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Early Immunotherapy and Longer Corticosteroid Treatment Are Associated With Lower Risk of Relapsing Disease Course in Pediatric MOGAD

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Abstract

Background and Objectives

We sought to identify early factors associated with relapse and outcome in paediatric-onset myelin oligodendrocyte glycoprotein antibody-associated disorders (MOGAD).

Methods

In a multicenter retrospective cohort of pediatric MOGAD (≤18 years), onset features and treatment were compared in patients with monophasic vs relapsing disease (including cases with follow-up ≥12 months after onset or relapse at any time) and in patients with final Expanded Disability Status Scale (EDSS) 0 vs ≥1 at last follow-up (including cases with follow-up >3 months after last event or EDSS0 at any time). Multivariable logistic regression models were used to evaluate factors associated with relapsing disease course and EDSS ≥ 1 at final follow-up.

Results

Seventy-five children were included (median onset age 7 years; median 30 months of follow-up). Presentation with acute disseminated encephalomyelitis was more frequent in children aged

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Glossary

ADEM = acute disseminated encephalomyelitis; **AQP4** = aquaporin-4; **CBA** = cell-based assay; **EEG** = electroencephalography; **EDSS** = Expanded Disability Status Scale; **MOGAD** = myelin oligodendrocyte glycoprotein antibody–associated disorder; **NfL** = neurofilament light chain; **NMOSD** = neuromyelitis optica spectrum disorder; **OCB** = oligoclonal bands; **ON** = optic neuritis; **TM** = transverse myelitis.

8 years or younger (66.7%, 28/42) than in older patients (30.3%, 10/33) ($p = 0.002$), whereas presentation with optic neuritis was more common in children older than 8 years (57.6%, 19/33) than in younger patients (21.4%, 9/42) ($p = 0.001$). 40.0% (26/65) of patients relapsed. Time to first relapse was longer in children aged 8 years or younger than in older patients (median 18 vs 4 months) ($p = 0.013$). Factors at first event independently associated with lower risk of relapsing disease course were immunotherapy <7 days from onset (6.7-fold reduced odds of relapsing course, OR 0.15, 95% CI 0.03–0.61, $p = 0.009$), corticosteroid treatment for ≥5 weeks (6.7-fold reduced odds of relapse, OR 0.15, 95% CI 0.03–0.80, $p = 0.026$), and abnormal optic nerves on onset MRI (12.5-fold reduced odds of relapse, OR 0.08, 95% CI 0.01–0.50, $p = 0.007$). 21.1% (15/71) had EDSS ≥ 1 at final follow-up. Patients with a relapsing course had a higher proportion of final EDSS ≥ 1 (37.5%, 9/24) than children with monophasic disease (12.8%, 5/39) ($p = 0.022$, univariate analysis). Each 1-point increment in worst EDSS at onset was independently associated with 6.7-fold increased odds of final EDSS ≥ 1 (OR 6.65, 95% CI 1.33–33.26, $p = 0.021$).

Discussion

At first attack of pediatric MOGAD, early immunotherapy, longer duration of corticosteroid treatment, and abnormal optic nerves on MRI seem associated with lower risk of relapse, whereas higher disease severity is associated with greater risk of final disability (EDSS ≥ 1).

Myelin oligodendrocyte glycoprotein (MOG) is a protein expressed in mature oligodendrocytes, located in the outermost layer of myelin sheath in the CNS. MOG antibody–associated disorders (MOGADs) define a subgroup of CNS inflammatory–acquired demyelinating syndromes distinct from MS[1-6] and aquaporin-4 (AQP4) positive neuromyelitis optica spectrum disorder (NMOSD),[7,8] typically including CNS clinical syndromes such as acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), transverse myelitis (TM), and AQP4-seronegative NMOSD.[5,9] Besides, atypical presentations have been more recently described, such as encephalitis and isolated seizures in the absence of CNS demyelination (or with predominant cortical/subcortical rather than white matter involvement) and more severe leukodystrophy-like phenotypes.[5,10-13]

MOGADs have a relapsing course in approximately 40%–56% of adults and in 27%–53% of children.[6,7,11,14-17] The persistence of positive MOG antibodies at follow-up has been repeatedly, although not invariably, reported to be associated with higher risk of a relapsing disease course.[2,4,8,11,14-16,18-22] However, current data do not allow a proper prediction of disease course or final outcome at MOGAD onset.[6,17,20,21,23-26]

In this Italian multicenter cohort of pediatric MOGAD, we strove to identify early clinical-paraclinical factors at disease onset associated with subsequent relapse and final outcome, with particular focus on modifiable factors such as treatment.

Methods

Inclusion Criteria and Data Collection

Patients with MOGAD (defined as positive serum MOG antibodies and at least 1 clinical event consistent with a MOGAD phenotype, as detailed below) and onset in pediatric age (aged 18 years or younger) in Italy were included. Data were collected retrospectively between November 2016 and August 2022, using a structured questionnaire filled in by the treating physician.

Operational Definitions

MOGAD syndromes were categorized as diagnosed by the treating physicians and defined according to the most recent available criteria and definitions including ADEM,[27] ON,[28] TM,[29] NMOSD,[30,31] clinically isolated syndrome,[27] and encephalitis.[11,13,32,33] Relapsing phenotypes were defined as either relapsing ADEM, ON, TM, or NMOSD; ADEM-ON (ADEM followed by ON)[5,34,35]; or relapsing CNS demyelination (relapsing MOGAD not falling into any of the other categories). Patients with MOG antibodies and final diagnosis MS[36] were excluded from the present cohort.

Relapses were defined as a new clinical episode occurring at least 1 month after the last acute attack[5] or, in the case of ADEM, at least 3 months after onset of the previous episode.[11,27] Disease course was categorized as monophasic or relapsing (≥2 total disease events including onset).

Neurologic severity in the acute phase and outcome at last follow-up were assessed using the Kurtzke Expanded Disability Status Scale (EDSS), assigned by the treating physicians and verified by the main investigators.

Investigations in the acute phase were assessed based on the available reports (brain MRI, CSF, electroencephalography [EEG], and MOG antibody testing). Data on type of MOG antibody assay were collected, although diagnosis through live cell-based assay (CBA), currently the gold standard,[37] was not a mandatory requirement for inclusion.

Overall duration of immunotherapy at first MOGAD event (onset) was recorded; in case of relapse while on immunotherapy, duration of treatment was considered as the time on immunotherapy at first MOGAD event until relapse. In case of rituximab, treatment duration was operatively considered to be prolonged for 6 months after rituximab initiation (or until B-cell repopulation if available).

