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A20 (TNFAIP3) Distinguishes Attack From Remission in Pediatric Patients With Monophasic MOGAD

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Background and Objectives

Acquired demyelinating syndromes associated with serum antibodies against myelin oligodendrocyte glycoprotein have been recognized as MOG-IgG–associated disorders (MOGADs). Patients with MOGAD show distinct features compared with individuals with multiple sclerosis (MS) or neuromyelitis optica spectrum disorders (NMOSDs). Up to 50% of patients experience relapsing disease courses, usually associated with persisting high MOG-IgG titers. However, further biomarkers are needed to discriminate monophasic from multiphasic MOGAD. Recently, lowered levels of tumor necrosis factor α–induced protein 3 (TNFAIP3, or A20) have been shown to be associated with attack in a small group of pediatric patients with MOGAD. The aim of this study was to evaluate A20 as a possible biomarker discriminating attack from remission in a larger cohort of pediatric patients with MOGAD.

Methods

In this cohort study, we tested 162 serum samples from 62 pediatric patients with MOGAD for A20 levels using commercially available ELISA kits. To compare A20 levels with those in non-MOGAD patients, we further included 46 serum samples from 37 pediatric patients with MS, NMOSD with AQP4-IgG, clinically isolated syndrome, or other neurologic disorders.

Results

In grouped analysis, A20 serum levels were significantly lower during attack compared with remission in patients with monophasic MOGAD. In grouped analysis of patients with multiphasic MOGAD, there was no such significant difference in A20 levels at attack vs remission. Among patients (n = 10) with paired attack and remission time points, there was a significant difference in A20 levels (p = 0.029). A20 levels were tendentially higher in patients on immunomodulatory treatments compared with untreated patients.

Discussion

Reflecting the anti-inflammatory role of A20, its relative decrease during attacks might even start before the patient's first symptoms. Thus, longitudinal evaluation of A20 at (yet to identifiable) standardized time points might have prognostic implications. Serum A20 levels in pediatric patients with MOGAD may help to distinguish attacks from remission in monophasic disease courses. Consequently, A20 needs to be prospectively investigated in standardized multicentric longitudinal study designs, with a focus on diagnostic, prognostic, and therapeutic implications.

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Supplementary Material

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Glossary

ADEM = acute disseminated encephalomyelitis; **ADEM-ON** = ADEM followed by optic neuritis; **ADS** = acquired demyelinating syndrome; **AQP4-IgG** = aquaporin-4-immunoglobulin G; **CIS** = clinically isolated syndrome; **LETM** = longitudinally extensive transverse myelitis; **MDEM** = multiphasic acute DEM; **MOGAD** = MOG-IgG–associated disorder; **MOG-IgG** = myelin oligodendrocyte glycoprotein–immunoglobulin G; **MS** = multiple sclerosis; **NMOSD** = neuromyelitis optica spectrum disorder; **OCB** = oligoclonal band; **ONDs** = other neurologic disorders; **RON** = recurrent ON; **TNFAIP3** = tumor necrosis factor α–induced protein 3.

Introduction

Acquired demyelinating syndromes (ADSs) are defined by acute-onset neurologic symptoms with evidence of CNS demyelination.[1] Monophasic and multiphasic phenotypes of pediatric ADS encompass acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), transverse myelitis (TM), pediatric-onset multiple sclerosis (MS), and neuromyelitis optica spectrum disorders (NMOSDs).[2] These phenotypes are pathogenetically distinct from each other and present with certain differences regarding age at onset, disease severity, treatment response, radiologic, pathologic, and CSF findings.[3-8] In addition, the detection of antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG) and the water channel protein aquaporin-4 (AQP4-IgG), respectively, helped to further distinguish MOG-IgG–associated disorders (MOGADs) from MS and AQP4-IgG–positive NMOSD and even showed that MOG-IgGs are associated with a non-MS course.[9-20] However, because of overlapping clinical presentations, final diagnosis directly at baseline is still challenging.

