High titers of myelin oligodendrocyte glycoprotein antibody are only observed close to clinical events in pediatrics

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Abstract

**Background:** Myelin oligodendrocyte glycoprotein (MOG)-IgG is increasingly detected in children with CNS demyelinating diseases. Due to the clinical overlap in children with CNS demyelination with and without MOG-IgG positivity, identifying distinct characteristics would help early diagnosis.

**Objective:** To compare the specific features that may help differentiate MOG-IgG positive from negative children with CNS demyelinating diseases. To compare characteristics of patients with high and low MOG-IgG titers.

**Methods:** Children with CNS demyelinating disorders with onset before 18 years of age who were tested for MOG-IgG at the University of California San Francisco were included. This retrospective study collected the following by chart review: demographic, clinical, MRI, CSF, and treatment data. Serum was tested for MOG-IgG at Mayo Clinic by live cell-based fluorescent activated cell sorting assay with titer $\geq 20$ confirming positivity.

**Results:** We assessed 65 MOG-IgG positive and 65 MOG-IgG negative patients. Median (IQR) age of onset was 7.6 (6.6) years for MOG-IgG positive and 13.8 (5.8) years for MOG-IgG negative (p<0.001). The female to male ratio was approximately 1:1 for the MOG-IgG positive group and 3:1 for the negative group (p=0.042). The most common initial diagnosis was demyelinating disease not otherwise specified (52.3%) in the positive group, compared to relapsing-remitting multiple sclerosis (41.5%) in the negative group (p<0.01). Optic nerve involvement (52.3%) was
the most common clinical localization at onset for the MOG-IgG positive group, while brainstem/cerebellar (49.2%) localization predominated in the MOG-IgG negative group. The positive group also presented more often with a severe event at disease onset than the negative group (81.5% vs 60.3%; p < 0.002). MOG-IgG positive children had a lower frequency of oligoclonal bands (15.8% vs 57.4%; p < 0.001). The frequency of baseline brain and spinal cord MRI abnormalities were similar in both groups; however, MOG-IgG positive patients more often had T2 hyperintense lesions in the optic nerves (26/43 vs 10/41; p < 0.001). Disease-modifying medications were used in 64.6% of MOG-IgG positive patients versus 80% of negative children. Of the 32 positive patients with follow-up titers, seven reverted to negative while two who tested negative initially converted to positive. Positive titers greater than 1:160 were only observed within four months of a clinical event (disease onset or relapse). Patients with high and low MOG-IgG titers were comparable in demographic and clinical characteristics.

Conclusion: Despite some clinical overlap, we report notable demographic, MRI and CSF differences between MOG-IgG positive and negative children with CNS demyelinating disorders at disease onset. High MOG-IgG titers were only observed close to a clinical event.

Keywords
Myelin oligodendrocyte glycoprotein (MOG); MOG antibody associated disease (MOGAD); MOG-IgG; CNS; Demyelinating disease; Pediatric

1. Introduction

Myelin oligodendrocyte glycoprotein (MOG) is highly immunogenic and uniquely expressed on the outermost surface of the myelin sheath in the central nervous system (CNS) (Antel, 2003, Reindl et al., 2020). MOG antibodies (MOG-IgG) are detected in about 30% of children with a first CNS demyelinating syndrome (Waters et al., 2020). The phenotype of MOG-associated disease (MOGAD) can overlap with multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), and other demyelinating diseases. Therefore, it is important to better understand its phenotype and underlying pathophysiology. Studies thus far suggest that the most common clinical phenotypes for MOGAD in children are optic neuritis (ON) and acute disseminated encephalomyelitis (ADEM)-like presentations (Waters et al., 2020, Hegen and Reindl, 2020, Lechner et al., 2016). MOG-IgG titers can fluctuate during disease course (Waters et al., 2020, Hacohen et al., 2018) and there is no consensus for optimal treatment strategies for MOGAD.

