RESEARCH ARTICLE OPEN ACCESS

Impaired Brain Growth in Myelin Oligodendrocyte Glycoprotein Antibody–Associated Acute Disseminated Encephalomyelitis

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Neurol Neuroimmunol Neuroinflamm 2023;10:e200066. doi:10.1212/NXI.0000000000200066

Abstract

Background and Objectives

Acute disseminated encephalomyelitis (ADEM) is the most common phenotype in pediatric myelin oligodendrocyte glycoprotein (MOG) antibody–associated disease. A previous study demonstrated impaired brain growth in ADEM. However, the effect of MOG antibodies on brain growth remains unknown. Here, we performed brain volume analyses in MOG-positive and MOG-negative ADEM at onset and over time.

Methods

In this observational cohort study, we included a total of 62 MRI scans from 24 patients with ADEM (54.2% female; median age 5 years), of which 16 (66.7%) were MOG positive. Patients were compared with healthy controls from the NIH pediatric MRI data repository and a matched local cohort. Mixed-effect models were applied to assess group differences and other relevant factors, including relapses.

Results

At baseline and before any steroid treatment, patients with ADEM, irrespective of MOG antibody status, showed reduced brain volume compared with matched controls (median [interquartile range] 1,741.9 cm3 [1,645.1–1,805.2] vs 1,810.4 cm^3 [1,786.5–1,836.2]). Longitudinal analysis revealed reduced brain growth for both MOG-positive and MOG-negative patients with ADEM. However, MOG-negative patients showed a stronger reduction (−138.3 cm^3 [95% CI −193.6 to −82.9]) than MOG-positive patients (−50.0 cm^3 [−126.5 to −5.2]), independent of age, sex, and treatment. Relapsing patients (all MOG positive) showed additional brain volume loss (−15.8 cm^3 [−68.9 to 37.3]).

Discussion

Patients with ADEM exhibit brain volume loss and failure of age-expected brain growth. Importantly, MOG-negative status was associated with a more pronounced brain volume loss compared with MOG-positive patients.

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Glossary

3D = three dimensional; **ADEM** = acute disseminated encephalomyelitis; **ADS** = acquired demyelinating syndrome; **EDSS** = Expanded Disability Status Scale; **GM** = gray matter; **IVIG** = IV immunoglobulin; **MDEM** = multiphasic ADEM; **MOG** = myelin oligodendrocyte glycoprotein; **MOGAD** = MOG antibody–associated disease; **MS** = multiple sclerosis; **NfL** = neurofilament light chain; **OND** = other neurologic disorders; **POMS** = pediatric-onset MS; **WBV** = whole-brain volume; **WM** = white matter.

Acute disseminated encephalomyelitis (ADEM) is a mostly monophasic disease that belongs to the clinical spectrum of acquired demyelinating syndromes (ADSs) including monophasic (e.g., optic neuritis and transverse myelitis) and relapsing forms (e.g., neuromyelitis optica spectrum disorders and multiple sclerosis [MS]).[1,2] ADEM is characterized by polyfocal neurologic deficits at onset, encephalopathy, and characteristic MRI findings, often with widespread involvement of different brain regions including the brainstem and spinal cord.[3,4] Most commonly, lesions are large and hazy, located in the subcortical and deep white matter (WM), but they can affect also cortical and deep gray matter (GM) areas and rarely show contrast enhancement.[4,5] The majority of patients with ADEM experience a monophasic course, whereas some have relapsing disease (e.g., multiphasic ADEM [MDEM]).

Recently, it was shown that ~50% of children with ADEM and a typical MRI pattern as well as nearly all children with subsequent episodes such as MDEM harbor serum IgG antibodies against the myelin oligodendrocyte glycoprotein (MOG) (MOG-abs).[6] This antibody is now considered to define a newly identified disease entity, termed MOG antibody–associated disease (MOGAD), which occurs both in children and adults.[7] In adults, MOGAD most often presents with optic neuritis or myelitis, whereas ADEM is the most common presentation in children. Although ADEM is typically a monophasic disease, a previous study showed reduced brain volume and failure of age-expected brain growth in children with monophasic ADS, including ADEM.[8] However, it is unclear whether failure of brain growth similarly affects MOG-ab–positive (MOG-positive) and MOG-ab-negative (MOG-negative) patients with ADEM. The aim of our study was, therefore, to compare longitudinal brain volume changes in children with MOG-positive and MOG-negative ADEM at first clinical presentation and over time.

Methods

Patients

Patients were recruited from 12 hospitals in Germany, Austria, Italy, and Latvia. Inclusion criteria were (1) diagnosis of ADEM according to the criteria of the International Pediatric Multiple Sclerosis Study Group[3]; (2) available high-resolution cerebral MRI scans including 3-dimensional (3D) T1-weighted Magnetization Prepared Rapid Gradient Echo Imaging without contrast agent and fluid-attenuated inversion recovery sequences at disease onset and before steroid treatment; and (3) availability of MOG-abs status.

Twenty-four patients with ADEM were included in the study, where 16 were MOG-positive (age 4.5 [3.2–5.5]; 8 females [50.0%]) and 8 MOG-negative patients (10.4 [5.4–13.1]; 5 females [62.5%]). Clinical outcome was measured by the Expanded Disability Status Scale (EDSS).

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Ethics Committee of the University Witten/Herdecke, Germany, and all caregivers provided informed consent.