The incidence of MOGAD is higher in the pediatric (0.31/100,000) than in the adult population (0.13/100,000).[21] MOG-IgGs are prevalent in approximately one-third of all pediatric patients with ADS and could be detected in approximately 53% of patients with ADEM, 40% of those with ON, and 18% of those with TM. AQP4-IgG–negative NMOSD presents in 40% of all pediatric patients as MOGAD subtype NMOSD-like phenotype.[4] The clinical phenotype seems to be age-dependent because of a changing MOG expression pattern during brain development. While younger children are more likely to have ADEM and ADEM-like presentations, older children and adults usually show an opticospinal phenotype (i.e., ON, TM, and brainstem affection).[7,21-24]

Diagnostic criteria were repeatedly proposed,[25-27] but in 2020, a broad consensus among European experts in pediatric neurology was reached focusing on clinical phenotypes (eTable 1), neuroimaging, biomarkers, treatment, and outcome.[4] More recently, an international panel proposed diagnostic criteria for adult and pediatric MOGAD in relation to different MOG-IgG titers.[27] In patients with clear positive titers, a core criterion is sufficient for diagnosis, whereas low titers need to be associated with core and supportive criteria.[27]

Prevalence of relapsing MOGAD varies because of differences in study designs, patient selection, and follow-up time and ranges between 30% and 50%.[22,28,29] Persisting MOG-IgG titers seem to predict a recurrent disease course in children (but not in adults) but can only be evaluated over time, meaning that there is no distinct biomarker at baseline indicating a monophasic or multiphasic course.[22,25,30,31]

The zinc finger (de)ubiquitinating enzyme A20 (or tumor necrosis factor α–induced protein 3, TNFAIP3) has gained attention recently because of its anti-inflammatory properties. Furthermore, A20 has been shown to inhibit NF-kB activation, be it TNF, IL-1, CD40, pattern recognition receptor, and T-cell and B-cell antigen receptor dependent. Sequence variants of (or located near) the *TNFAIP3* gene in humans are associated with autoimmune diseases.[32-36] Thus, low serum levels of A20 could be a risk or even prognostic factor of autoimmune events. An initial study showed that decreased serum levels of A20 in patients with MOGAD are associated with attack.[37] Accordingly, this easily measurable serum biomarker deserves a retrospective evaluation in a larger study cohort addressing the following questions: (1) are A20 levels different during attack and remission in pediatric MOGAD, (2) are A20 levels different in patients with monophasic and multiphasic MOGAD, (3) is there a correlation between A20 levels and disease-modifying treatments, (4), are A20 levels different in MOGAD compared with non-MOGADs such as MS or NMOSD, (5) are A20 levels different during attack and remission in multiphasic neurologic diseases such as MS, and (6) is there a correlation between A20 level and MOG IgG titer?

Additional biomarkers, such as neurofilament light chain, in neuroimmunologic disorders are currently under investigation.[38] Others, such as optical coherence tomography, are already used in disease phenotypes with affection of the optic nerves. However, we still miss biomarkers distinguishing monophasic from multiphasic MOGAD at baseline, which would have prognostic and therapeutic implications.

Methods

Patients

Since 2009, more than 1,000 pediatric patients with a first suspected episode of ADS were included in our prospective

BIOMARKER study for MOG-IgG and AQP4-IgG testing. Serum and (partly) CSF samples were referred from different centers in Austria, Germany, Switzerland, Lithuania, Turkey, Canada, Sweden, Egypt, Croatia, Argentina, Great Britain, Ukraine, and Italy and analyzed in the neurologic research laboratory of the Department of Neurology, Medical University of Innsbruck, Austria.

For the recruitment from our cohort for the assessment of A20 levels in this retrospective observational study, we used the following inclusion criteria: (1) complete data set of the first event (clinical phenotype, MRI, and CSF results); (2) availability of existing serum samples to evaluate A20 at onset/relapse and/or remission; (3) MOG-IgG and AQP4-IgG testing at baseline and, if existent, at relapse; and (4) written informed consent by the caregivers and/or patients.

Remission was defined as at least 30 days after attack, meaning that every sample taken between baseline and day 29 after onset or attack was considered an attack/relapse sample. This corresponds to the time needed between 2 separate attacks in MS. Considering the possible influence of disease-modifying treatments on A20 levels, we defined untreated serum samples as samples taken before any treatment or 30 days after the last treatment.

Race and ethnicity were assessed using the medical records. In this study, for non-White patients, families selected their regional descent from a list provided (e.g., Near or Middle East). Our control group consisted of pediatric patients from our BIOMARKER study with MS, clinically isolated syndrome (CIS), NMOSD, or other neurologic disorders (ONDs). Clinical data at onset and follow-up were obtained using a standardized questionnaire or the medical discharge summary from the referring physician. Diagnoses were established following the revised International Pediatric MS Study Group criteria, the EU pediatric MOG consortium consensus, and the International MOGAD Panel proposed criteria.[4,27,39]

Data of the included patients have already been reported in previous studies.[8,22,29,31,40-42] However, so far, we have never analyzed serum A20 levels in our cohort.

