 was detected in 25 of 51 patients (49%) at some point in the clinical disease course (Figure 1B). AQP4-IgG was detected in only 2 patients (4%), including 1 adult; both relapsed.

Relapse Likelihood by MOG-IgG1 Serostatus

Seventeen patients, including 8 adults, fulfilled criteria for persistent seropositivity (eTable and eFigure in the Supplement). Eight of 9 children (89%) had at least 1 relapse in a median (range) follow-up period of 75 (15-236) months. These children experienced a total of 22 relapses (median [range] attacks per patient, 3 [1-6]), including 5 ADEM-ON relapses, 5 ON relapses, 7 cerebral relapses, 3 myelitis relapses, 1

Table. Clinical and Serological Characteristics of Pediatric and Adult Patients With Acute Disseminated Encephalomyelitis (ADEM)

Characteristic	Median (Range)			P Value[a]	P Value[b]
	Persistent MOG-IgG1 Positivity	Transient MOG-IgG Positivity	AQP4-IgG and MOG-IgG Negativity		
Children					
No.	9	4	17	NA	NA
Age at onset, y	4 (2-9)	6.5 (4-8)	7 (1-17)	.16	.18
Female, No. (%)	5 (56)	2 (50)	6 (35)	.85	.32
White race, No. (%)	7 (78)	3 (75)	13 (77)	.91	.94
Preceding infection/vaccination, No. (%)[c]	6 (67)	4 (100)	13 (76)	.19	.92
Initial MOG-IgG1 titer	40 (20-1000)	70 (40-1000)	0	.35	NA
Time from initial to final MOG-IgG1 evaluation, mo	39.5 (3-180)	7 (3-72)	NA	.01	NA
Final MOG titer	100 (20-1000)	0	NA	NA	NA
Relapsing course, No. (%)	8 (89)	0	6 (35)	.002	.009
Time from symptom onset to second attack, mo	9.5 (4-180)	NA	4.25 (3.5-72)	NA	.30
ADEM EDSS score at nadir	5 (1-10)	3 (2-7)	6 (2-10)	.85	.50
EDSS score at last follow-up	0 (0-4)	0 (0-3)	0 (0-9)	.39	.51
Duration of follow-up, mo	75 (15-236)	32 (24-114)	36 (3-203)	.88	.19
Subsequent post-ADEM relapse, No. (%)					
Myelitis	1 (11)	0	0	.49	.16
Optic neuritis	4 (44)	1 (25)	3 (18)	.51	.14
Adults					
No.	8	4	7	NA	NA
Age at onset, y	26 (22-45)	22.5 (18-45)	28 (21-57)	.30	.68
Female, No. (%)	6 (75)	2 (50)	3 (43)	.39	.21
White race, No. (%)	6 (75)	3 (75)	6 (86)	>.99	.61
Preceding infection/vaccination, No. (%)[c]	6 (75)	4 (100)	6 (86)	>.99	.61
Initial MOG-IgG1 titer	70 (40-1000)	40 (20-1000)	0	.41	NA
Time from initial to final MOG-IgG1 evaluation, mo	25.5 (16-153)	12.5 (3-16)	NA	.01	NA
Final MOG titer	100 (20-1000)	0	NA	NA	NA
Relapsing course, No. (%)	7 (88)	1 (25)	3 (43)	.03	.02
Time from symptom onset to second attack, mo	4 (2-6)	NA	3 (3-6)	NA	NA
ADEM EDSS score at nadir	6 (4-8)	7.5 (4-8)	6 (3-7)	.22	.86
EDSS score at last follow-up	1.5 (0-3)	1.5 (0-3)	0 (0-6)	.73	.71
Duration of follow-up, mo	39 (10-161)	16 (13-27)	34 (15-217)	>.99	>.99
Subsequent post-ADEM relapse, No. (%)					
Myelitis	1 (13)	0	0	.46	.33
Optic neuritis	7 (88)	1 (25)	2 (29)	.03	.02

Abbreviations: AQP4, aquaporin 4; EDSS, Expanded Disability Status Scale; MOG, myelin oligodendrocyte glycoprotein; NA, not applicable.

[a] Comparison between persistent MOG-IgG positivity and transient MOG-IgG positivity.

[b] Comparison between persistent MOG-IgG positivity and AQP4-IgG and MOG-IgG negativity.