MOG-Ab Testing

Serum samples from all patients obtained at onset of the first clinical presentation were analyzed for the presence of IgG MOG and aquaporin-4 antibodies by live cell-based immunofluorescence assays. MOG-abs were tested using full-length MOG (alpha-1 isoform) and IgG (heavy and light chain and constant chain, 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 end-point titers. Titer levels of ≥1:160 were classified as MOG positive as previously described.[9]

MRI Data Acquisition and Analysis

All patients had a baseline high-resolution 3D T1-weighted Magnetization Prepared Rapid Gradient Echo Imaging cerebral MRI sequence without contrast agent at disease onset before steroid treatment. A total of 38 additional follow-up scans were available from 16 patients, of whom 12 (MOG-pos: n = 10) patients had a follow-up MRI time of ≥3 months with a median time to last MRI of 17.5 months (range: 3–61 months) after disease onset.

Patient MRI data were compared with (1) healthy controls from the NIH Pediatric MRI Data Repository. The NIH MRI study of normal brain development created a database to characterize healthy brain development and can now be used as a control data source for studies on childhood disorders.[10] In addition, patient MRI data were compared with (2) age- and sex-matched controls with normal MRI scans with other neurologic disorders (OND: e.g., migraine and tension-type headache). These controls were all scanned at the Children's Hospital Datteln, Witten/Herdecke University, Germany. Preprocessing of MRI

data included lesion filling as described previously.[11] MRI scans were then analyzed using Functional Magnetic Resonance Imaging of the Brain Software Library Structural Image Evaluation with Normalisation of Atrophy Cross-sectional (SIENAX) brain volume measurements as applied in previous studies.[11,12] SIENAX estimates normalized whole brain volume (WBV), GM volume, WM volume, and ventricular CSF volume by using tissue-type segmentation.[13,14]

Statistical Analysis

Medians along with interquartile ranges (IQRs) are reported for continuous variables, relative and absolute frequencies for categorical variables. In addition, boxplots are used to compare the values of baseline WBV and ventricular, gray, and WM volume at disease onset to (1) matched healthy controls from the NIH cohort (1:5, n = 120) and to (2) local controls with ONDs and normal MRI (1:1). Differences in brain volume between groups were analyzed with linear mixed models with random intercept by individual to account for the repeated measurement structure of the data and to allow a heterogeneous number of measurements per patient. To correctly model the association of age with brain volume, we included logarithms and second- or third-order polynomials in the regression model and assessed interaction effects between age and patient groups, based on the best model. MOG status, relapse at or prior to MRI (as a time-varying factor), immunotherapy at the time of MRI, EDSS score (0 or >0), sex, and age at baseline were included in all models. Because of the inclusion of sex and age, all observations from the controls were included in these models, irrespective of matching. All statistical analyses were performed using R[15] and additional R packages.[16-20]

Data Availability

Anonymized data and codes will be shared by request from any qualified investigator.

Results

A total of 24 patients with ADEM were included in the study (16 MOG positive and 8 MOG negative). MOG-positive patients were substantially younger than MOG-negative patients (4.5 years [3.2–5.5] vs 10.4 [5.4–13.1]). Six patients (all MOG positive) had further episodes during their disease course ranging from 1 to 6 relapses. The median EDSS score at 3 years after the initial episode was 0 (IQR: 0–1), with a median time to last clinical follow-up of 34 months (IQR: 24–57 months). At last follow-up, 4/8 (50%) MOG-negative patients and 5/16 (31.3%) MOG-positive patients had a residual deficit (EDSS score >1). Further patient demographic data are provided in Table 1.

Reduced Brain Volume in Children With ADEM at Baseline

At baseline and before steroid therapy, children with ADEM showed reduced WBV by −68.5 cm^3 compared with matched local controls (median [IQR] 1,741.9 cm^3 [1,645.1–1,805.2] vs 1,810.4 cm^3 [1,786.5–1,836.2]) and by −39.8 cm^3 to matched NIH controls (median [IQR] 1,781.7 cm^3 [1,719.5–1,829.1], Figure 1A, Table 2; reduced by −46.8 cm^3 compared with combined control groups, Figure 1A, Table 3).

Correspondingly, patients had increased ventricular volume by 7.9 cm^3 compared with local controls (34.3 cm^3 [26.0–43.1] vs 26.4 cm^3 [20.7–31.5]) and by 12.2 cm^3 compared with the NIH controls (22.1 cm^3 [18.4–28.9], Figure 1B, Table 2; increased by 11.9 cm^3 compared with combined control groups, Figure 1A, Table 3). Grey matter volume at baseline was similar to controls (Figure 1C, Table 3), whereas WM volume was reduced by −44.8 cm^3 compared with controls (Figure 1D, Table 3).

Baseline Brain Volume Loss Specifically Pronounced in Patients With MOG-Negative ADEM

Brain volume at baseline was substantially reduced in MOG-negative patients by −85.8 cm^3 compared with controls (1,702.9 [1,621.7–1,738.0] vs 1,788.7 [1,734.1–1,827.3]; Figure 2A; Table 4). In MOG-positive patients, brain volume was similar compared with controls (1,764.3 [1,660.5–1,836.3] vs 1,790.1 [1,728.3–1,831.9); Figure 2A; Table 4). Ventricular volume at baseline was increased in both MOG-negative (by 13.6 cm^3) and MOG-positive patients (by 11.6 cm^3) compared with their respective controls (Figure 2B; Table 4). Gray matter volume was similar in both MOG-positive and MOG-negative patients compared with controls (Figure 2C; Table 4). WM volume was reduced in both MOG-negative (by −54.7 cm^3) and MOG-positive (by −40.0 cm^3) patients compared with controls (Figure 2D; Table 4).