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies.

Statistical Analysis

Data collection was subject to data availability; therefore, in the Results, denominators may differ.

Clinical features and treatment factors at first MOGAD event were compared in patients with monophasic disease course (defined as absence of relapse after at least 12-month follow-up) vs relapsing course (relapse at any time) and in patients with EDSS ≥1 (including only patients with follow-up >3 months after last event)[9] vs EDSS 0 at last follow-up (after any time).

The Mann-Whitney *U* test was used to test for group differences in continuous and ordinal data and the Chi square or Fisher exact test for binary data as appropriate.

A multivariable logistic regression model was used to evaluate the independent effects of prespecified variables of interest on monophasic vs relapsing disease course. Predictor variables were age at disease onset, sex, abnormal brain on MRI at first disease event, abnormal optic nerve(s) on MRI at first disease event, abnormal spine on MRI at first disease event, time from disease onset to first immunotherapy, duration of corticosteroid treatment at first disease event, and use of additional noncorticosteroid treatments. To maximise the number of cases that could be included in the model, MRI spine was assumed to be normal in patients in whom it was not undertaken (i.e., those without any clinical signs or symptoms suggestive of myelitis). Continuous variables (age at disease onset, time to first immunotherapy, duration of corticosteroid treatment) were binarized: The binarization threshold for age was set at 12 years to align with the recent literature,[17] and the binarization thresholds for time to first immunotherapy and duration of corticosteroid treatment were set at the midpoint between the medians of the monophasic and relapsing groups. Kaplan-Meier curves for relapse-free survival were plotted and subgroup comparisons (selected according to significance in the multivariable model) conducted with univariate Cox proportional hazards regression.

A second logistic regression model was used to evaluate the independent effects of the same predictor variables on EDSS ≥1 vs EDSS 0 at final follow-up, with 2 additional predictor variables also included: relapsing vs monophasic disease course and worst EDSS at first disease event (entered as a continuous variable).

The significance threshold was set at $p < 0.05$ for all statistical tests. Statistical analysis used Python 3.8 with *scipy.stats*, *statsmodels*, and *lifelines*.

Standard Protocol Approvals, Registrations, and Patient Consents

The study complied with the general ethical requirements for retrospective observational studies. In particular, no experimental interventions were performed and patient identity cannot be retrieved from the manuscript.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

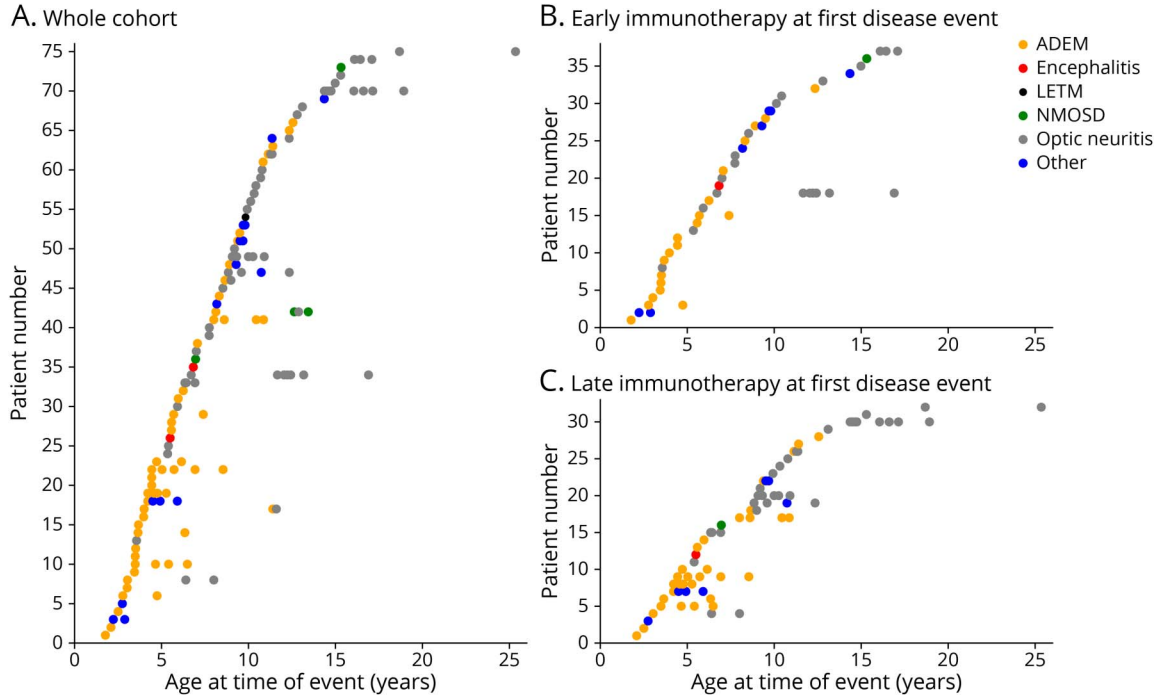
Descriptive Data on the Study Population

Demographics and Clinical Data at First MOGAD Event

Our cohort included 75 patients with MOGAD with onset in pediatric age in Italy, with total 136 disease events, followed up for median 30 months from onset (mean 40.9, range 1–130; data available in 75/75) (Figure 1A, Table 1A, eTable 1, links.lww.com/NXI/A764). Patients were referred by 20 Italian centers and were residents of 14 different Italian regions (eFigure 1, links.lww.com/NXI/A764). Disease onset was between 2008 and 2022 (≥2014 in 86.7%, 65/75). Median age at onset was 7 years (mean 7.7, range 1.8–18.6; data available in 75/75), with 73.3% (55/75) of patients between ages 3 and 10 years at onset.

The commonest events at presentation were ADEM (50.7%, 38/75) and ON (37.3%, 28/75). Presentation with ADEM was more frequent in children aged 8 years or younger at onset (66.7%, 28/42) than in older patients (30.3%, 10/33) ($p = 0.002$) (Figure 1A) and slightly more frequent in male patients (60.0%, 21/35) compared with female patients (42.5%, 17/40) ($p = 0.130$). Conversely, presentation with ON (with/without CNS lesions) was more common in children older than 8 years at onset (57.6%, 19/33) than in younger patients (21.4%, 9/42) ($p = 0.001$) and slightly more frequent in female patients (47.5%, 19/40) compared with male patients (25.7%, 9/35) ($p = 0.052$).