Despite the increasing recognition MOGAD, there remain many uncertainties regarding the pathogenicity of these antibodies and the heterogeneity of disease course. These issues also lead to uncertainty about best management. Due to its higher prevalence in pediatrics compared to adults (Hacohen et al., 2017), children are an ideal group in which to compare disease phenotypes between MOGAD and other CNS demyelinating disorders.

This study aims to characterize the clinical, biological and MRI presentation, disease course, and treatment in MOG-IgG positive versus negative children with a CNS demyelinating syndrome, as well as compare disease phenotype in those with high and low MOG-IgG titers.
2. Methods

2.1. Study design and participants

This single center retrospective cohort study includes consecutive patients seen at the University of California, San Francisco (UCSF) Pediatric MS center who presented with a CNS demyelinating event before 18 years of age. MOG-IgG positive patients whose samples were collected between October 2006 and June 2020 were included. Consecutive MOG-IgG negative patients were included until the same number as the MOG-IgG positive group was reached. Demographic, clinical, and MRI data were collected from chart review.

2.2. Measurements

Children who tested seropositive at any point in their disease course were included in the MOG-IgG positive group, while children in the negative group never tested seropositive for MOG-IgG. For comparison of high versus low titer MOG-IgG groups, we included each patient’s highest titer within the first four months of a clinical event. Low titers outside of that time period could be due to the longer time from disease onset or a relapse and were therefore excluded.

The initial and final diagnoses were based on evaluation by UCSF pediatric MS specialists (AA, AR, CF, EW). We used published consensus diagnostic criteria for ADEM, MS (2017 McDonald criteria), NMOSD, radiologically isolated syndrome (RIS), and clinically isolated syndrome (CIS) (Thompson et al., 2018, Wingerchuk et al., 2015, Tardieu et al., 2016, Krupp et al., 2007). The demyelinating disease not otherwise specified (DDNOS) category included those with at least one demyelinating event who did not meet criteria for the aforementioned demyelinating diagnoses. MOGAD is classified under the umbrella of DDNOS in our registry. Relapses were defined as new or worsening acute demyelinating events occurring at least 30 days from a previous event, lasting for more than 24 hours and not accompanied by fever or infection.

Clinical events were categorized as mild, moderate, or severe based on interference with daily activities: mild for “no change in daily activities,” moderate for “interferes with some daily activities,” and severe for “major interference with daily activities.” Disease-modifying treatment included: use of oral glucocorticosteroids for greater than three months (chronic steroids group), use of two or more intravenous immunoglobulin (IVIG) infusions at least four weeks apart (chronic IVIG group), and use of steroid-sparing immunosuppressive or MS disease-modifying therapies.

“Baseline data” for CSF and MRI refers to first available results after disease onset. Baseline brain, orbit, and spinal cord MRIs were reviewed for the presence of T2-hyperintense foci, gadolinium enhancing foci, and longitudinally extensive transverse myelitis (LETM). LETM was defined as foci with a length equal to or greater than three vertebral segments in the spinal cord (Nightingale et al., 2011). “Recovery Expanded Disability Status Scale (EDSS)” scores were collected when available within the first year of disease onset, excluding those that were within three months of a clinical event.
This study was approved by the Institutional Review Board at UCSF. All patients and their parents provided assent and consent for use of their information for research.

2.3. Serum testing

All serum samples, including retrospective research serum, were tested at the Mayo Clinic (Rochester, MN) for MOG-IgG with a live cell-based assay using full length MOG in its conformational form as previously described (Sechi et al., 2021). Sera were screened at 1:20 dilution and positive samples were titrated at either 1:20, 1:40, 1:100, and ten-fold dilutions thereafter for samples tested during clinical care or in doubling dilutions for research samples and for both groups end-titers ≥:20 were considered positive for MOG-IgG with a cell-based assay. Serum was tested as part of routine clinical care prospectively from November 2017. Forty-nine MOG-IgG positive patients and 30 negative had banked research serum which was retrospectively tested to obtain MOG-IgG titer closer to disease onset. When available, both clinical and research sera were considered in analyses.