Assessment of A20

A20 levels of included serum samples were analyzed using a commercially available TNFAIP3 ELISA kit (MyBiosource, CA) following manufacturer's instructions. All samples were tested in duplicates. The detection range of the assay was 23.5 to 1,500 pg/mL. The intra-assay precision coefficient of variation was <8%, and the interassay precision coefficient of variation was <10%. The optical density was determined at 450 nm, and the reference wavelength was set at 560 nm. All A20 levels were square root transformed before statistical analysis.

Antibody Assays and CSF Examination

Serum samples from all patients included in the study were analyzed for the presence of MOG-IgG by live cell-based immunofluorescence assays. MOG-IgGs were tested using full-length MOG (α-1 isoform) and IgG-specific (heavy and light chains, Dianova) 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 twofold increments to determine the end point titers. Titer levels of ≥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.[43] Seronegativity was 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.

The presence of oligoclonal bands (OCBs) was assessed by isoelectric focusing as part of diagnostic evaluation in most patients. Type 2 and type 3 patterns were defined as positive OCBs.[44]

Standard Protocol Approvals, Registrations, and Patient Consents

Our study has been approved by the Ethics Committee of the Medical University of Innsbruck, Austria (AN4095). All patients and/or their caregivers provided written informed consent.

Statistical Analysis

We used the robust linear mixed model with the robustlmm package in R to test the association between attack and remission A20 measures. The robust mixed model is suitable for data with repeated measures and can account for possible outlier values. The robust model was adjusted for age, sex, steroid status, medication status, batch, and experimental batch (robustlmm: cran.r-project.org/web/packages/robustlmm/vignettes/rlmer.pdf).

For paired-sample comparison, we used a paired *t* test to compare attack and remission samples.

Data Availability

Any data not included in the article can be provided in anonymized form on request from any qualified researcher.

Results

Demographics of the Study Cohort

Within the abovementioned study cohort, 62 of 172 pediatric patients with detectable MOG-IgG fulfilled the inclusion criteria as well as recently proposed diagnostic criteria for MOGAD.[4,27] All of these MOG-IgG–positive patients were tested negative for AQP4-IgG. At baseline, 34 of 62 patients (55%) presented with ADEM, 15 of 62 (24%) with ON (9/15 unilateral, 6/15 bilateral), 7 of 62 (11%) with NMOSD-like phenotype, and 6 of 62 (10%) with longitudinally extensive TM ([LETM], meaning affection of the spinal cord over 3 segments).

We had 162 available serum samples from these 62 patients. The median age in this group was 5 (range 0–17) years, 33 were female and 29 male, 51 of 62 patients were White, 8 of 62 were from the Near or Middle East, 2 of 62 were South Asian, and 1 of 62 was North African. Median MOG-IgG titers at baseline were 1:2,560 (ADEM), 1:2,560 (ON), 1:320 (TM), and 1:1,280 (NMOSD-like phenotype). Patients diagnosed with MS, CIS, or NMOSD did not show any MOG-IgG (Table 1 provides CSF results).

Of these 62 patients, 38 had a monophasic disease course: 24 with ADEM, 6 with ON (1/6 unilateral, 5/6 bilateral), 4 with LETM, and 4 with NMOSD-like phenotype. The mean duration of follow-up for these 38 patients was 36 (range 4–137) months.

The remaining 24 of 62 patients developed a multiphasic disease course: 9 had recurrent ON (RON), 6 had multiphasic ADEM (MDEM), 5 had NMOSD-like phenotype, 3 had ADEM followed by ON (ADEM-ON), and 1 had overall 3 episodes of LETM. For these 24 patients, we could assess a mean follow-up duration of 68.5 (range 31–140) months.

To compare A20 levels in patients with MOGAD, we further included a control group consisting of 46 serum samples from 37 pediatric patients: 20 fulfilled 2017 McDonald criteria for MS, 1 presented with CIS, and 2 showed AQP4-IgG and were diagnosed as NMOSD (Table 2 provides more details). The remaining 14 of 37 patients had other neurologic disorders (4 with viral meningitis, 2 with frontal lobe epilepsy, 2 with first generalized seizure, 1 with postinfectious cerebellitis, 1 with pons glioma, 2 with polyradiculoneuropathy, 1 with dissection of the right vertebral artery, 1 with cerebral palsy, 1 with anterior spinal artery infarction, 1 with facial nerve palsy, 1 with chronic pain disorder). The median age in this group was 14 (range 0–17) years, 18 were female and 19 male, 36 of 37 patients were White, and 1 of 37 was from the Near or Middle East.

All patients with MOGAD, MS, NMOSD, and CIS and, if appropriate, some of the patients with ONDs received cerebral and, partly, spinal MRI; however, because radiologic parameters were not the focus of our study, we report this fact to emphasize the importance of imaging for differential diagnosis in the included patient groups.