Figure 1 Disease Event Clinical Syndromes



A total of 136 disease events were reported in 75 patients presenting with MOG-antibody–associated disorders (panel A). Presentation with acute disseminated encephalomyelitis (ADEM) was more common in patients aged 8 years or younger at onset ($p = 0.002$) while presentation with optic neuritis was more common in patients older than 8 years ($p = 0.001$). Data on time to treatment at first disease event were available in 69/75 patients; the subgroup of patients receiving immunotherapy <7 days of initial symptom onset (panel B) were less likely to follow a relapsing disease course compared with those not receiving any immunotherapy <7 days of symptom onset (panel C) ($p = 0.002$). LETM, longitudinally extensive transverse myelitis; NMOSD, neuromyelitis optica spectrum disorder.

Worst EDSS at first event was median 3.8 (mean 4.2, range 1–8.5, data available in 68/75). None of the patients required admission to the intensive care unit at onset (0%, 0/75).

Investigations at First MOGAD Event

At onset, brain MRI disclosed parenchymal lesions in 73.6% (53/72), more frequently in children aged 8 years or younger at onset (90.2%, 37/41) than in older patients (51.6%, 16/31) ($p < 0.001$). Optic nerve involvement at first MRI was detected in 48.6% (35/72), slightly more frequently in female patients (59.0%, 23/39) than in male patients (36.4%, 12/33) ($p = 0.056$) (bilateral optic nerve involvement in 57.1%, 20/35; longitudinal optic nerve involvement for ≥ half of its length in 50.0%, 17/34; optic nerve head swelling in 34.3%, 12/35; chiasma involvement in 25.7%, 9/35). Spine MRI at onset was abnormal in 41.8% (23/55) (longitudinally extensive TM extending over ≥3 vertebral segments in 52.2%, 12/23), only slightly less frequently in children aged 8 years or younger at onset (36.1%, 13/36) than in older patients (52.6%, 10/19) ($p = 0.238$).

CSF was abnormal (pleocytosis and/or CSF-restricted oligoclonal bands [OCBs])[35] in 60.0% (36/60). CSF-restricted OCBs were slightly more frequent in children aged 8 years or younger at onset (22.6%, 7/31) than in older patients (8.0%, 2/25) ($p = 0.140$).

EEG was abnormal in 71.4% (30/42) of cases (slow or disorganized activity in 64.3%, 27/42; epileptic activity in 16.7%, 7/42; recorded seizures in 4.8%, 2/42; recorded status epilepticus in 2.4%, 1/41).

In patients with available data on MOG antibody assay (94.7%, 71/75), CBAs were used in all (live CBA in 59/71, fixed CBA in 9/71, CBA not otherwise specified in 3/71).[27] MOG antibody titres and follow-up MOG antibody tests were not homogeneously available and therefore were not analyzed. In a subset of patients with available data on both serum and CSF MOG antibodies (14/75), 64.3% (9/14) had positive serum and negative CSF antibodies, and 35.7% (5/14) had positive serum and CSF antibodies.

Treatment at First MOGAD Event

96.0% (72/75) of patients received immunotherapy at first event: 74.7% (56/75) corticosteroids only, 16.0% (12/75) corticosteroids plus IVIG only, and 5.3% (4/75) corticosteroids plus other combinations of immunotherapy (plasma exchange and/or rituximab and/or mycophenolate mofetil, with or without additional IVIG).

Immunotherapy was started median 5.5 days after symptom onset (mean 9.4, range 0–75; data available in 66/75). The proportion of patients who received immunotherapy <7 days from symptoms onset was significantly lower among patients with disease onset in the years 2008–2013 (11.1%, 1/9) compared with those who presented in the years 2014–2022

Table 1 Demographics, Investigations, Treatment at First Disease Event, Overall Disease Course, and Outcome in the Total Pediatric Cohort of Patients With MOGAD (A), in Children With Monophasic vs Relapsing Disease (B), and in Patients With EDSS 0 vs EDSS > 0 at Last Follow-up (C) (Univariate Analysis)

	A	B			C		
	Total cohort (n = 75)	**Monophasic (n = 39)[a]**	**Relapsing (n = 26)[a]**	***p* Value**	**A. Final EDSS 0 (n = 56)[b]**	**Final EDSS ≥1 (n = 15)[b]**	***p* Value**
Demographics							
Female patients	40/75 (53.3%)	20/39 (51.3%)	15/26 (57.7%)	0.612	31/56 (55.4%)	6/15 (40.0%)	0.290
White race[c]	64/72 (88.9%)	35/38 (92.1%)	21/24 (87.5%)	0.669	50/55 (90.9%)	12/13 (92.3%)	1.000
Age at onset (y)	Median 7, mean 7.7, range 1.8–18.6 (d.a. 75/75)	Median 6.9, mean 7.3, range 1.8–15.3 (d.a. 39/39)	Median 7.4, mean 7.6, range 2.1–18.6 (d.a. 26/26)	0.995	Median 6.3, mean 7.1, range 1.8–18.6 (d.a. 56/56)	Median 9.7, mean 9.1, range 3.4–15.3 (d.a. 15/15)	**0.042**
≥12 years	12/75 (16.0%)	4/39 (10.3%)	4/26 (15.4%)	0.703	6/56 (10.7%)	4/15 (26.7%)	0.202
Type of first MOGAD event							
ADEM	38/75 (50.7%)	16/39 (41.0%)	16/26 (61.5%)	0.105	29/56 (51.8%)	7/15 (46.7%)	0.725
ON (±CNS lesions)	28/75 (37.3%)	16/39 (41.0%)	8/26 (30.8%)	0.401	21/56 (37.5%)	5/15 (33.3%)	0.766
NMOSD	2/75 (2.7%)	2/39 (5.1%)	0/26 (0.0%)	0.513	1/56 (1.8%)	1/15 (6.7%)	0.380
CIS	4/75 (5.3%)	2/39 (5.1%)	2/26 (7.7%)	1.000	3/56 (5.4%)	1/15 (6.7%)	1.000
Encephalitis (±ON)	2/75 (2.7%)	2/39 (5.1%)	0/26 (0.0%)	0.513	2/56 (3.6%)	0/15 (0.0%)	1.000
Isolated LETM	1/75 (1.3%)	1/39 (2.6%)	0/26 (0.0%)	1.000	0/56 (0.0%)	1/15 (6.7%)	0.211
Severity at first MOGAD event							
Worst EDSS at first event	Median 3.8, mean 4.2, range 1–8.5 (d.a. 68/75)	Median 3.3, mean 4.3, range 1–8.5 (d.a. 38/39)	Median 3, mean 4.1, range 1–8.5 (d.a. 21/26)	0.623	Median 3, mean 4, range 1–8.5 (d.a. 51/56)	Median 7, mean 5.1, range 3–8 (d.a. 14/15)	0.072
EDSS ≥4	34/68 (50.0%)	17/38 (44.7%)	10/21 (47.6%)	0.832	22/51 (43.1%)	10/14 (71.4%)	0.061
Investigations at MOGAD onset							
Abnormal brain MRI	53/72 (73.6%)	28/39 (71.8%)	18/23 (78.3%)	0.574	42/55 (76.4%)	8/13 (61.5%)	0.306
Abnormal optic nerves on MRI	35/72 (48.6%)	25/39 (64.1%)	7/23 (30.4%)	**0.010**	26/55 (47.3%)	7/13 (53.8%)	0.670
Abnormal spine MRI	23/55 (41.8%)	13/35 (37.1%)	7/12 (58.3%)	0.200	17/46 (37.0%)	5/7 (71.4%)	0.113
Abnormal CSF	36/60 (60.0%)	18/33 (54.5%)	11/18 (61.1%)	0.651	30/47 (63.8%)	4/10 (40.0%)	0.287
CSF white blood cells >4 μL	35/58 (60.3%)	18/32 (56.3%)	10/18 (55.6%)	0.962	29/46 (63.0%)	4/9 (44.4%)	0.459
CSF-restricted OCBs[d]	9/56 (16.1%)	5/33 (15.2%)	3/14 (21.4%)	0.679	7/43 (16.3%)	2/10 (20.0%)	1.000
CSF proteins >45 mg/dL	7/58 (12.1%)	5/32 (15.6%)	1/17 (5.9%)	0.650	4/45 (8.9%)	2/10 (20.0%)	0.298