2.4. Statistical analysis

Prism 9 (GraphPad Software) was used for all statistical analyses. Qualitative analyses and descriptions of variables by means, medians, ranges, and interquartile ranges were used. Percentage and frequency were reported for categorical variables. T-test, Mann-Whitney and Kruskal-Wallis test were used as appropriate, to compare data between MOG-IgG positive and negative groups, as well as between high and low titer MOG-IgG groups. Differences were considered statistically significant when p <0.05.

3. Results

3.1. Baseline characteristics

The baseline and follow-up characteristics of the 65 MOG-IgG positive and 65 negative patients are presented in Table 1. MOG-IgG positive children were significantly younger and did not have female preponderance. Although Hispanic patients were underrepresented in the MOG-IgG positive compared to the negative group, no difference was observed between races.

The severity of initial events included 63 negative cases as two had a final diagnosis of RIS (Table 1). The MOG-IgG positive group had a greater proportion of patients with a severe initial event and CSF white blood cell count ≥50 cells per microliter, but a lesser proportion of patients with oligoclonal bands and elevated IgG index. For those with elevated WBC in CSF, the mean percentage of eosinophils was 1.3% and lymphocytes was 64.6% in the MOG-IgG positive group, while it was 2% and 70.5%, respectively, in the negative group.

Although 64 MOG-IgG positive and all 65 MOG-IgG negative patients had baseline brain MRIs, only 53 and 56 respectively received contrast. Although a greater proportion of patients had optic nerve involvement on MRI in the MOG-IgG positive group, brain and spinal cord characteristics were similar in both groups, including no difference in the proportion of patients with LETM. The patients with LETM in the MOG-IgG negative
group had an initial diagnosis of DDNOS (n=5), CIS (n=2), and RRMS (n=2), while those in the positive group had DDNOS (n=5) and ADEM (n=2).

3.2. Clinical localization at onset

Clinical localization(s) at onset is represented in Figure 1. 52.3% of MOG-IgG positive children presented with optic neuritis at onset. Of those, 73.5% had bilateral optic neuritis.

Although there was a similar number of patients with unilateral optic neuritis at onset in both groups (n=9), a higher proportion of MOG-IgG positive patients presented with bilateral optic neuritis at onset, compared to negative patients (n=25, 38.5% vs. n=10, 15.4%, p=0.005). Other clinical localizations at onset, including cerebrum, brainstem/ cerebellar and spinal cord, were similar in the two groups.

3.3. Follow-up characteristics

Median follow-up duration was similar in the MOG-IgG positive and negative groups (Table 1). Median annualized relapse rate tended to be higher in the negative group. Forty-two of the positive (64.6%) and 34 of the negative (54.0%) had a second event.

3.4. First disease-modifying therapy

First disease-modifying therapy (DMT) differed between the two groups (p=0.001) (Figure 2). By the time of last follow-up, 35.4% of MOG-IgG positive patients and 20.0% of MOG-IgG negative patients had not received any DMT. Chronic IVIG was only used in the MOG-IgG positive group (n=2, 3.1%). MOG-IgG positive patients were more likely to receive glatiramer acetate, dimethyl fumarate or rituximab for first DMT while the negative patients were more likely to receive interferon beta. In the group who did not receive chronic treatment, eight of the 23 MOG-IgG positive patients relapsed, while one out of 13 in the negative group relapsed.

3.5. Diagnosis throughout follow-up

The distribution of initial diagnoses differed between the MOG-IgG positive and negative groups (p<0.01) (Figure 3). DDNOS and RRMS were the most frequent initial and last follow-up diagnoses in the positive and negative groups, respectively. All MOG-IgG positive patients who were tested for aquaporin-4 antibodies were negative. In the MOG-IgG positive group, patients who converted to RRMS at last follow-up met 2017 McDonald criteria, had low positive MOG-IgG titers, and one had positive bands of the four patients who were tested for OCBs.