A20 Levels in MOGAD Patient Groups

We evaluated 208 serum samples for A20 levels: 162 of 208 (78%) were from MOGAD, and 46 of 208 (22%) were from other patients. Of the 62 pediatric patients with MOGAD, 84 of 162 samples were from 38 children with a monophasic disease course: 28 of 84 samples were taken at attack and 56 of 84 in remission, meaning that we had 2 to 9 remission samples from 12 of 38 patients. The median A20 level at attack was 80.44 (range 0–225) pg/mL and in remission was 104.54 (range 0–1,179.44) pg/mL.

The remaining 78 of 162 serum samples were taken from patients with multiphasic MOGAD: 16 from attack and 62 during remission. The median time between attack and

Table 1 Demographic, Clinical, and Laboratory Data at Disease Onset

	Patients with MOGAD	MOGAD-ADEM	MOGAD-ON	MOGAD-TM	MOGAD-NMOSD–like phenotype	Control patients	MS	CIS	NMOSD	ONDs
Patients		34/62	15/62	6/62	7/62		20	1	2	14
Median age in y (IQR)		4 (3)	11 (4)	7 (3)	5 (5,5)		14 (2.25)	8 (0)	14 (0)	11 (6.75)
Female:male		15:19	9:6	3:3	1:6		12:8	1:0	1:1	4:10
Race and ethnicity		28/34 White, 5/34 Near or Middle East, 1/34 South Asian	12/15 White, 3/15 Near or Middle East	6/6 White	5/7 White, 1/7 North African, 1/7 South Asian		20/20 White	1/1 White	2/2 White	13/14 White, 1/14 Near or Middle East
Median MOG-IgG titer at baseline (range)		1:2,560 (1:320-40,960)	1:2,560 (1:320-1:5,120)	1:480 (1:160-1:5,120)	1:1,280 (1:160-1:2,560)		0	0	0	—
Median CSF cells/μL (range)		23 (0–338)[a]	1 (0–117)[b]	36.5 (3–109)	38.5 (1–151)[d]		9 (0–50)[e]	na	11 (5–17)	—
CSF OCBs		5/33[a]	1/15[b]	1/5[c]	1/6[d]		14/18[f]	0/0	0/2	—

Abbreviations: ADEM = acute disseminated encephalomyelitis; CIS = clinically isolated syndrome; IQR = interquartile ratio; MDEM = multiphasic acute disseminated encephalomyelitis; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder; ONDs = other neurologic disorders.
[a] Available in 33 of 34 patients.
[b] Available in 14 of 15 patients.
[c] Available in 5 of 6 patients.
[d] Available in 6 of 7 patients.
[e] Available in 17 of 20 patients.
[f] Available in 18 of 20 patients.

Table 2 Demographic, Clinical, and Laboratory Data After Final Diagnosis

	Monophasic MOGAD with	ADEM phenotype	ON phenotype	TM phenotype	NMOSD-like phenotype	Relapsing MOGAD	ADEM-ON phenotype	MDEM phenotype	RON phenotype	NMOSD-like phenotype	TM phenotype
Patients	38	24/38	6/38	4/38	4/36	24	3/24	6/24	9/24	5/24	1/24
Median age in y (IQR)	5 (2.75)	4 (3)	12 (1.5)	6 (6.5)	6 (7.25)	8 (6.25)	5 (4.5)	3 (2)	11 (4)	12 (8)	9 (0)
Female:male	17:21	10:14	2:4	2:2	3:1	16:8	1:2	3:3	7:2	5:0	0:1
Samples on attack to remission	28:56	23:35	3:8	1:7	1:6	16:62	2:8	6:13	5:32	3:7	0:2
Serum samples treated with disease-modifying treatments	2/84	0/2	0/2	0/2	2/2	33/78	1/33	7/33	21/33	4/33	0/33
Serum samples treated with steroids	12/84	11/12	0/12	0/12	1/12	18/78	1/18	6/18	6/18	5/18	0/18
Median A20 level in pg/mL (range; IQR) at attack	80.44 (0–225; 41.58)	82.54 (7.06–225; 41.22)	3.46 (0–91.49; 45.74)	67.89 (-; 0)	101.47 (-; 0)	101.0 (0-3,449.22; 71.26)	59.65 (29.24–90.06; 30.41)	104.55 (84.62–267.07; 18.11)	118.73 (0–3,449.22; 191.68)	103.87 (37.88–269.66; 115.89)	na
Median A20 level in pg/mL (range; IQR) in remission	104.54 (0-1,179.44; 102.19)	111.90 (0–1,179.44; 119.01)	134.68 (31.03–267.53; 83.90)	94.69 (11.11–143.69; 88.77)	72.33 (38.70–166.73; 44.64)	101.56 (0-3,715.78; 62.62)	165.96 (101.40–1,588.62; 56.53)	126.76 (4.23–445.15; 256.47)	96.72 (32.15–3,715.78; 28.94)	104.91 (3.85–153.40; 81.48)	1.16 (0–2.32; 1.16)
Follow-up duration (range) in mo	37.5 (13–137)	38 (13–137)	37 (17–70)	39.5 (24–60)	30 (23–47)	68.5 (31–140)	89 (50–99)	64 (43–78)	60 (31–86)	87 (62–140)	71