Continued

Table 1 Demographics, Investigations, Treatment at First Disease Event, Overall Disease Course, and Outcome in the Total Pediatric Cohort of Patients With MOGAD (A), in Children With Monophasic vs Relapsing Disease (B), and in Patients With EDSS 0 vs EDSS > 0 at Last Follow-up (C) (Univariate Analysis) *(continued)*

	A	B			C		
	Total cohort (n = 75)	**Monophasic (n = 39)[a]**	**Relapsing (n = 26)[a]**	***p* Value**	**A. Final EDSS 0 (n = 56)[b]**	**Final EDSS ≥1 (n = 15)[b]**	***p* Value**
Abnormal EEG	30/42 (71.4%)	15/21 (71.4%)	9/15 (60.0%)	0.473	23/32 (71.9%)	6/8 (75.0%)	1.000
Slow or disorganized activity	27/42 (64.3%)	13/21 (61.9%)	8/15 (53.3%)	0.607	21/32 (65.6%)	5/8 (62.5%)	1.000
Epileptic activity	7/42 (16.7%)	4/21 (19.0%)	2/15 (13.3%)	1.000	5/32 (15.6%)	2/8 (25.0%)	0.611
IT at MOGAD onset							
Any immunotherapy (IT)	72/75 (96.0%)	39/39 (100.0%)	24/26 (92.3%)	0.156	53/56 (94.6%)	15/15 (100.0%)	1.000
Intravenous corticosteroids (CS)	71/75 (94.7%)	39/39 (100.0%)	23/26 (88.5%)	0.060	53/56 (94.6%)	14/15 (93.3%)	1.000
Oral corticosteroids (CS)	57/75 (76.0%)	31/39 (79.5%)	19/26 (73.1%)	0.548	42/56 (75.0%)	11/15 (73.3%)	1.000
Intravenous immunoglobulin	13/75 (17.3%)	7/39 (17.9%)	3/26 (11.5%)	0.728	9/56 (16.1%)	3/15 (20.0%)	0.708
Therapeutic plasma exchange	2/75 (2.7%)	2/39 (5.1%)	0/26 (0.0%)	0.513	1/56 (1.8%)	1/15 (6.7%)	0.380
Rituximab	2/75 (2.7%)	2/39 (5.1%)	0/26 (0.0%)	0.513	1/56 (1.8%)	1/15 (6.7%)	0.380
Mycophenolate mofetil	2/75 (2.7%)	2/39 (5.1%)	0/26 (0.0%)	0.513	1/56 (1.8%)	1/15 (6.7%)	0.380
≥2 different ITs (= CS + other IT)	16/75 (21.3%)	10/39 (25.6%)	3/26 (11.5%)	0.164	12/56 (21.4%)	3/15 (20.0%)	1.000
Days from onset to first IT (any)	Median 5.5, mean 9.4, range 0–75 (d.a. 66/75)	Median 5, mean 7.2, range 0–75 (d.a. 36/39)	Median 10, mean 11.6, range 1–40 (d.a. 21/26)	**0.014**	Median 5, mean 9.8, range 0–75 (d.a. 51/56)	Median 6.5, mean 8.1, range 1–15 (d.a. 12/15)	0.380
Any IT <7 days from onset	37/69 (53.6%)	26/36 (72.2%)	7/23 (30.4%)	**0.002**	30/54 (55.6%)	6/12 (50.0%)	0.727
Duration of CS (wk)	Median 5, mean 7.6, range 0–48 (d.a. 75/75)	Median 6, mean 9.7, range 1–48 (d.a. 39/39)	Median 3.8, mean 5.1, range 0–27 (d.a. 26/26)	**0.014**	Median 5, mean 8.3, range 0–48 (d.a. 56/56)	Median 5, mean 5.8, range 0.5–24 (d.a. 15/16)	0.325
≥4 weeks	52/75 (69.3%)	32/39 (82.1%)	13/26 (50.0%)	**0.006**	40/56 (71.4%)	9/15 (60.0%)	0.530
≥5 weeks	47/75 (62.7%)	29/39 (74.4%)	12/26 (46.2%)	**0.021**	37/56 (66.1%)	8/15 (53.3%)	0.363
Duration of overall IT (any) (wk)	Median 5, mean 11.9, range 0–248 (d.a. 75/75)	Median 6, mean 17.8, range 1–248 (d.a. 39/39)	Median 3.8, mean 5.2, range 0–27 (d.a. 26/26)	**0.009**	Median 5.5, mean 12.5, range 0–248 (d.a. 56/56)	Median 5, mean 11.6, range 0.5–108 (d.a. 15/15)	0.376
≥4 weeks	52/75 (69.3%)	32/39 (82.1%)	13/26 (50.0%)	**0.006**	40/56 (71.4%)	9/15 (60.0%)	0.530
Final diagnosis							
ADEM (Mono/Rel)	30/75 (40.0%)	16/39 (41.0%)	8/26 (30.8%)	0.401	24/56 (42.9%)	5/15 (33.3%)	0.505