3.6. Brain biopsy characteristics

Two MOG-IgG positive cases had stereotactic brain biopsies. Overt demyelination was reported based on Luxol Fast Blue (LFB) staining and axons were relatively intact on Bielschowsky and neurofilament staining. There were intense inflammatory infiltrates, with more prominent monocyte lineage cells (dense macrophage and polymorphonuclear rather than lymphocyte infiltration). There were no pathological findings in the meninges and arachnoid fibrovascular tissue.
3.7. MOG-IgG titers in relation to time from a clinical event

High MOG-IgG titers (> 1:160) were only observed within four months of disease onset or a clinical relapse (Figure 4). Based on this observation, we categorized MOG-IgG positive patients as high (> 1:160) and low titer (≤1:160) groups for further analysis.

3.8. Characteristics of patients with high versus low MOG-IgG titers

To compare high and low MOG-IgG titer groups, we excluded patients who had a low titer collected more than four months from a clinical event due to the length of time from their event (Figure 4). The demographic and clinical characteristics, DMT use, and annualized relapse rate were similar in groups with high and low MOG-IgG titers (Table 2). Although four patients were initially diagnosed as RRMS in the high MOG-IgG titer group, the final diagnosis of all patients with high titers was DDNOS as confirmed MOGAD cases.

3.9. Serial MOG-IgG titers

Thirty-one MOG-IgG positive patients had more than one MOG-IgG sample (Figure 5). Eight (26%) of those patients were MOG-IgG seronegative at some point during their disease course. Two of them initially tested negative for MOG-IgG, and later converted to a low positive titer (1:20 and 1:100). Conversely, six patients who initially tested positive converted to negative. Of those, only one had further follow-up testing after seroconversion (three negative MOG-IgG tests over a year and a half).

4. Discussion

Although we confirm some clinical and MRI overlap between MOG-IgG positive and negative patients with CNS demyelination, MOGAD patients had a younger age of onset without female preponderance and were more likely at onset to have bilateral optic neuritis. MOGAD was also more likely to have elevated WBC count and no oligoclonal bands in CSF. Pathologically, MOGAD remains under-described. Our two patients who had a brain biopsy had overt demyelination, intact axons, and monococyte infiltration, primarily with macrophages and polymorphonuclear cells (PMN). All of these findings are similar to previous reports (Reindl et al., 2020, Höftberger et al., 2020, Fernandez-Carbonell et al., 2016, Ikeda et al., 2015). Interestingly, in our cohort we also found a greater proportion of positive patients with severe initial events. Considering more MOG-IgG positive patients had severe events at onset, they actually recovered to a similar or lower EDSS score compared to the negative patients, suggesting better recovery. Despite similar follow-up duration compared to other studies and a trend in declining titers after a clinical event, a lower proportion of our patients with serial testing became seronegative (26% vs. 40–50%) (Waters et al., 2020, Hacohen et al., 2017, Fernandez-Carbonell et al., 2016, Di Pauli et al.,
This may be due to less than half of our MOG-IgG positive patients having follow-up titers.

We found significant higher optic nerve involvement in MOG-IgG positive patients in baseline MRI and indicated a higher proportion of patients with LETM (> 3 vertebral segments) in the MOG-IgG positive group on baseline MRI imaging as previously reported. According to Baumann et al. (Baumann et al., 2020), cervical and thoracic MRI involvement was also seen frequently in MS patients, which may be why we did not observe a significant difference in spinal cord involvement in the MOG-IgG positive group compared to the negative. Although the rate of patients who relapsed in the MOG-IgG positive group is high (~64%), it is in line with other studies (Sepúlveda et al., 2016, Cobo-Calvo et al., 2021).