More Severe Brain Volume Loss in MOG-Negative vs MOG-Positive Patients

Linear mixed-effect models showed failure of age-expected brain growth in both patients with MOG-positive and MOG-negative ADEM compared with controls: in MOG-negative patients, brain volume was reduced by −138.3 cm^3 (95% CI −193.6 to −82.9) and in MOG-positive patients by −50.0 cm^3 (95% CI −126.5 to −5.2) (Figure 3A). Brain volume was reduced in MOG-negative compared with MOG-positive patients by −88.23 cm^3 (95% CI −147.31 to −29.15). These effects were independent of other potentially relevant variables, including age, sex, immune therapy at the time of MRI, and EDSS score. Immune therapy at the time of MRI scan (reflecting a few follow-up scans during monotherapy or a combination of corticosteroids, IV immunoglobulin (IVIG), and/or rituximab) was associated with reduced brain volume (−139.1 cm^3 [−204.9 to −73.4]).

Correspondingly, a linear mixed model for ventricular volume showed increased volume over time in both MOG-negative (18.2 [11.0–25.4]) and in MOG-positive patients (12.1 [7.2–17.1]), independent of other variables including immunotherapy (18.9 [12.9–24.8]) (Figure 3B). Models for

Table 1 Demographic and Clinical Data of the Cohort of 24 Children With ADEM

	MOG negative (n = 8)	MOG positive (n = 16)	Total (N = 24)
Age			
Median (IQR)	10.41 (5.37–13.06)	4.51 (3.23–5.53)	5.02 (3.23–9.33)
Sex			
Male	3 (37.5%)	8 (50.0%)	11 (45.8%)
Female	5 (62.5%)	8 (50.0%)	13 (54.2%)
Diagnosis			
ADEM	8 (100.0%)	10 (62.5%)	18 (75.0%)
ADEMON	0 (0.0%)	3 (18.8%)	3 (12.5%)
MDEM	0 (0.0%)	3 (18.8%)	3 (12.5%)
Oligoclonal bands			
No	7 (87.5%)	13 (81.2%)	20 (83.3%)
Yes	1 (12.5%)	3 (18.8%)	4 (16.7%)
CSF cell count			
Median (IQR)	10.00 (5.00–18.00)	32.50 (11.50–54.50)	22.00 (9.00–49.50)
Missing	1 (12.5%)	0 (0%)	1 (4.17%)
Monophasic disease			
No	0 (0.0%)	6 (37.5%)	6 (25.0%)
Yes	8 (100.0%)	10 (62.5%)	18 (75.0%)
Relapsing disease			
No	8 (100.0%)	10 (62.5%)	18 (75.0%)
Yes	0 (0.0%)	6 (37.5%)	6 (25.0%)
No. of relapses			
Median (IQR)	0.00 (0.00–0.00)	0.00 (0.00–1.00)	0.00 (0.00–0.25)
Any immune therapy			
No	8 (100.0%)	13 (81.2%)	21 (87.5%)
Yes	0 (0.0%)	3 (18.8%)	3 (12.5%)
Any steroids			
No	8 (100.0%)	15 (93.8%)	23 (95.8%)
Yes	0 (0.0%)	1 (6.2%)	1 (4.2%)
Any IVIG			
No	8 (100.0%)	13 (81.2%)	21 (87.5%)
Yes	0 (0.0%)	3 (18.8%)	3 (12.5%)
Any rituximab			
No	8 (100.0%)	15 (93.8%)	23 (95.8%)
Yes	0 (0.0%)	1 (6.2%)	1 (4.2%)
Time last EDSS score (mo)			
Median (IQR)	32.50 (24.00–50.50)	34.00 (24.75–57.00)	34.00 (24.00–56.50)

Continued

Table 1 Demographic and Clinical Data of the Cohort of 24 Children With ADEM *(continued)*

	MOG negative (n = 8)	MOG positive (n = 16)	Total (N = 24)
Last EDSS score			
Median (IQR)	0.50 (0.00–2.25)	0.00 (0.00–0.25)	0.00 (0.00–1.00)
Residual deficit			
No	4 (50.0%)	11 (68.8%)	15 (62.5%)
Yes	4 (50.0%)	5 (31.2%)	9 (37.5%)
EDSS score > 0			
0	4 (50.0%)	11 (68.8%)	15 (62.5%)
>0	4 (50.0%)	5 (31.2%)	9 (37.5%)
Whole brain volume (cm^3)			
Median (IQR)	1,702.90 (1,621.65–1,737.95)	1,764.26 (1,660.53–1,836.31)	1,741.93 (1,645.09–1,805.18)
Ventricular volume (cm^3)			
Median (IQR)	35.64 (20.59–43.07)	34.25 (28.10–42.95)	34.25 (26.00–43.07)
Grey matter volume (cm^3)			
Median (IQR)	1,020.34 (855.00–1,098.78)	1,058.52 (1,004.05–1,106.88)	1,043.84 (985.42–1,102.61)
White matter volume (cm^3)			
Median (IQR)	708.42 (683.27–767.22)	710.40 (676.49–722.00)	709.85 (676.49–735.34)

Abbreviations: ab = antibody; ADEM = acute disseminated encephalomyelitis; EDSS = Expanded Disability Severity Score; IQR = interquartile range; MOG = myelin oligodendrocyte glycoprotein; OCB = oligoclonal band.

GM showed reduced volume in MOG-negative by −103.5 cm^3 (−151.5 to −55.4) but not in MOG-positive patients (−8.0 [−66.4 to 50.4]) with a negative effect of current immune therapy (−134.4 [−198.0 to −70.8]) (Figure 3C). In contrast, WM volume showed brain volume loss in both MOG-negative by −50.7 cm^3 (−92.2 to −9.3) and MOG-positive patients by −52.6 cm^3 (−81.0 to −24.1) without a relevant effect of immune therapy at the time of MRI (Figure 3D).