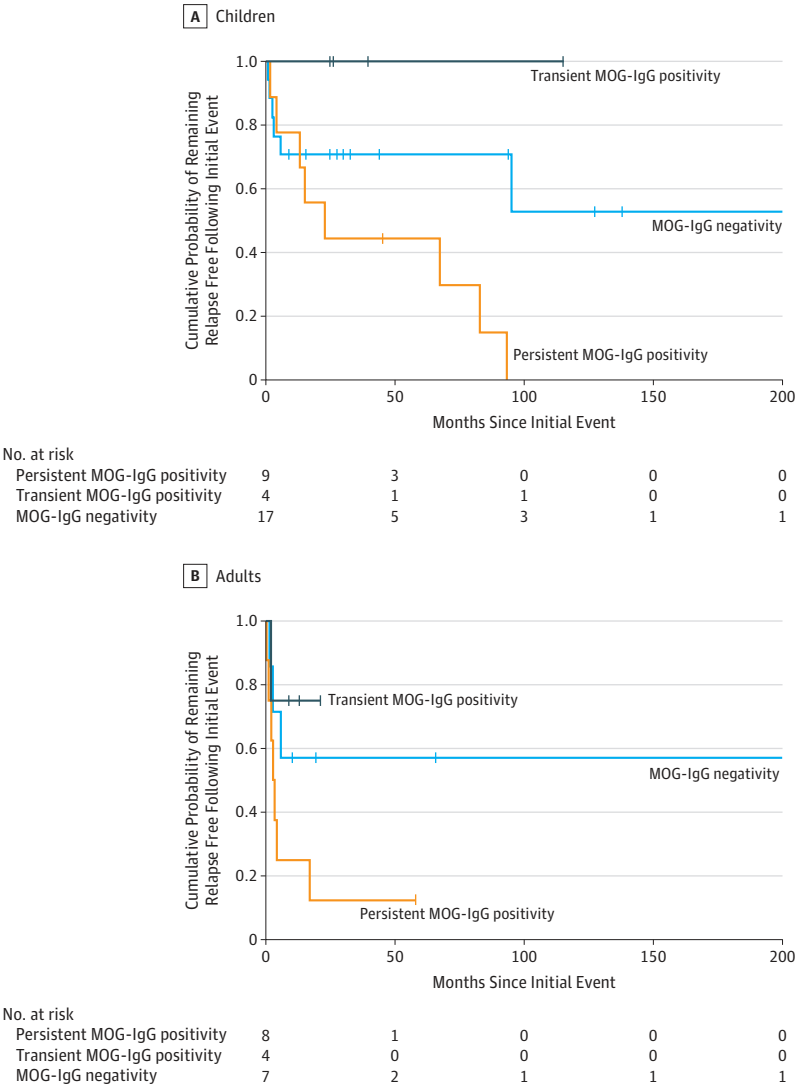
[c] A preceding event was noted in 39 patients (76%), including fever in 12 patients (6 adults), upper respiratory tract infection in 18 (6 adults), gastrointestinal tract infection in 3 (1 adult), urinary tract infection in 1 (1 adult), and recent immunization in 5 (3 adults). Four had elevated mycoplasma IgM (2 adults) and 2 had evidence of recent Epstein-Barr virus infection (1 adult).

encephalomyelitis relapse, and 1 myelitis plus ON relapse. Seven of 8 adults (88%) had at least 1 relapse after a median (range) follow-up period of 39 (10-161) months. These adults experienced a total of 29 relapses (median [range] attacks per patient, 3 [3-6]), including 21 ON relapses, 2 cerebral relapses, 2 encephalomyelitis relapses, 2 ADEM-ON relapses, and 2 myelitis relapses.

Figure 3 shows 2 representative adult patients with persistent MOG-IgG1 seropositivity, abnormal magnetic resonance imaging findings at ADEM diagnosis, and subsequent disease evolution. No patient was assigned a clinical diagnosis of MS at last follow-up.

Eight patients, including 4 adults, met criteria for transient seropositivity. None of the 4 children relapsed after a median (range) follow-up period of 32 (24-114) months; their diagnoses remained monophasic ADEM. Only 1 of 4 adults (25%) relapsed after a median (range) follow-up period of 16 (13-27) months. This patient subsequently relapsed with multifocal demyelination and ON after 22 months of follow-up. The seronegative second serum specimen was drawn in the remis-

Figure 2. Kaplan-Meier Curves Showing Cumulative Probability of Remaining Relapse Free Following Initial Event in Children and Adults



A, Log-rank test: $P = .02$. B, Log-rank rest: $P = .11$. Tick marks indicate censored patients.

sion phase during immunotherapy with azathioprine and prednisone. All available cerebrospinal fluid specimens from 13 patients were negative for MOG-IgG1, and 5 paired serum specimens were positive.