Continued

Table 1 Demographics, Investigations, Treatment at First Disease Event, Overall Disease Course, and Outcome in the Total Pediatric Cohort of Patients With MOGAD (A), in Children With Monophasic vs Relapsing Disease (B), and in Patients With EDSS 0 vs EDSS > 0 at Last Follow-up (C) (Univariate Analysis) *(continued)*

	A	B			C		
	Total cohort (n = 75)	**Monophasic (n = 39)[a]**	**Relapsing (n = 26)[a]**	***p* Value**	**A. Final EDSS 0 (n = 56)[b]**	**Final EDSS ≥1 (n = 15)[b]**	***p* Value**
ON (± CNS lesions) (Mono/Rel)	27/75 (36.0%)	65/39 (41.0%)	7/26 (26.9%)	0.244	21/56 (37.5%)	4/15 (26.7%)	0.435
CNS demyelination (Rel)	6/75 (8.0%)	0/39 (0.0%)	6/26 (23.1%)	n/a	3/56 (5.4%)	3/15 (20.0%)	0.104
ADEM-ON (Rel)	4/75 (5.3%)	0/39 (0.0%)	4/26 (15.4%)	n/a	3/56 (5.4%)	0/15 (0.0%)	1.000
NMOSD (Mono/Rel)	3/75 (4.0%)	2/39 (5.1%)	1/26 (3.8%)	1.000	1/56 (1.8%)	2/15 (13.3%)	0.111
CIS (Mono)	2/75 (2.7%)	2/39 (5.1%)	0/26 (0.0%)	n/a	2/56 (3.6%)	0/15 (0.0%)	1.000
Encephalitis (Mono)	2/75 (2.7%)	2/39 (5.1%)	0/26 (0.0%)	n/a	2/56 (3.6%)	0/15 (0.0%)	1.000
Isolated LETM (Mono)	1/75 (1.3%)	1/39 (2.6%)	0/26 (0.0%)	n/a	0/56 (0.0%)	1/15 (6.7%)	0.211
Outcome							
Length of follow-up (mo)	Median 30, mean 40.9, range 1–130 (d.a. 75/75)	Median 29, mean 38.9, range 12–122 (d.a. 39/38)	Median 51.5, mean 57.9 range 18–130 (d.a. 26/26)	**0.007**	Median 30, mean 39.2, range 4–126 (d.a. 56/56)	Median 39, mean 50.1, range 5–130 (d.a. 15/15)	0.205
Relapsing course (≥2 total events)[a]	26/65 (40.0%)	0/39 (0.0%)	26/26 (100.0%)	n/a	15/49 (30.6%)	9/14 (64.3%)	**0.022**
Relapsing course (≥3 total events)[a]	16/65 (24.6%)	0/39 (0.0%)	16/26 (61.5%)	n/a	7/49 (14.3%)	7/14 (50.0%)	**0.009**
Total number of disease events[a]	Median 1, mean 1.9, range 1–8 (d.a. 65/65)	1	Median 3, mean 3.3, range 2–8 (d.a. 26/26)	n/a	Median 1, mean 1.5, range 1–5 (d.a. 49/49)	Median 2.5, mean 3.1, range 1–8 (d.a. 14/14)	**0.005**
EDSS at last follow-up[b]	Median 0, mean 0.4, range 0–4 (d.a. 71/71)	Median 0, mean 0.2, range 0–4 (d.a. 39/39)	Median 0, mean 0.7, range 0–3 (d.a. 24/24)	**0.023**	0	Median 1.8, mean 1.8, range 1–4 (d.a. 15/15)	n/a
EDSS ≥1[b]	15/71 (21.1%)	5/39 (12.8%)	9/24 (37.5%)	**0.022**	0/56 (0.0%)	15/15 (100%)	n/a
EDSS ≥2[b]	7/71 (9.9%)	2/39 (5.1%)	5/24 (20.8%)	0.095	0/56 (0.0%)	7/14 (46.7%)	n/a

Abbreviations: ADEM = acute disseminated encephalomyelitis; ADEM-ON = ADEM followed by optic neuritis; CIS = clinically isolated syndrome; CNS = CNS; CS = corticosteroid; CSF = CSF; d.a. = data available; EDSS = Expanded Disability Status Scale; EEG = electroencephalography; IgG = immunoglobulin G; IT = immunotherapy; LETM = longitudinally extensive transverse myelitis; Mono = monophasic; Mono/Rel = monophasic or relapsing; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disorder; NMOSD = neuromyelitis optica spectrum disorder; n/a, statistical test not applicable; OCBs = oligoclonal bands; ON = optic neuritis; Rel = relapsing.
Bold indicates statistically significant values at univariate analysis.
[a] For the study of monophasic vs relapsing disease, only patients with follow-up duration ≥12 months from onset (or with relapse at any time) were included in the analysis (65/75).
[b] For the study of patients with final EDSS 0 vs ≥1, only patients with available follow-up of >3 months after last event (or with EDSS 0 at any time) were included in the analysis (71/75).
[c] Other races were Asian (5/72) and Black or African American (3/72); data not available in 3/75.
[d] The presence of CSF-restricted oligoclonal bands (OCBs) was recorded.[49]
Among the 9/56 patients with CSF-restricted OCBs, 2/9 had 1 single band. Additional 7/56 patients had identical serum and CSF OCBs in CSF ('mirror pattern').

(52.2% 36/60) (p = 0.010). Median duration of immunotherapy after the first event was 5 weeks (mean 11.9, range 0–248; data available in 75/75) and ≥4 weeks in 69.3% (52/75). In this latter subgroup of patients, the immunotherapy used for ≥4 weeks was corticosteroids in 100% (52/52), with additional plasma exchange, IVIG, rituximab, and/or mycophenolate mofetil in 25.0% (13/52).