Increased Ventricular Volume in Patients With Relapses

Six patients with ADEM (all MOG positive) had relapses during the course of the disease (3 MDEM and 3 ADEM-optic neuritis) ranging from 1 to 6 episodes over the entire disease course. Three patients received low-dose oral steroids on alternating days for the first 3 months after disease onset. In addition, 3 children with relapsing MOGAD received continuous IVIG, and 1 patient started with additional rituximab therapy.

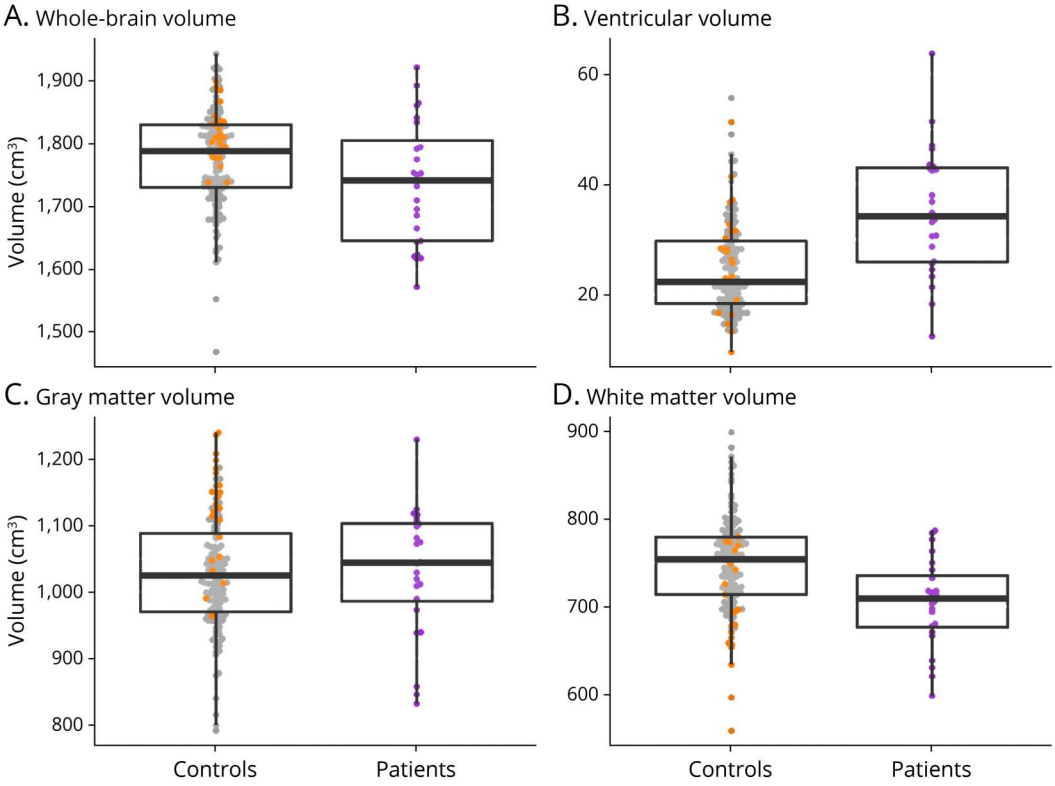
Relapsing disease (all MOG positive) was associated with an increase in ventricular volume by 8.8 cm^3 (4.3–13.3), independent of immune therapy. However, the overall net effect on brain volume in relapsing MOG-positive patients was less pronounced compared with the brain volume loss observed in MOG-negative patients (Figure 3A).

Discussion

In this study, we show that both patients with MOG-positive and MOG-negative ADEM experience brain volume loss and failure of age-expected brain growth. However, brain volume loss is more pronounced in MOG-negative patients. Remarkably, the difference of MOG-negative and MOG-positive WBV loss is driven by GM loss in MOG-negative patients, whereas the amount of WM volume loss is similar in both groups. Relapsing disease in MOG-positive patients is associated with an additional negative effect on brain volume (increased ventricular volume) over time compared with monophasic MOG-positive patients. This suggests that MOG-ab status carries prognostically relevant information with worse brain health outcomes in patients with MOG-negative ADEM indicating differences in underlying pathophysiologic processes.

Impairment of age-expected brain growth has been previously shown by us and others in children with MS, the prototypical demyelinating disease with a chronic disease course.[11,21] In addition, we showed that children with pediatric-onset MS (POMS) had substantially reduced brain volumes already at disease onset, suggesting potential detrimental disease activity prior to first clinical presentation.[11] Over time, patients with POMS show additional brain volume loss and impaired brain growth, which is most likely attributed to cumulating brain-

Figure 1 Brain MRI Volumes at Baseline in ADEM



Local controls (orange dots; matched 1:1; n = 24) with normal MRI (left) vs NIH healthy controls (gray dots; matched 1:5; n = 120) vs patients with ADEM (n = 24). (A) Whole-brain volume. (B) Ventricular volume. (C) Gray matter volume. (D) White matter volume. Controls are matched for age and sex. All volumes are normalized to skull size. ADEM = acute disseminated encephalomyelitis.

damaging effects due to the chronic disease course in MS, despite treatment with baseline disease-modifying therapies. In a recent study, it was observed that the disease-modifying treatment fingolimod significantly reduced the rate of brain volume loss for up to 2 years compared with interferon β-1a in POMS.[22] Of interest, another study[8] could show that also patients with a monophasic demyelinating event including ADEM and other forms of monophasic non-MS demyelinating syndromes experienced impaired age-expected brain growth.