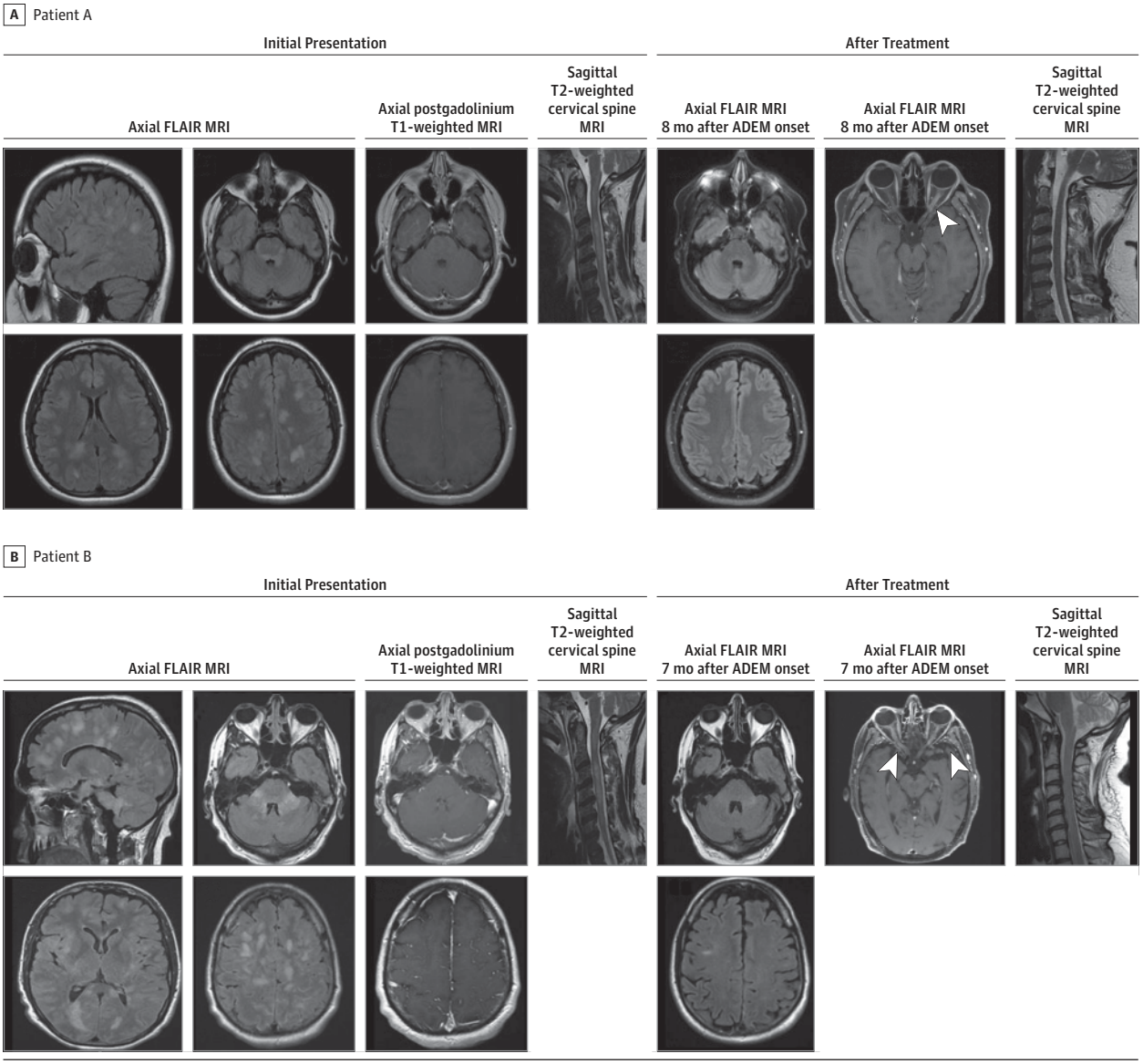
Of 24 patients with AQP4-IgG and MOG-IgG seronegativity, including 7 adults, 6 of 17 children (35%) and 2 of 7 adults (29%) had at least 1 relapse after median (range) follow-up periods of 36 (3-203) months and 34 (15-217) months, respectively. Relapses in the 6 children included 4 ON relapses, 1 ADEM-ON relapse, 3 cerebral relapses, and 1 TM relapse. Final diagnoses in the pediatric group were monophasic ADEM in 11 children, relapsing-remitting MS in 3, IDD not fulfilling MS criteria in 2, and NMOSD in 1 (Figure 2). Relapses in the 2 adult patients included 2 ON relapses and 1 encephalitis relapse. Final diagnoses in the adult group were monophasic ADEM in 5 adults, IDD in 1, and recurrent steroid-responsive encephalopathy in 1. None of the 10 serial samples from patients with AQP4-IgG and MOG-IgG negativity seroconverted.