Abbreviations: ADEM = acute disseminated encephalomyelitis; IQR = interquartile ratio; MDEM = multiphasic acute disseminated encephalomyelitis; MOGAD = MOG-IgG–associated disorder; NMOSD = neuromyelitis optica spectrum disorder; ON = optic neuritis; RON = recurrent ON; TM = transverse myelitis.

subsequent remission sample was 247 (range 46–2,583) days. The median A20 level at attack was 101.0 (range 0–3,449.22) pg/mL and in remission was 101.56 (range 0–3,715.78) pg/mL (Table 2 provides further details).

Four serum samples were excluded from further analysis because of A20 levels over 1,000 pg/mL (1,179.44, 1,588.62, 3,715.78, 3,449.22 pg/mL): 3 of 4 with monophasic disease course and 1 of 4 with multiphasic disease course.

A20 Levels at Attack vs Remission in Monophasic and Multiphasic MOGAD

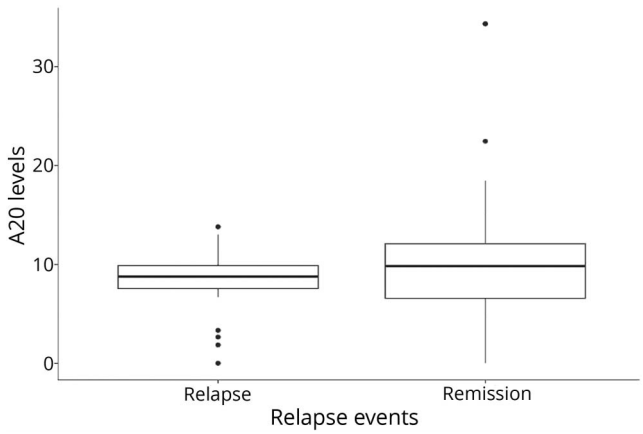
A20 levels in patients with monophasic MOGAD during attack were significantly lower than during remission (p = 0.031) (Figure 1). Patients with multiphasic MOGAD did not show different A20 levels at attack vs remission (p = 0.075). A20 levels at attack were tendentially lower in monophasic than in multiphasic patients, albeit without statistical significance. There was no difference in the A20 levels between monophasic and multiphasic patients during remission.

A20 Is Decreased at Attack in Paired Attack-Remission Samples

In the subset of patients with MOGAD with both attack and remission time points, we compared change in A20 levels in a paired analysis.

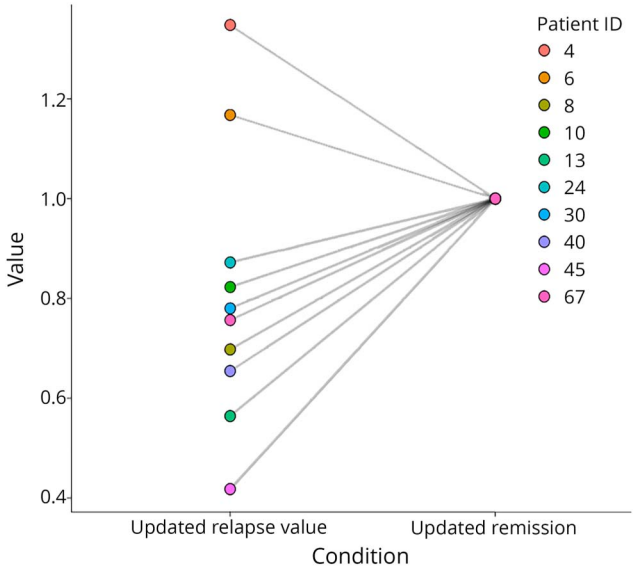
In these 10 patients (5/10 monophasic and 5/10 multiphasic), whose attack and remission samples were tested in the same batch, we could show a statistically significant fold change with the paired t test (p = 0.029, Figure 2 and eTable 2 for individual results).