This could be partly related to retrospective nature of studies that tend to overestimate the proportion of patients who relapse since they are more likely to follow up. In addition, there could be a referral bias toward more severe or relapsing disease to a tertiary referral center like ours. We observed a high rate of MS DMT use in the MOG-IgG positive group. MOG-IgG testing became available commercially in 2017 so it was difficult to identify MOGAD clinically until then. As such, patients may have been diagnosed with MS and treated with MS-DMT.

A MOG-IgG titer of 1:160 has been noted to be potentially significant in several studies (Reindl et al., 2020, Di Pauli et al., 2011, Rostasy et al., 2012, Mader et al., 2011, Jarius et al., 2016). In our cohort, MOG-IgG titers greater than 1:160 were only observed within four months from a clinical event. Demographic and clinical features were similar in the high and low MOG-IgG titer groups based on titers obtained within four months of a clinical event.

Strengths of our study include evaluation of patients at the same site by physicians trained in pediatric MS and use of the same sensitive MOG-IgG cell-based assay testing for all serum samples (Mayo Clinic), which limited variability. Consideration of time from a clinical event allowed for more specific comparisons of patients with high and low MOG-IgG titers. Limitations include the retrospective nature of the study and inter-patient variability in the timing of clinical, MRI and CSF evaluations and MOG-IgG testing in relation to disease onset. MRI protocols varied based on facilities where scans were obtained and not all images could be reviewed to describe more finely exact location of lesions and their precise features. Although our study had a relatively small sample size, it was a reasonable number of patients for such a rare disease, MOGAD in pediatrics. Recovery EDSS was not always available as many patients were initially seen at outside hospitals. As MOG-IgG positivity may decrease over time, we cannot exclude that a few MOGAD patients may be included in the MOG-IgG negative group. The MOG-IgG cell-based assay test was not commercially available until November 2017, and thus, some samples were tested retrospectively on stored sera.

Our study suggests that MOG-IgG titers are higher closer to disease onset or a relapse. Younger patients with an initial severe event and/or bilateral ON presentations should be suspected to have MOGAD. Due to the rarity of MOGAD, prospective multi-center studies with testing at regular intervals and consistent MRI protocols are needed.
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Fig. 1.
Clinical localization at onset. The graph shows proportion of patients (%) with various clinical localization at onset. ** p=0.005.
First DMT use according to MOG-IgG status. Chronic steroids and IVIG use were defined as: *Chronic steroids: >3 months. **Chronic IVIG: 2 or more infusions 4 weeks apart.
Fig. 3.
Initial to diagnosis at last follow-up MOG-IgG status. The arrows represent changes from initial to diagnosis at last follow-up.
Demyelinating disease not otherwise specified (DDNOS), relapsing remitting multiple sclerosis (RRMS), clinically isolated syndrome (CIS), acute disseminated encephalomyelitis (ADEM), neuromyelitis optica spectrum disorder (NMOSD), and radiological isolated syndrome (RIS).
Fig. 4.
Highest MOG-IgG titer in relation to time from most recent clinical event. A clinical event is either disease onset or a relapse that is closest to the sample collection date. Titers greater than 1:160 were only observed within four months of a clinical event.
Fig. 5.
Serial MOG-IgG Titers in the MOG-IgG Positive Group. This graph shows the timing from onset to MOG-IgG testing by titer. High MOG-IgG titers are >1:160. *Relapse: relapses that occurred between serial MOG-IgG titers.
Table 1
Baseline and follow-up characteristics according to MOG-IgG serostatus