Disease Course and Final Outcome

40.0% (26/65) of patients had a relapsing disease course. A total of 87 clinical events occurred in 26 relapsing patients, including onset events (median 3 events/patient, mean 3.3, range 2–8; data available in 26/26). 61.5% (16/26) of relapsing patients had more than one relapse (≥3 total disease events). The first relapse occurred at median 6.5 months after onset (mean 15.6, range 1–80; data available in 26/26). Time to first relapse was longer in children aged 8 years or younger than in older patients (median 18 vs 4 months) (p = 0.013) (eTable 1, links.lww.com/NXI/A764), and short-term relapses (≤6 months of onset) occurred less frequently in children aged 8 years or younger (3/15, 20.0%) than in older patients (9/11, 81.8%) (p = 0.002). At first relapse, 96.2% (25/26) of patients received immunotherapy: 46.2% (12/26) corticosteroids only, 19.2% (5/26) corticosteroids plus IVIG only, 11.5% (3/26) IVIG only, and 19.2% (5/26) corticosteroids plus other combinations of immunotherapy (rituximab and/or azathioprine and/or mycophenolate mofetil, with or without additional IVIG).

At last follow-up, EDSS in the total cohort was median 0 (mean 0.4, range 0–4; data available in 71/71); 78.9% (56/71) had EDSS 0. Of the 15/69 patients with final EDSS ≥1, data on the type of residual deficits were available in 14/15: visual sequelae in 7/14 (mild in 4/7), motor sequelae in 4/15 (gait disturbances 1/4, tremor or other movement disorder 3/4), epilepsy in 4/14 (ongoing antiseizure medications at last follow-up 3/4), cognitive difficulties in 4/14 (IQ in the lower range 2/4, IQ below normal range 1/4, school difficulties 1/4), behavioral or psychiatric issues in 4/14 (oppositional behaviour 2/14, mood disorder 2/14), and other in 2/15 (urinary sphincter problems 1/2, sensory sequelae 1/2).

The most frequent final diagnoses were monophasic or relapsing ADEM (40.0%, 30/75) and monophasic or relapsing ON (36.0%, 27/75) (Table 1A).

Clinical Features and Treatment Factors Associated With Relapsing Disease Course

Univariate Comparison

In the univariate comparisons of monophasic vs relapsing disease course patients (Table 1B), those with relapsing disease course had a longer interval from symptom onset to first initiation of immunotherapy (median 10 vs 5 days, p = 0.014). 78.8% (26/33) of patients receiving immunotherapy within less than 7 days had a monophasic course (Figure 1B), compared to 38.5% (10/26) of those who did not receive any immunotherapy within less than 7 days (p = 0.002) (Figure 1C). Relapsing patients had a shorter median duration of corticosteroid treatment at first event (median 3.8 vs 6 weeks, p = 0.014).

Multivariable Logistic Regression

Fifty-eight patients were included in the multivariable logistic regression model for relapsing disease course (Table 2). Early initiation of immunotherapy at first disease event (<7 days from symptom onset) was independently associated with 6.7-fold reduced odds of relapsing disease course (OR 0.15, 95% CI 0.03–0.61, p = 0.009). Use of corticosteroid treatment for 5 weeks or longer at first event was independently associated with 6.7-fold reduced odds of relapsing course (OR 0.15, 95% CI 0.03–0.80, p = 0.026). Presence of abnormal optic nerves on MRI at first event was independently associated with 12.5-fold reduced odds of relapsing course (OR 0.08, 95% CI 0.01–0.50, p = 0.007). Figure 2 shows the estimated probability of relapse-free survival according to time from disease onset. 61.5% (16/26) of patients with relapsing disease course had their first relapse within 1 year of disease onset. Among those with relapsing disease and abnormal optic nerves on initial MRI, 71.4% (5/7) had their first relapse within 6 months of disease onset, compared with 31.3% (5/16) of those with relapsing disease and normal optic nerves on initial MRI (p = 0.06).

Clinical Features and Treatment Factors Associated With Abnormal Neurologic Examination at Final Follow-up

Univariate Comparison

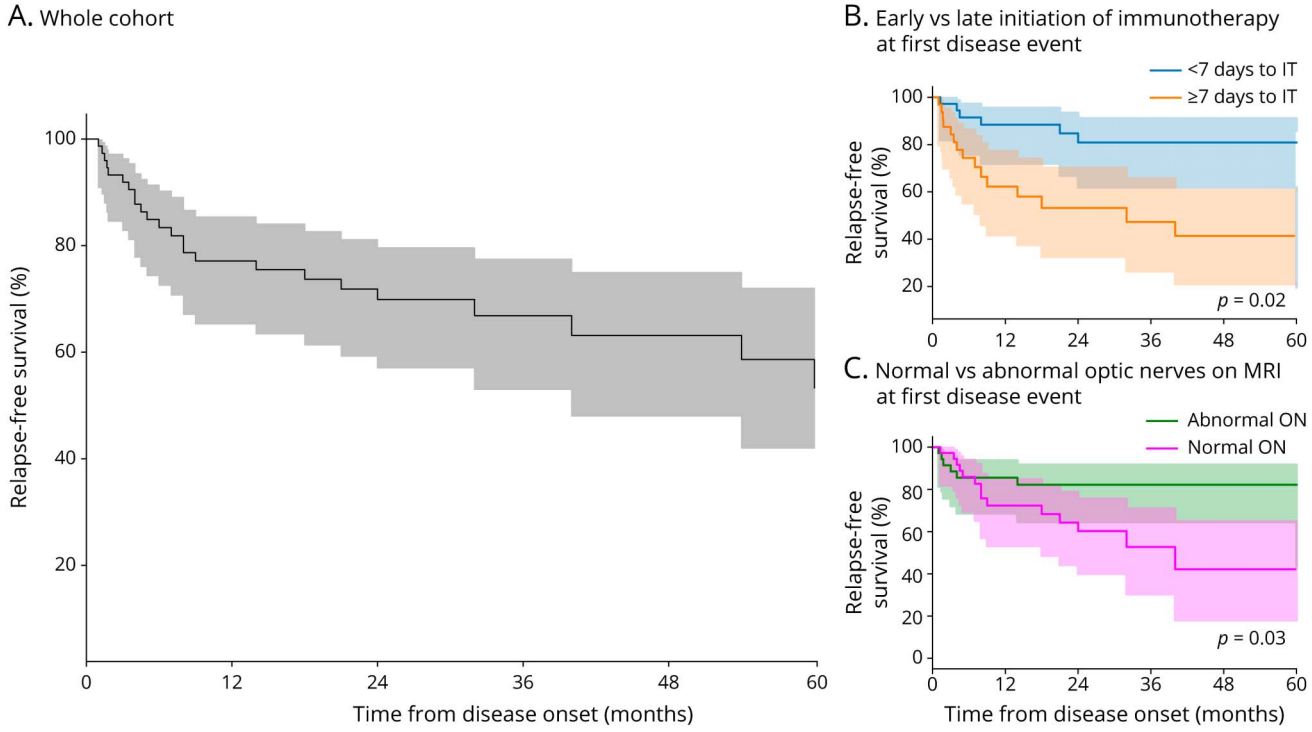
The proportion of patients with final EDSS ≥1 at last follow-up was higher among those with relapsing disease course