It has long been suspected that ADEM might encompass a more heterogeneous group of different neuroinflammatory syndromes.[1] The presence of MOG-abs in around 50% of patients with ADEM leads to the identification of a unique subset of children with ADEM often with characteristic MRI finding and clinical symptoms belonging to the newly defined disease spectrum of MOGAD.[7] Our study now shows that both patients with MOG-positive and MOG-negative ADEM have brain volume loss and impaired brain growth. However, MOG-negative patients are substantially more affected both at baseline and at follow-up compared with MOG-positive patients. Importantly, the disease course of MOG-negative ADEM and the majority of MOG-positive ADEM is monophasic. In line with this, we recently showed that children with the autoimmune and mostly monophasic N-methyl-D-aspartate receptor encephalitis similarly showed dramatic failure of brain growth over time.[12] This suggests that monophasic (i.e., nonchronic) demyelinating and other neuroinflammatory events in the developing brain can lead to volume loss and failure of brain growth. Although a single inflammatory event might be enough to cause these observed brain damages, a chronic inflammatory component in these neuroinflammatory diseases such as in ADEM cannot be excluded. Of interest, the observed brain volume loss at baseline seemed to be restricted to patients with MOG-negative ADEM. Although the multiple and large lesions in brain MRI scans of patients with ADEM at acute presentation would rather suggest brain edema, the found brain volume loss at baseline is surprising. Because this volume loss is only observed in MOG-negative ADEM, this might suggest a potentially chronic (as in POMS) or developmental brain disorder requiring a better understanding of disease pathology in patients with MOG-negative ADEM.

Over one-third of MOG-positive (and none of the MOG-negative) patients in our study had a relapsing disease course, which is in line with the previous literature suggesting relapsing diseases in up to 50% of patients with MOG-positive ADEM.[7] As in chronic POMS, children with relapsing forms of MOGAD may have recurrent attacks with repeated damage

Table 2 Demographic and MRI Volumetric Data of Patients With ADEM, Matched Local Controls With Normal-Appearing MRI (NAMRI), and Matched Healthy NIH Controls

	Local controls (n = 23)	NIH controls (n = 120)	Patients (n = 24)	Total (N = 167)
Age				
Median (IQR)	5.34 (3.28–9.65)	5.25 (3.03–9.38)	5.02 (3.23–9.33)	5.25 (3.04–9.64)
Sex				
Male	11 (47.8%)	55 (45.8%)	11 (45.8%)	77 (46.1%)
Female	12 (52.2%)	65 (54.2%)	13 (54.2%)	90 (53.9%)
Whole-brain volume (cm^3)				
Median (IQR)	1,810.35 (1,786.47–1,836.16)	1,781.65 (1,719.51–1,829.05)	1,741.93 (1,645.09–1,805.18)	1,784.46 (1,722.06–1,830.41)
Ventricular volume (cm^3)				
Median (IQR)	26.43 (20.74–31.52)	22.05 (18.37–28.90)	34.25 (26.00–43.07)	24.42 (19.06–31.52)
Gray matter volume (cm^3)				
Median (IQR)	1,125.39 (1,050.10–1,169.01)	1,012.53 (964.49–1,055.88)	1,043.84 (985.42–1,102.61)	1,026.96 (970.79–1,093.61)
White matter volume (cm^3)				
Median (IQR)	694.55 (661.90–751.62)	759.90 (721.75–786.88)	709.85 (676.49–735.34)	744.97 (705.99–777.73)

Abbreviations: ADEM = acute disseminated encephalomyelitis; IQR = interquartile range.

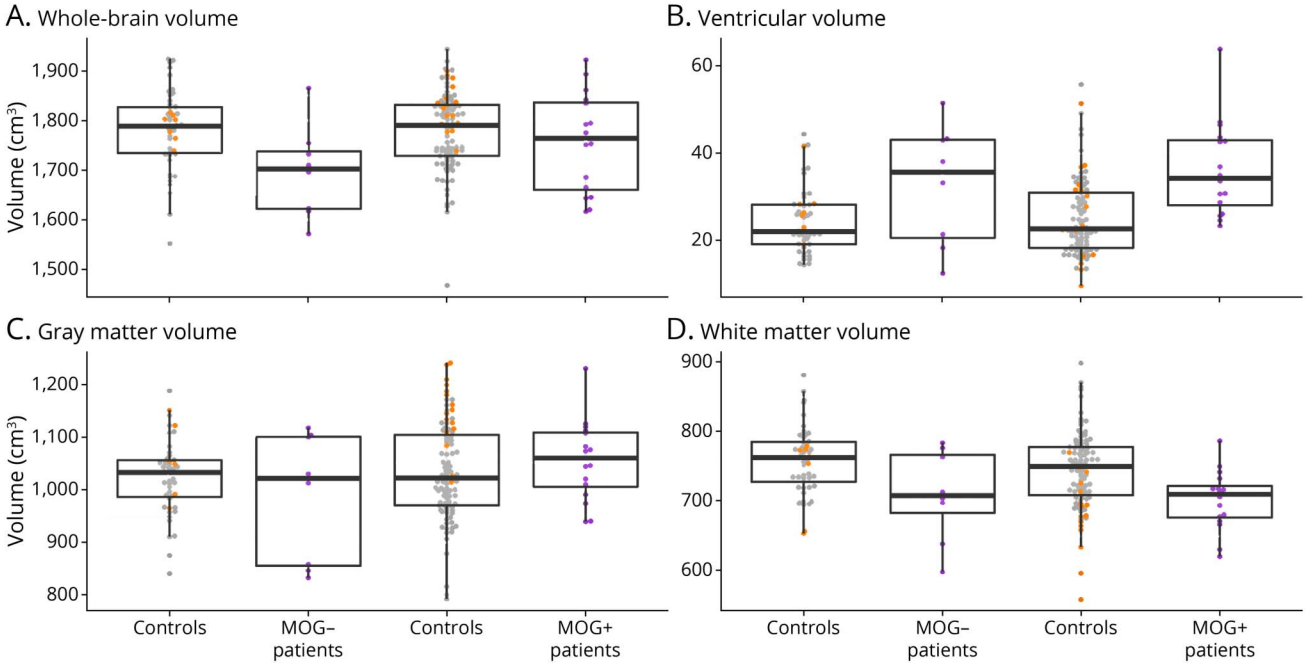
to the developing brain. Indeed, we found that patients with relapsing MOGAD showed more brain volume loss (indirectly suggested by increased ventricular volume) compared with patients with monophasic MOGAD. However, the overall negative effect on brain growth in these patients with relapsing MOGAD was less severe compared with the damage in patients with MOG-negative ADEM despite their monophasic disease course. This is supported by the observation that WM volume is similarly reduced in both MOG-positive and MOG-negative patients, whereas GM is only affected in