Figure 1 Patients With Monophasic MOGAD: Attack vs Remission



We compared the attack samples with the remission samples in the monophasic patients. We have used a robust linear mixed model for this analysis, A20 values were log transformed. The analysis was adjusted for sex, batch, disease-modifying treatment, steroid treatment, and experimental part (1/2). Batch stands for the different product batches of the purchased ELISA plates, immunomodulatory and steroid treatment reflects whether a sample was treated or untreated, and the experimental part means that the experiments were performed by 2 independent investigators (C.L. and S.S.). p = 0.031. MOGAD = MOG-IgG–associated disorder.

Figure 2 Paired Attack-Remission MOGAD Serum Samples



In the subset of patients with MOGAD with both attack and remission time points, we compared fold change in A20 levels (square root transformed) in a paired analysis. MOGAD = MOG-IgG–associated disorder.

A20 Levels and Treatment Regimens

Considering all patients, except those with ONDs, A20 levels during attack or remission did not correlate with steroid treatment; i.e., A20 levels in steroid-treated patients were not significantly different from A20 levels in steroid-naïve patients.

In addition, we analyzed the A20 levels in patients treated with immunomodulatory therapies during or within 30 days before serum sampling. Samples (4/206) from patients with NMOSD were excluded from this analysis because of a small sample size.

We compared 35 of 202 samples from 11 patients with MOGAD (4/12 with NMOSD-like phenotype, 3/12 with MDEM, 3/12 with RON, 1/12 with ADEM-ON) and 7 of 202 samples from 7 patients with MS treated with immunomodulatory therapies (24/42 with IV immunoglobulins, 6/42 with interferon β-1a, 5/42 with azathioprine, 3/42 with natalizumab, 1/42 with fingolimod, 1/42 with dimethyl fumarate, 1/42 with interferon β-1a or natalizumab, 1/42 with mycophenolate mofetil), with the remaining 160 of 202 untreated serum samples.

We observed a tendency for higher A20 levels in treated samples from patients on immunomodulatory therapy compared with untreated samples. However, this difference was not statistically significant during either relapse or remission.

A20 Levels in Non-MOGAD Patients

In our control group of 37 patients, we analyzed A20 levels in 46 serum samples: 24 of 46 from 20 with MS, 1 of 46 from 1

Table 3 A20 Levels in Reported Patient Groups

	Monophasic MOGAD	Relapsing MOGAD	MS	CIS	NMOSD	ONDs
Median A20 level in pg/mL (range; IQR) at attack	80.44 (0–225.0; 41.58)	101.0 (0–3,449.22; 71.26)	59.87 (12.46–132.62; 69.36)	48.28	37.88	—
Samples evaluated at attack	28/84	16/78	15/24	1/1	1/4	—
Median A20 level in pg/mL (range; IQR) in remission	104.54 (0–1,179.44; 102.19)	101.56 (0–3,715.78; 62.62)	54.35 (2.20–125.45; 22.68)	—	52.74 (34.58–71.61; 18,52)	—
Samples evaluated in remission	56/84	62/78	9/24	0/1	3/4	—
Median A20 level in pg/mL (range; IQR)	—	—	—	—	—	53.01 (6.80–145.76; 69.63)
Samples evaluated	—	—	—	—	—	17

Abbreviations: CIS = clinically isolated syndrome; IQR = interquartile ratio; MOGAD = MOG-IgG–associated disorder; - = not applicable; ONDs = other neurologic disorders.

with CIS, 4 of 46 from 2 with NMOSD, and 17 of 46 from 14 patients with ONDs. In patients with MS, A20 levels at attack and remission were significantly different ($p = 0.043$) and, of interest, were slightly higher at an attack compared with during remission, the opposite of our findings for patients with MOGAD (Table 3). During an attack, the A20 level in 1 patient with NMOSD was lower than during remission; however, owing to sample size, no significance could be shown.

Overall, A20 levels in this group were not significantly different from A20 levels in patients with MOGAD.

A20 Does Not Correlate With MOG-IgG Titers

In our cohort of patients with MOGAD, A20 levels did not correlate with MOG-IgG titers, sex, or age at onset in a simple linear regression model. MOG-IgG titers at onset were not significantly different between monophasic and relapsing patients.