The hazard ratio for relapses in those with persistent MOG-IgG1 positivity compared with those with AQP4-IgG and MOG-IgG1 seronegativity was 3.1 (95% CI, 1.1-8.9; $P = .04$) for children and 5.5 (95% CI, 1.4-22.5; $P = .02$) for adults. Of pediatric and adult patients with persistent seropositivity, 80% and 70%, respectively, would be expected to experience relapse within 2 years of ADEM compared with no children with transient seropositivity and 20% of adults with transient seropositivity (Figure 2).

Maintenance Immunotherapies and MOG-IgG1 Titers Over Time

Immunotherapy was used in 5 of 9 children (56%) and 6 of 8 adults (75%) with persistent seropositivity and in 3 of 17 children (18%) and 1 of 7 adults (14%) with AQP4-IgG and MOG-

Figure 3. Detailed Magnetic Resonance Imaging (MRI) Changes of Representative Adults With Persistent MOG-IgG1 Positivity at Onset and Follow-up



Axial fluid-attenuated inversion recovery (FLAIR) MRI, axial postgadolinium T1-weighted MRI, and sagittal T2-weighted cervical spine MRI at initial presentation are shown; T2-weighted hyperintensities were not associated with enhancement. These abnormalities improved after treatment. A, Patient A is a woman in her 20s. After 19 months of follow-up, she experienced 3 relapses as well as 2 episodes of left-sided optic neuritis 6 months and 11 months after ADEM onset with good recovery with rituximab therapy, with an Expanded Disability Status Scale score of 0. She developed left optic neuritis after prednisone dose reduction (arrowhead). B, Patient B is a man in his 40s. After 25 months of follow-up, he experienced 4 relapses after prednisone dose reduction, including bilateral optic neuritis 4 months, 7 months and 16 months and right-sided optic neuritis 24 months after ADEM onset with good recovery with azathioprine therapy, with an Expanded Disability Status Scale score of 1. He developed bilateral optic neuritis after prednisone dose reduction (arrowheads).

IgG seronegativity. After initiation of immunotherapy (eTable and eFigure in the Supplement), MOG-IgG1 titer declined in 4 patients, was undetectable in 2, remained unchanged in 4, and increased in 2.

Population-Based MOG-IgG–Seropositive ADEM Cohort

Data from a 2018 population-based epidemiologic study[13] with data collected from January 1, 1995, to December 31, 2015, showed that MOG-IgG1 was the most commonly identified antibody in the setting of autoimmune encephalitis, with a prevalence of 1.9 per 100 000 and an incidence of 0.1 per 100 000 individuals. In this study, 10 patients, including 7 adults, fulfilled ADEM criteria. Four patients (40%) were positive for MOG-IgG.

Four patients with MOG-IgG–positive ADEM from a previous population-based study[13] were analyzed separately to overcome referral bias. The median (range) age of patients with seropositivity was 28 (2-45) years, and 14 (50%) were female. One adolescent patient had a relapsing course. This patient relapsed 5 years later with ON and recurrent encephalomyelitis

and had persistent MOG-IgG seropositivity. Interestingly, this patient's cerebrospinal fluid at onset was also positive for anti-NMDA receptor IgG by cell-based assay. Three adult patients with MOG-IgG seropositivity were also included in the study,[13] and all had a diagnosis of monophasic ADEM after a median (range) follow up of 132 (48-264) months. Two patients had MOG-IgG1 positivity at onset but lacked a follow-up sample, and 1 patient was seropositive while asymptomatic (sample collected 75 months after ADEM onset [titration wasn't performed owing to limited quantity available]).