Table 3 Demographic and MRI Volumetric Data of Patients With ADEM and Combined Control Patients (Local Controls and NIH Controls)

	Group control (n = 143)	Group patient (n = 24)	Total (N = 167)
Age			
Median (IQR)	5.25 (3.04–9.64)	5.02 (3.23–9.33)	5.25 (3.04–9.64)
Sex			
Male	66 (46.2%)	11 (45.8%)	77 (46.1%)
Female	77 (53.8%)	13 (54.2%)	90 (53.9%)
Whole brain volume (cm^3)			
Median (IQR)	1,788.68 (1,730.88–1,830.41)	1,741.93 (1,645.09–1,805.18)	1,784.46 (1,722.06–1,830.41)
Ventricular volume (cm^3)			
Median (IQR)	22.40 (18.41–29.80)	34.25 (26.00–43.07)	24.42 (19.06–31.52)
Gray matter volume (cm^3)			
Median (IQR)	1,024.66 (969.67–1,087.33)	1,043.84 (985.42–1,102.61)	1,026.96 (970.79–1,093.61)
White matter volume (cm^3)			
Median (IQR)	754.63 (714.49–780.09)	709.85 (676.49–735.34)	744.97 (705.99–777.73)

Abbreviations: ADEM = acute disseminated encephalomyelitis; IQR = interquartile range.

Figure 2 Brain Volumes at Baseline in MOG-Negative vs MOG-Positive ADEM



Baseline MRI whole-brain volume in patients with MOG-negative vs MOG-positive ADEM compared with NIH healthy controls (gray dots) and local controls (orange dots) with normal MRI. (A) Whole-brain volume. (B) Ventricular volume. (C) Gray matter volume. (D) White matter volume. Controls are matched for age and sex. All volumes are normalized to skull size. ADEM = acute disseminated encephalomyelitis; MOG = myelin oligodendrocyte glycoprotein.

MOG-negative patients but not MOGAD. This selective effect on GM seems to contradict previous studies in children with ADS, which showed brain volume loss mainly driven by reduced WM growth. Nevertheless, similar to our study, they found that GM volumes were not reduced at onset but showed impaired age-expected growth over time.[8] This is an important observation in POMS but also monophasic ADS, where GM loss, specifically deep GM volume loss (e.g., thalamus), has been repeatedly shown as an important and early region of brain damage.[21,23-26] Importantly, the previous study on brain volume in pediatric ADS did not differentiate between MOG-positive and MOG-negative ADEM.[8] Although ADEM is primarily regarded as a WM disease, evidence from clinical, imaging, and neuropathologic studies suggests that cortical involvement is part of the disease process, which was particularly shown in association with MOG-abs.[27-29] In line with this, a recent neuropathological study using autopsies and biopsies from children and adults with ADS and serum MOG-abs found that MOGAD pathology was characterized by the presence of perivenous and confluent WM demyelination, with an overrepresentation of intracortical demyelinated lesions compared with typical MS.[27] Moreover, several reports described patients with MOG-abs including children who have symptoms of encephalitis clinically indistinguishable from viral or other autoantibody-mediated forms.[29,30] In particular, children with MOGAD encephalitis can also have other MRI features such as involvement of cortical regions with absent diffusion restriction and absent contrast enhancement and a remarkable resolution of findings after high-dose steroid treatment.[29] Further evidence of neuroaxonal injury in ADEM comes from studies that assessed serum neurofilament light chain (NfL) levels—a marker of axonal integrity—in patients with MOG-positive ADS other than MS. NfL levels were significantly elevated compared with controls and POMS suggesting relevant axonal damage in this condition.[31,32] These findings are in line with our observation of brain volume loss over time including both WM and GM volume loss in patients with MOG-positive ADEM. Moreover, our findings suggest that GM damage might be even more prominent in patients with MOG-negative ADEM. This highlights the need for a better understanding of the pathology in MOG-negative ADEM, which might potentially encompass a heterogeneous group of neuroinflammatory conditions.