Table 2 Independent Association of Key Clinical Features and Treatment Factors With Relapsing Disease Course

Variable	Adjusted odds ratio (95% CI) for relapsing disease course	*p* Value
Age 12 years or older at disease onset	1.07 (0.09–12.31)	0.959
Female sex	1.18 (0.25–5.52)	0.834
Abnormal brain on MRI at first disease event	0.55 (0.06–4.82)	0.593
Abnormal optic nerves on MRI at first disease event	0.08 (0.01–0.50)	**0.007**
Abnormal spine on MRI at first disease event	1.21 (0.22–6.66)	0.829
Immunotherapy <7 days from disease onset	0.15 (0.03–0.61)	**0.009**
≥5 weeks corticosteroid treatment at first disease event	0.15 (0.03–0.80)	**0.026**
Use of additional noncorticosteroid treatments	0.55 (0.07–4.30)	0.568

Bold indicates *p* values that are statistically significant.

Figure 2 Relapse-Free Survival



Kaplan-Meier survival estimates for the first 5 years after disease onset are shown for the whole cohort (panel A, n = 75) and 2 subgroup comparisons: those with early (<7 days from disease onset, n = 37) vs late (≥7 days from disease onset or no immunotherapy, n = 32) initiation of first immunotherapy (IT) at first disease event (panel B) and those with normal (n = 37) vs abnormal (n = 35) optic nerve (ON) appearance on MRI at first disease event (panel C). Shaded areas indicate 95% confidence interval. *p* values were derived froPm univariate Cox proportional hazards regression.

compared with those with monophasic disease (37.5% [9/24] vs 12.8% [5/39], $p = 0.022$) (Table 1B). A higher proportion of those with final EDSS ≥1 had multiple relapses (≥3 total disease events) compared with those with final EDSS 0 (50.0% [7/14] vs 14.3% [7/49], $p = 0.009$) (Table 1C).

Multivariable Logistic Regression

Fifty-four patients were included in the multivariable logistic regression model for abnormal neurologic examination at final follow-up (EDSS ≥1) (Table 3). Each 1-point increment in worst EDSS score at first disease event was independently associated with 6.7-fold increased odds of abnormal neurologic examination (EDSS ≥1) at final follow-up (OR 6.65, 95% CI 1.33–33.26, $p = 0.021$).

Discussion

Factors at MOGAD disease onset predictive of a relapsing disease course or final outcome are only partially understood. In this study, we sought to identify early factors at first event of pediatric MOGAD associated with subsequent risk of relapse and final neurologic outcome, with focus on modifiable factors such as treatment.

One of our main findings was the observation that early initiation of immunotherapy at onset (defined using a data-driven threshold of less than 7 days from symptom onset) was independently associated with 6.7-fold reduced odds of subsequent relapsing disease course ($p = 0.009$), while controlling for key clinical characteristics, lesion site on onset MRI, and other treatment factors in a multivariable model. Although a role for early treatment in determining final outcome in MOGAD has been hypothesized,[6] and the effects of early immunotherapy have been extensively explored in other neuroinflammatory diseases,[38-43] this has not been thoroughly investigated in pediatric MOGAD so far. Our data support the notion that early immunosuppression could be beneficial not just in limiting disability as observed in other conditions but especially in modifying the long-term relapse risk, possibly preventing or reducing the consolidation of a chronic autoimmune reaction within the CNS; although, this remains a speculation based on clinical observations, and definite evidence is lacking. Ongoing progress in refining the clinical and paraclinical characterization of MOGAD including phenotypic expansion[10] will be helpful to support early diagnosis of the disorder in the full spectrum of patients. However, it should also be acknowledged that at present, most centers are not able to routinely provide MOG antibody results within a few days[6]; new-onset neuroinflammatory disorders should therefore be treated early and empirically with immunotherapy without waiting for antibody results, in the appropriate clinical context. In this regard, the time to treatment seems to have improved over the years in our cohort, with a

Table 3 Independent Association of Key Clinical Features and Treatment Factors With Abnormal Neurologic Examination (EDSS ≥1) at Final Follow-up

Variable	Adjusted odds ratio (95% CI) for EDSS ≥1 at final follow-up	*p* Value
Age 12 years or older at disease onset	6.96 (0.32–150.26)	0.216
Female sex	0.05 (0.00–1.24)	0.068
Abnormal brain on MRI at first disease event	0.03 (0.00–3.10)	0.141
Abnormal optic nerve(s) on MRI at first disease event	64.20 (0.67–6,189.95)	0.074
Abnormal spine on MRI at first disease event	1.80 (0.08–39.68)	0.710
Immunotherapy <7 days from disease onset	1.84 (0.11–31.95)	0.675
≥5 weeks corticosteroid treatment at first disease event	0.02 (0.00–1.02)	0.051
Use of additional noncorticosteroid treatments	0.37 (0.02–7.17)	0.510
Relapsing disease course	11.75 (0.76–182.80)	0.078
Worst EDSS score at first disease event	6.65 (1.33–33.26)	**0.021**

Abbreviation: EDSS = Expanded Disability Status Scale.
Bold indicates *p* values that are statistically significant.

significantly higher proportion of patients treated early (<7 days of onset) in the most recent years compared with the years 2008–2013 ($p = 0.010$).

The second main finding of our study was the observation that use of corticosteroids for 5 weeks or longer at first disease event was independently associated with 6.7-fold reduced odds of relapsing disease course ($p = 0.026$), consistently with previous reports.[13,16,21,24] The optimal duration of corticosteroid treatment at first event is still debated both in adults and children,[6,19,25] considering that most patients with MOGAD will have a monophasic disease course and the potential corticosteroid-related side effects but also in view of the observed corticosteroid dependency.[23] In the light of our results and of previous literature data,[6,14,21,24] a cautious and slow oral corticosteroid taper in at least 5 weeks (suggested maximum 3 months in the recent European pediatric MOG consortium consensus[25] and in 3–6 months by other authors[6]) seems reasonable if well tolerated, possibly partially replaced by monthly IVIG for 3–6 months in case of corticosteroid side effects and also in view of recent favourable data on IVIG in MOGAD.[6,24]

The analysis of the effect of different treatment combinations, representing a clinical research priority yet to be fully clarified, did not show any significant results in our cohort, although our power to detect such effects was strongly limited by the very small number of patients receiving noncorticosteroid treatments.