Discussion

Patients presenting with acute multifocal neurological and radiographic findings suspicious for ADEM are a diagnostic and therapeutic challenge, as the differential diagnosis is broad and the decision to recommend immunotherapy is difficult since many cases remain monophasic.[14,15] Our study demonstrates that relapse occurs in 88% of patients presenting with ADEM and persistent MOG-IgG1 seropositivity. The relapse attack is usually ON. By contrast, only 12% of patients with ADEM and transient seropositivity relapse. These data, confirming similar conclusions reported from a pediatric ADEM series,[16] expand the clinical utility to adult ADEM.

Further, our study is consistent with prior observations that MOG-IgG1-associated demyelinating disease is not prototypic MS. No patient who was initially diagnosed with ADEM and was seropositive for AQP4-IgG or MOG-IgG1 was assigned a diagnosis of MS at last follow-up. In contrast, 3 children with AQP4-IgG and MOG-IgG1 negativity had been assigned a clinical diagnosis of MS.

The detection of MOG-IgG1 in most patients who experienced relapse is similar to a 2018 study that identified MOG-IgG1 in 98% of pediatric patients who relapsed with ON after initial presentation with ADEM.[17] More than half of the patients with transient MOG-IgG1 seropositivity became seronegative spontaneously without immunotherapy. This contrasts with the persistence of AQP4-IgG seropositivity with rare conversion to seronegativity even with immunotherapy. The immunobiological mechanisms underlying the transience of MOG-IgG1 seropositivity remain elusive. The high prevalence of infections preceding ADEM suggests a role for infection in triggering this transient immune response. Genetic factors, both immunogenetic and neurogenetic, may also play a role. Delineating the roles of autoantibody and effector T cells should also shed light on this phenomenon.

In this study, only 1 in 5 patients with MOG-IgG1 seropositivity would have fulfilled criteria for AQP4-IgG–seronegative NMOSD. Recent reports from large cohorts suggest that approximately 30% of patients with MOG-IgG positivity meet NMOSD criteria.[9,12,18-21] It is clear that diagnostic criteria are needed for MOG-IgG–associated disorders. We[22,23] and others[24] have argued for molecular-based diagnostic criteria that allow early diagnosis at the initial attack of limited disease (eg, ON, TM, and ADEM). This allows better characterization of disease pathogenesis, offers options for earlier appropriate treatment, and facilitates inclusion criteria for clinical trials. Despite some clinical and radiographic overlap with AQP4-IgG–positive NMOSD, MOG autoimmunity differs with respect to disability outcomes[12,25] and neuropathology.[19] We propose the diagnostic criteria in the **Box** for MOG-IgG–associated disorders. These criteria require detection of MOG-IgG by clinically validated cell-based assay and the presence of 1 or more of the following core clinical findings: ADEM, encephalomyelitis,[4,17,19] ON,[26] TM,[18] and brain or brainstem demyelination.[27,28] In patients in whom clinical correlation is unclear, alternative serological testing should be considered (eg, IgG1 targeting full-length human MOG expressed on live cells).[1]

Box. Proposed Diagnostic Criteria for Myelin Oligodendrocyte Glycoprotein (MOG-IgG)–Associated Disorders[a]

1. Laboratory finding[b]: serum positive for MOG-IgG by cell-based assay[c]
2. Clinical findings: any of the following presentations:
   1. ADEM
   2. Optic neuritis, including CRION
   3. Transverse myelitis (ie, LETM or STM)
   4. Brain or brainstem syndrome compatible with demyelination
   5. Any combination of the above
3. Exclusion of alternative diagnosis

Abbreviations: ADEM, acute demyelinating encephalomyelitis; CRION, chronic relapsing inflammatory optic neuropathy; LETM, longitudinally extensive transverse myelitis; STM, short-segment transverse myelitis.

[a] Must meet all 3 criteria.

[b] Transient seropositivity favors lower likelihood of relapse.

[c] In abscense of serum, positivity in cerebrospinal fluid would allow fulfillment of criteria 1.

Limitations

This study has limitations. We acknowledge that the relapse frequency presented here may be higher than expected in other settings because of referral bias. Relapsing patients are also likely overrepresented because of the challenge of obtaining a follow-up serum specimen from patients with monophasic ADEM. Although the persistence of seropositivity is associated with increased relapse risk, this is not the only determinant factor for relapse because some pediatric and adult patients with persistent seropositivity have a monophasic course. This is also supported by the 25% of relapsing patients with MOG-IgG–positive ADEM from our population-based epidemiology study[13] in contrast to the 60% of relapsing patients seen here. MOG-IgG1 seropositivity aids the diagnosis of ADEM and offers prognostic insight in longitudinal evaluation.