We did not find an association between persistent clinical deficits (measured as physical disability on the EDSS score) and brain volume loss, given adjustment for other influential variables. Consistent with previous literature, the majority of our patients had a full clinical recovery.[1] However, long-term cognitive deficits have been repeatedly reported in children with ADEM despite full clinical recovery, suggesting potential subclinical long-term brain damage.[33-36] Further studies are needed to correlate long-term brain volume development with cognitive outcome.

Table 4 MRI Volumetric Data of Patients With MOG-Negative and MOG-Positive ADEM vs Respective Combined Control Patients (Local Controls and NIH Controls)

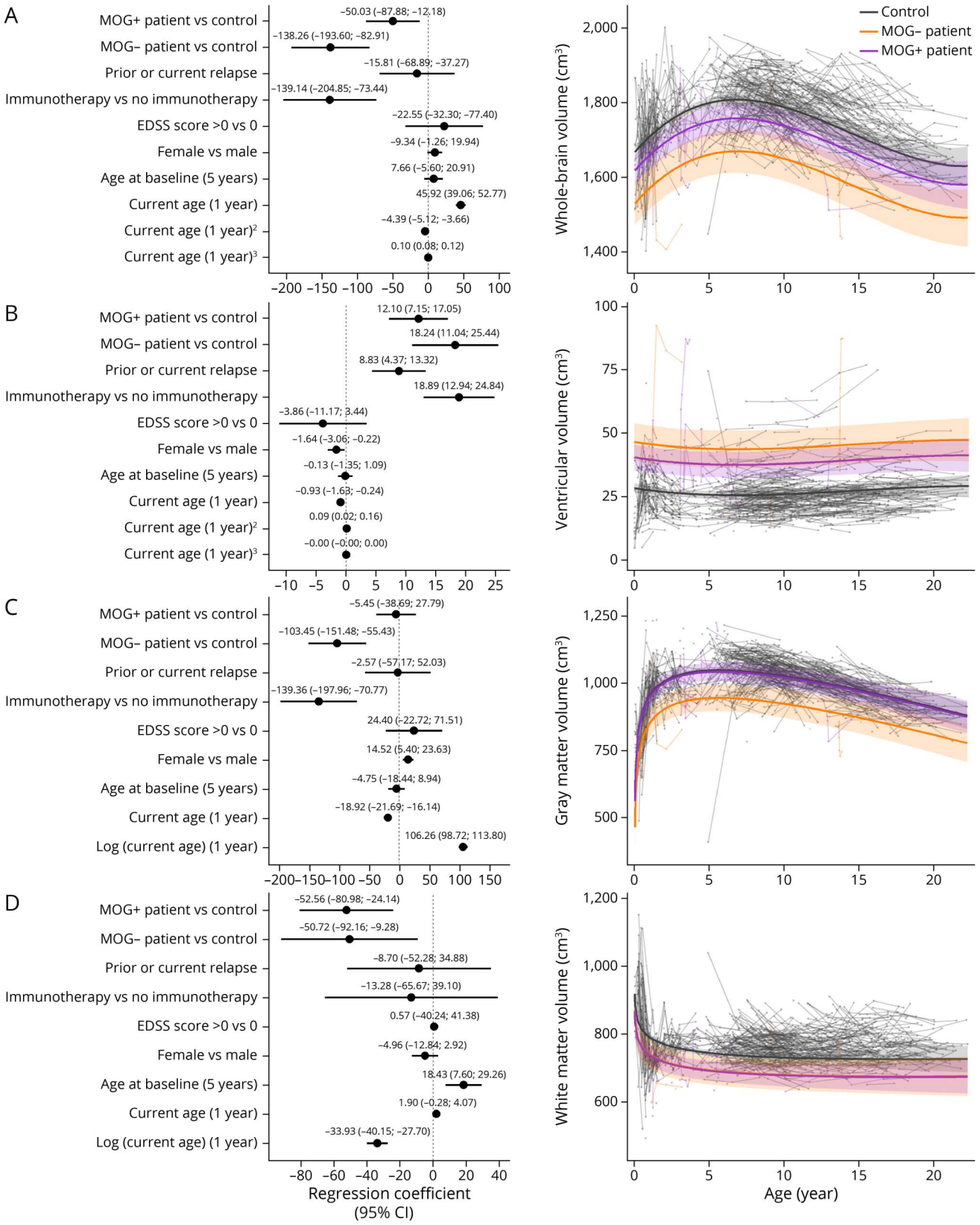
	Control (MOG-matched) (n = 47)	MOG-patients (n = 8)	Control (MOG+ matched) (n = 96)	MOG+ patient (n = 16)	Total (N = 167)
Age					
Median (IQR)	11.36 (6.22–13.18)	10.41 (5.37–13.06)	4.33 (3.04–5.62)	4.51 (3.23–5.53)	5.25 (3.04–9.64)
Sex					
Male	18 (38.3%)	3 (37.5%)	48 (50.0%)	8 (50.0%)	77 (46.1%)
Female	29 (61.7%)	5 (62.5%)	48 (50.0%)	8 (50.0%)	90 (53.9%)
Whole-brain volume (cm^3)					
Median (IQR)	1,788.68 (1,734.07–1,827.30)	1,702.90 (1,621.65–1,737.95)	1,790.11 (1,728.29–1,831.91)	1,764.26 (1,660.53–1,836.31)	1,784.46 (1,722.06–1,830.41)
Ventricular volume (cm^3)					
Median (IQR)	22.01 (19.16–28.23)	35.64 (20.59–43.07)	22.63 (18.28–30.96)	34.25 (28.10–42.95)	24.42 (19.06–31.52)
Gray matter volume (cm^3)					
Median (IQR)	1,031.37 (984.75–1,054.17)	1,020.34 (855.00–1,098.78)	1,021.30 (968.87–1,102.73)	1,058.52 (1,004.05–1,106.88)	1,026.96 (970.79–1,093.61)
White matter volume (cm^3)					
Median (IQR)	763.13 (728.05–785.94)	708.42 (683.27–767.22)	750.44 (708.98–778.59)	710.40 (676.49–722.00)	744.97 (705.99–777.73)