Another early factor associated with disease course in our cohort was abnormal optic nerve(s) on MRI at disease onset, which was independently associated with 12.5-fold reduced odds of relapsing disease course ($p = 0.007$). This finding seems contrary to some recent literature data,[17] although important differences in our study should be highlighted, such as the inclusion of an exclusively pediatric cohort and the fact that abnormal optic nerves on MRI in our study occurred as part of another syndrome in several cases and not just isolated ON.[17] It should also be noted that, among the patients who did relapse, those with optic nerve involvement at first MRI tended to do so slightly earlier: 71.4% (5/7) had their first relapse within 6 months of disease onset, compared with 31.3% (5/16) of those with normal optic nerves on initial MRI (Figure 2). Whether children with optic nerve involvement represent a specific subset of patients with MOGAD (eTable 2, links.lww.com/NXI/A764), who relapse early but overall less than the rest of the patients, remains only a provisional speculative hypothesis. However, and most importantly, the association of abnormal optic nerve(s) on onset MRI and lower risk of subsequent relapse should be taken with caution, in view of the intrinsic limitations relative to neuroimaging data collection in our study (different MRI scanners, heterogenous scanning protocols, lack of a central neuroimaging review) which could have strongly influenced our data.

As with other neuroinflammatory disorders,[42,43] worse severity in the acute phase of first event was associated with greater risk for long-term neurologic sequelae in our cohort: Each 1-point increment in worst EDSS at first attack was independently associated with 6.7-fold increased odds of abnormal neurologic examination at final follow-up (EDSS ≥ 1) ($p = 0.021$). This supports the idea that early disease events seem highly consequential in patients with MOGAD and onset attack is a major determinant of final disability,[6,14] as also suggested by the observation that neuronal degeneration biomarkers such as neurofilament light chain (NfL), a marker of axonal damage, increase mostly during this disease phase.[44]

Promisingly, serum NfL at first demyelinating event has also been suggested to correlate with neuroradiologic disease burden and risk of subsequent relapse,[45] although this was not evaluated in our cohort.

Moreover, in univariate analysis (although not reaching statistical significance in the multivariable model), the proportion of patients with EDSS ≥1 at last follow-up was higher in the subgroup of relapsing patients than in those with monophasic disease (p = 0.022), suggesting an additional negative effect of cumulative disease attacks on final outcome, consistent with previous literature data[6,8] but warranting further confirmation.

The overall characteristics of our cohort reflect the pertinent literature, with no obvious racial bias nor sex preponderance[6,14] and ADEM being the most common type of presentation, especially among younger patients,[9,17,23] ON being preponderant in older children, and with limited representation of other clinical phenotypes, such as TM, NMOSD, and encephalitis.[9] As regards investigations, brain involvement at onset MRI was slightly more frequent in younger children, as already described in the literature,[6,9] and nearly half of the patients in our cohort, regardless of the overall main clinical syndrome, had optic nerve involvement at first MRI. In these latter patients, there was a high proportion of bilateral optic nerve involvement, longitudinal optic nerve involvement for at least half of its length, and optic nerve head swelling, reflecting the known features of MOG-associated ON.[14,23,46-48] CSF-restricted OCBs[49] were found in less than 1 every 5 patients in our cohort,[6] slightly more frequently in younger children.[17] In our cohort, and similar to the literature, 40.0% of children relapsed,[15] with 24.6% experiencing multiple relapses, often spanning over several years[15]; however, most (61.5%) of those with relapsing disease had their first relapse within 1 year of disease onset,[15] with higher rate of short-term relapses in older patients. Final outcome was overall favourable in most of our patients similar to other pediatric data and generally better compared with adult MOGAD cohorts.[6,16]

The main strengths of our study are the collection of detailed data on clinical characteristics, treatments, and importantly treatment timing and duration, from a multicenter collaboration including the main centers treating pediatric neuroinflammatory disorders in Italy with wide representation of all the country (eFigure 1, links.lww.com/NXI/A764), giving us confidence that referral bias is unlikely and the full spectrum of pediatric MOGAD (including less severe and monophasic cases) is represented. Limitations include the retrospective nature of data collection, the modest number of patients to power statistical analyses, and a lack of complete homogeneity as regards antibody testing (i.e., live vs fixed CBA and data on the type of assay not available in a few cases), also because of the large span of disease onset (2008–2022). Moreover, antibody titres at onset and at follow-up were heterogeneously available in our cohort; therefore, they were not analyzed. Neuroimaging data were also strongly limited by the use of different scanners, heterogeneous protocols, and the lack of a central review (neuroimaging data were assessed based on the available official neuroimaging reports). Similarly, EEG data was not reviewed centrally. Moreover, follow-up duration was significantly longer in relapsing than in monophasic patients. Finally, the inherent limitations of the clinical neurologic score used (EDSS) should be acknowledged, especially for patients with ON. Therefore, our results warrant confirmation in larger, and ideally prospective, cohorts.

This study represents a real-life multicenter investigation of pediatric MOGAD, with focus on the relationship between early factors at disease onset and subsequent risk of relapse and poor outcome.

In our cohort, early treatment, longer duration of corticosteroid therapy (≥5 weeks), and abnormal optic nerve at MRI at first event were significantly associated with reduced risk of subsequent relapse, highlighting the importance of adequate timing and duration of immunotherapy. Whereas, the main determinant of final outcome was the severity of disease at first event, with additional negative effect of cumulative additional attacks (only shown at univariate analysis in our cohort, to be confirmed by further studies).

In clinical practice, the identification of early markers for disease course and outcome are useful to inform family counselling and most importantly to guide a more personalized and targeted disease monitoring and treatment, offering the unique potential of intervening in the natural history of the disease.

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Continued

Appendix *(continued)*

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Appendix *(continued)*

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Appendix *(continued)*

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Early Immunotherapy and Longer Corticosteroid Treatment Are Associated With Lower Risk of Relapsing Disease Course in Pediatric MOGAD

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