Conclusions

On the basis of these observations, it is our current practice in follow-up of patients with MOG-IgG1 positivity after an inflammatory demyelinating event to retest serologically at 6

months. For patients with persistent seropositivity, initiation of immunotherapy should be considered to prevent relapse. Immunotherapy could be considered earlier if a patient initially with seropositivity relapsed before 6 months. However, randomized clinical trials are needed to assess the benefit of immunotherapy. A prospective longitudinal serological evaluation will be helpful to determine the ideal timing for retesting and other factors to assist prognostication.

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Author Affiliations: Department of Neurology, Mayo Clinic, Rochester, Minnesota (López-Chiriboga, Majed, Dubey, McKeon, Flanagan, Tillema, Weinshenker, Lennon, Keegan, Lucchinetti, Pittock); Center for Multiple Sclerosis and Autoimmune Neurology, Mayo Clinic, Rochester, Minnesota (López-Chiriboga, Majed, Fryer, Dubey, McKeon, Flanagan, Jitprapaikulsan, Kothapalli, Tillema, Chen, Weinshenker, Wingerchuk, Sagen, Gadoth, Lennon, Keegan, Lucchinetti, Pittock); Department of Laboratory Medicine, Mayo Clinic, Rochester, Minnesota (Fryer, McKeon, Jitprapaikulsan, Kothapalli, Gadoth, Lennon, Pittock); Department of Ophthalmology, Mayo Clinic, Rochester, Minnesota (Chen); Department of Neurology, Mayo Clinic, Scottsdale, Arizona (Wingerchuk); Department of Immunology, Mayo Clinic, Rochester, Minnesota (Lennon).

Author Contributions: Drs López-Chiriboga and Pittock had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: López-Chiriboga, Majed, Sagen, Pittock.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: López-Chiriboga, Majed, Dubey, Kothapalli, Chen, Sagen, Pittock.
Critical revision of the manuscript for important intellectual content: López-Chiriboga, Fryer, Dubey, McKeon, Flanagan, Jitprapaikulsan, Tillema, Chen, Weinshenker, Wingerchuk, Gadoth, Lennon, Keegan, Lucchinetti, Pittock.
Statistical analysis: López-Chiriboga, Majed, Dubey, Kothapalli, Lennon, Lucchinetti.
Administrative, technical, or material support: Majed, Fryer, Jitprapaikulsan, Sagen, Lucchinetti.
Study supervision: Tillema, Pittock.

Conflict of Interest Disclosures: Dr McKeon has a patent pending for glial fibrillary acidic protein and microtubule-associated protein 1B as markers of neurological autoimmunity and paraneoplastic disorders; has consulted for Grifols, MedImmune, and Euroimmun; and has received research support from MedImmune and Euroimmun. Dr Flanagan has received research support from MedImmune. Dr Weinshenker has received royalties from RSR, Oxford University, Hospices Civils de Lyon, and MVZ Labor PD Dr. Volkmann und Kollegen GbR for a patent of NMO-IgG as a diagnostic test for neuromyelitis optica (NMO) and related disorders. Dr Weinshenker also serves as a member of an adjudication committee for clinical trials in NMO being conducted by MedImmune and Alexion; as a consultant for Caladrius Biosciences and Brainstorm Therapeutics regarding potential clinical trials for NMO; and as a member of a data safety monitoring committee for clinical trials conducted by Novartis. Dr Wingerchuk has received research support paid to Mayo Clinic by Alexion and Terumo BCT and serves as a consultant for MedImmune and Caladrius Biosciences. Dr Lennon has received royalties for technology relating to aquaporin 4 (AQP4) antibodies for diagnosis of NMO and its spectrum disorders, is a named inventor on filed patents that relate to functional AQP4/NMO-IgG assays and NMO-IgG as a cancer marker, and has a patent pending for glial fibrillary acidic protein and microtubule-associated protein 1B as markers of neurological autoimmunity and paraneoplastic disorders. Dr Pittock is a named inventor on filed patents that relate to functional AQP4/NMO-IgG assays and NMO-IgG as a cancer marker; has consulted for Alexion and MedImmune; and has received research support from Grifols, MedImmune, and Alexion. All compensation for consulting activities is paid directly to Mayo Clinic. No other disclosures were reported.

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