Abbreviations: ADEM = acute disseminated encephalomyelitis; IQR = interquartile range; MOG = myelin oligodendrocyte glycoprotein.
Patients were matched to NIH controls at a ratio of 1:5 (MOG negative: 8 vs 40 and MOG positive 16 vs 80). In addition, we matched patients to local controls at a ratio 1:1 (1 control for MOG negative had to be excluded in retrospect due to artifacts leading to n = 7). Total control cohort for MOG-negative (n = 47) and MOG-positive patients (n = 96).

Limitations of our study include the relatively small sample size, as well as the limited and heterogeneous number of follow-up MRI scans, mostly as a result of the MRI quality inclusion criteria. To address this, we applied mixed-effect linear models to account for variable visit numbers and intervals. Although treatment effects on brain volume on follow-up scans cannot be excluded, we included a simplified treatment variable in the models (operationalized as any type of immune therapy—i.e., corticosteroids, IVIG, or rituximab—at or 4 weeks before the time of the MRI scan) and as such showed that the observed effects were independent of treatment. However, neither the study design nor the available number of patients and follow-up MRI scans during treatment were sufficient to draw reasonable conclusions on specific treatment effects. Another limitation is the multicenter design with different MRI scanners in the study. However, the applied analysis software has been shown to be relatively robust to scanner differences when assessing WBV.[37] In addition, we included a second control group from the site with the most patient MRI scans (21 out of 62 scans) to best control for scanner bias. As such, these local German controls showed some differences in brain volumes compared with the larger US NIH control cohort. However, the observed findings in patient brain volume changes were consistent when comparing patients with either control group separately. In future studies, each patient should ideally have its corresponding control measured at the same scanner. However, importantly, the multicenter setting of the NIH control cohort reflects the multicenter design of our study and thus increases the robustness of the observed findings. Although most children had no neurologic sequelae, no neuropsychological tests were performed to address potential cognitive impairment as a result of brain volume and specifically GM volume loss. Future studies should include these parameters in a prospective longitudinal study design.

In summary, our study analyzed in detail volumetric MRI changes in pediatric ADEM with and without MOG-abs at disease onset and over time. We show that patients with both MOG-positive and MOG-negative ADEM show substantial brain volume loss and impaired brain growth over time with a more pronounced effect in MOG-negative patients. Although relapsing ADEM (i.e., MDEM and ADEM-ON) is associated with more brain volume loss compared with monophasic MOG-positive ADEM, the

Figure 3 Longitudinal Brain Volume Development



Linear mixed-effect model for brain volume over time in patients (orange: MOG positive; purple: MOG negative) vs controls (black). (A) Whole-brain volume. MOG negative vs MOG positive: −88.23 cm^3 (95% CI −147.31 to −29.15). (B) Ventricular volume. (C) Gray matter volume. (D) White matter volume. Each dot represents 1 single MRI scan, and each line connects multiple MRI scans from 1 individual. Regression coefficients for each linear model with 95% CI. MOG = myelin oligodendrocyte glycoprotein.

strongest impairment of brain growth is observed in MOG-negative patients. Of interest, this additional brain volume loss of MOG-negative patients is primarily driven by loss of GM volume. These findings have important implications for the acute and long-term management of children with ADEM including cognitive assessment and counseling of parents and caregivers.

Study Funding

F. Bartels is a participant in the BIH-Charité Clinician Scientist Program funded by the Charité–Universitätsmedizin Berlin and the Berlin Institute of Health. C. Finke and F. Bartels are supported by the Berlin School of Mind and Brain, Humboldt-University, Berlin, Germany. C. Finke is supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation), grant numbers 327654276 (SFB 1315), FI 2309/1-1 (Heisenberg Program), and FI 2309/2-1; and the German Ministry of Education and Research (BMBF), grant number 01GM1908D (CONNECT-GENERATE). K. Rostásy was supported by grants number 14158 and 15918 from the Jubileumsfond of the Austrian National Bank. Markus Reindl was supported by a research grant BIG WIG MS from the Austrian Federal Ministry of Science, Research and Economy.

Disclosure

F. Bartels, B. Baumgartner, A. Blaschek, E.M. Wendel, A. Bertolini, M. Karenfort, M. Baumann, R. Cleaveland, A. Wegener-Panzer, T. Reindl, and C. Finke report no disclosures. G. Cooper received speaker honoraria from Merck and Bayer, unrelated to this study. M. Reindl receives payments for antibody assays (AQP4- and anti-neuronal antibodies) and for AQP4- and MOG-antibody validation experiments organized by Euroimmun (Germany). K. Rostásy received speaker's honoraria from Merck and served on the advisory board of the PARADIGM study without payment. Go to Neurology.org/NN for full disclosures.

Publication History

Received by *Neurology: Neuroimmunology & Neuroinflammation* May 4, 2022. Accepted in final form October 10, 2022. Submitted and externally peer reviewed. The handling editor was Editor Josep O. Dalmau, MD, PhD, FAAN.

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Continued

Appendix *(continued)*

Name	Location	Contribution
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Kevin Rostásy, MD	Witten/Herdecke University, Children's Hospital Datteln, Department of Pediatric Neurology, Datteln, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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