Discussion

We present a study cohort of 62 children and adolescents with MOGAD and our evaluation of A20 levels as a possible biomarker distinguishing attack from remission, and monophasic from multiphasic disease courses, respectively. A20 levels were significantly lower during attack compared with remission in patients with monophasic MOGAD. In patients with multiphasic MOGAD, no such significant difference in A20 levels was observed between attack and remission. A20 levels at attack were lower in monophasic than in multiphasic disease courses, however, without statistical significance. This finding is quite surprising considering that multiphasic disease courses might be immunologically more active than monophasic ones. There was no difference in A20 levels during remission between monophasic and multiphasic patients. Accordingly, these results support a role for A20 as a biomarker when it comes to distinguishing disease activity from remission in pediatric patients with monophasic MOGAD, who usually represent most of the cases. On the one hand, these results indicate the prospective evaluation of A20 levels with the question of whether there are prognostic dynamics of the levels that indicate an impending attack. On the other hand, the trend toward a difference in A20 levels at attack between monophasic and multiphasic patients requires a higher number of cases to achieve statistical significance. Should this prove to be true in a larger study, A20 would have the potential to offer a prediction of a monophasic or multiphasic course.

In patients with monophasic NMOSD-like phenotype and RON, A20 levels during attack (1 sample for NMOSD-like phenotype, 5 samples for RON) were insignificantly higher than in remission (6 samples for NMOSD-like phenotype, 32 samples for RON), which is contradictory to the lower A20 levels during attack in all other clinical phenotypes and counterintuitive regarding the anti-inflammatory role of A20 and its assumed consumption during a attack. These results might be due to small sample size, however, could also reflect that different clinical phenotypes have varied dynamics of inflammation and by that A20 levels. Larger study cohorts are needed to further evaluate these specific results.

In our paired attack-remission samples, A20 levels were significantly lower at an attack, consistent with a previous report.[37] However, our sample size was limited, with only a subset of patients who had both attack and remission samples tested in the same batch. A20 levels also tended to be higher in samples taken after steroid or other immunomodulatory treatment, albeit without statistical significance. There was no correlation of A20 levels with MOG-IgG.

Reflecting A20's anti-inflammatory role, its relative decrease during attack might even start before the patient's first symptoms. Thus, longitudinal evaluation of A20 at (yet to identifiable) standardized time points might have prognostic implications; i.e., assessing decreasing A20 levels over time

might have even therapeutic consequences. Decreased A20 levels in serum samples of 2 patients with MOGAD who were defined as being "pre-relapse" were already reported: The first sample was taken from their patient 1 2 months before a relapse, reporting "mild visual symptoms" and headache without "radiologic correlation," and the second one from patient 5, who developed "significant new headache not responsive to standard medication."[37]

Owing to the retrospective design of this study, only a small number of longitudinal serum samples were available to compare A20 levels during attack and remission in individual patients and no serum samples were taken shortly before a new attack. Therefore, the possibility that A20 levels might be lower before an attack needs to be further evaluated prospectively. The classification of the 2 patients mentioned above reported by Saxena et al. may represent the earliest phases of an attack in patients with MOGAD.

In our analysis of paired samples from 10 patients with attack and remission time points, we found a statistically significant fold change. Further longitudinal studies assessing A20 levels in the same patient are needed to evaluate the progress of A20 levels over time.

This is one of the first studies evaluating serum A20 levels in patients with autoimmune disease, and overall, assessed A20 levels in patients with MOGAD seem to be higher than in previous reports.[37,45] While serum samples in our study were evaluated with ELISA kits from the same manufacturer as those used by Saxena et al., Xu et al. used a different one. Saxena et al. reported A20 levels between 0.00 and 56.01 pg/mL in their patients, depending on either attack or remission, and between 0.00 and 111.61 pg/mL in their healthy control group. Xu et al. did not state all individual A20 levels, but their figure showed A20 levels below 60 pg/mL in their patient and below 20 pg/mL in their healthy control group. These discrepancies support the obvious need for reference values of A20 levels in all age groups in a cohort of pediatric and adult healthy controls. Another possible and yet to be excluded reason for different A20 levels might be the different ethnical origins between our, Saxena's and Xu's study cohort. While most our patients were White, Saxena's cohort was fairly mixed and Xu's cohort, despite not reported, was most likely mainly East Asian. Because 14 patients of our control group, not considering those with MS and NMOSD, were diagnosed with ONDs, a real comparison with Saxena's and Xu's healthy controls was not possible.

Considering 4 excluded A20 values above 1,000 pg/mL (1,179.44, 1,588.62, 3,715.78, 3,449.22), we were not able to find any common potential reasons for these statistical outliers. They were neither all treated with steroids shortly before the samples were taken, nor were the samples hemolyzed or more often thawed or refrozen than other included samples. Of course, a methodical reason for these high values might be possible as well.

A20 levels in the pediatric patients with MS were slightly higher at an attack vs remission time points. These findings in patients with MS are intriguing and might reflect different disease pathomechanisms compared with MOGAD. Another theoretic explanation might be that all included patients experienced disease activity even if they had no clinical symptoms and were categorized for our study as being in remission. A20 levels in remission were tendentially, but not significantly, higher in patients with MOGAD and MS treated with immunomodulatory drugs compared with those without ongoing treatment. Whether elevated A20 levels correlate with treatment or reflect more active disease courses prompting the treating physicians to start immunomodulatory treatment remains unclear and needs to be further elucidated. We could show no difference between monophasic and multiphasic disease courses in this analysis.

For steroids, a correlation with A20 levels could not be shown, although one would have expected it as the glucocorticoid receptor cooperates with NF-kB stimulating the expression of anti-inflammatory genes such as *TNFAIP3*.[46] Because steroids are the standard treatment regimen in all attacks, whether associated with MOGAD, MS, or NMOSD, we could not include patients who did not receive steroids during attack. Therefore, elevated A20 levels at least 30 days after attack could still be influenced by steroid treatment; however, if compared with A20 levels in patients with ONDs, it seems that A20 levels increased to probably normal ranges. If A20 levels were independent of steroid treatment, this would allow for better comparability across different study cohorts without the need to account for steroid treatment. Because a certain influence of steroids would be physiologically feasible, this aspect needs further evaluation with larger cohorts and standardized time points to collect serum samples.

Recent studies mainly focused on genetic testing in the context of A20[32-36] and were, therefore, less susceptible to influences than evaluation of the product of *TNFAIP3* gene expression with ELISA. Further studies are needed in pediatric patients with ADS including both genetic and immunologic methods.

This study has several limitations. Because the focus of serum sample assessment was to prospectively evaluate MOG-IgG titers and not A20 levels, our study protocol planned evaluations every 6 months. While MOG-IgG titers may not be influenced by current viral infections or recent vaccinations, A20 levels might be and our clinical report form did not specifically ask for these potential biases.

In addition, 25 of 62 patients with MOGAD had multiphasic disease courses. This is indeed in line with recent studies[22,28,29] but might be caused by our multicentric study design as potential reason for patients with complicated, i.e., multiphasic, multiphasic disease courses to be overrepresented. Another potential bias arose from our inclusion criteria, which included patients from our BIOMARKER

study with 1 or more available serum samples. As a result, our study cohort may not reflect the general MOGAD patient cohort.

A20 levels may be influenced by yet-to-be-detected stimuli such as viral infections or medications. Our control group, excluding patients with MS and NMOSD, consisted of patients with ONDs, partly infectious, which might also affect A20 levels and hence skew the A20 results we used for our analysis. Our heterogeneous control group subsumed as "other neurologic disorders" is another limitation of this study. While we could include a certain number of pediatric patients with MS, only 1 patient with NMOSD was included in our analysis. Future studies should address this limitation and include pediatric healthy controls, with special focus on possible factors influencing A20 levels.

Regarding the abovementioned contradictory results of A20 levels in 2 subgroups, another important limitation might be lack of robustness of A20 as a possible biomarker.

Another possible limitation of our study is our combination of onset and genuine relapse samples with attack samples. While it is likely that, pathophysiologically, onset and relapse are comparable, future, prospective studies could evaluate A20 levels of the time points of first attack, i.e., onset, and further attacks, i.e., relapses, separately. Each serum sample was frozen at −80°C for different time points and thawed again for A20 measurement. To our knowledge, there are no data about potential influence of storage time on A20 levels, and hence, it cannot be excluded that this factor had an influence on A20 levels.

In conclusion, A20 levels in pediatric patients with MOGAD may help to distinguish attacks from remission in monophasic disease courses. Therefore, A20 needs to be prospectively investigated in standardized multicentric longitudinal study designs, with a focus on diagnostic, prognostic, or even therapeutic implications.

In addition, it is suggestive that the A20 levels may be higher in treated than in untreated samples. While we were only able to show a certain trend in our patients, albeit without statistical significance, the possible influence of disease-modifying treatments on A20 levels should continue to be explored in future studies.

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Author Contributions

C. Lechner: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. S. Saxena: analysis or interpretation of data. H.A. Lokhande: analysis or interpretation of data. M. Breu: major role in the acquisition of data. A. Eisenkölbl: major role in the acquisition of data. M. Karenfort: major role in the acquisition of data. A. Klein: major role in the acquisition of data. S. Leiz: major role in the acquisition of data. M. Preisel: major role in the acquisition of data. T. Rooney: major role in the acquisition of data. M. Rosso: analysis or interpretation of data. M. Schimmel: major role in the acquisition of data. E.M. Wendel: major role in the acquisition of data. M. Reindl: major role in the acquisition of data. M. Baumann: major role in the acquisition of data. K. Rostasy: major role in the acquisition of data. T. Chitnis: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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