| Characteristics                        | MOG-IgG Positive (n=65) | MOG-IgG Negative (n=65) | P-value  |
|----------------------------------------|-------------------------|-------------------------|----------|
| Age at symptom onset, median years (IQR) | 7.6 (6.6)               | 13.8 (6.8)              | <0.001 * |
| Female, n (%)                          | 36 (55.4)               | 48 (73.8)               | 0.042 ** |
| White, n (%)                           | 46 (74.2)               | 53 (82.8)               | 0.28 **  |
| Hispanic, n (%)                        | 24 (36.9)               | 38 (58.5)               | 0.022 ** |
| **Event Severity**                     |                         |                         |          |
| Mild, n (%)                            | 1 (1.5)                 | 12 (19.0)               | 0.001 ***|
| Moderate, n (%)                        | 11 (16.9)               | 13 (20.6)               |          |
| Severe, n (%)                          | 53 (81.5)               | 38 (60.3)               |          |
| **Baseline CSF**                       |                         |                         |          |
| Presence of oligoclonal bands, x/n (%) | 6/38 (15.8)             | 27/47 (57.4)            | <0.001 **|
| Elevated IgG index, x/n (%)            | 6/33 (18.2)             | 18/40 (45)              | 0.02 **  |
| WBC ≥50 cells/µl, x/n (%)              | 19/61 (31.1)            | 7/52 (13.4)             | 0.04 **  |
| Protein ≥45.3 mg/dL, x/n (%)           | 23/54 (42.5)            | 13/50 (26.0)            | 0.09 **  |
| **Baseline Brain MRI**                 |                         |                         |          |
| Presence of T2-hyperintense foci, x/n (%) | 54/64 (83.1)           | 57/65 (87.7)            | 0.79 **  |
| Proportion of patients with enhancing foci, x/n (%) | 31/53 (58.5)   | 37/56 (66)              | 0.43 **  |
| **Optic Nerve Involvement on Baseline MRI** |                     |                         |          |
| Presence of T2- hyperintense foci, x/n (%) | 26/43 (60.5)          | 10/41 (24.4)            | <0.001 **|
| Proportion of patients with enhancing foci, x/n (%) | 24/26 (92.3)    | 9/10 (90)               | 0.99 **  |
| **Baseline Spinal Cord MRI**           |                         |                         |          |
| Presence of cord T2- hyperintense foci, x/n (%) | 21/53 (39.6)          | 31/54 (57.4)            | 0.08 **  |
| Proportion of patients with enhancing foci, x/n (%) | 10/21 (47.1)        | 15/31 (48.4)            | 0.99 **  |
| Proportion of patients with LETM (≥3 vertebral segments), x/n (%) | 7/21 (33.3)       | 9/31 (29.0)             | 0.76 **  |
| **Follow-up**                          |                         |                         |          |
| Recovery EDSS, median (median months to evaluation within first year of onset) | 1.0 (6.2)           | 1.5 (6.1)               | 0.97 *   |
| Follow-up duration, median years (IQR) | 3.5 (6.0)              | 2.8 (3.0)               | 0.34 *   |
| ARR, median (IQR)                      | 0.43 (0.5)             | 0.49 (0.4)              | 0.09 *   |
| Time from onset to first relapse, median months (IQR) | 7.3 (18.9)         | 5.12 (53.0)             | 0.26 *   |

* Mann Whitney test.

** Fisher’s exact test.

*** Chi-squared test for trend.

* Patients with a final diagnosis of RIS were not evaluated for event severity.

b Patients with T2- hyperintense foci who did not receive gadolinium are excluded.
Interquartile range (IQR), white blood cell (WBC), longitudinally extensive transverse myelitis (LETM), expanded disability status scale (EDSS), annualized relapse rate (ARR).
Table 2
Characteristics of patients with high vs. low MOG-IgG titer

| Characteristic                              | High MOG-IgG titer > 1:160 (n=18) | Low MOG-IgG titer ≤ 1:160 (n=28) | P-value  |
|---------------------------------------------|------------------------------------|-----------------------------------|----------|
| Age at symptom onset, median years (IQR)   | 8.4 (6.8)                          | 8.9 (7.8)                         | 0.58*    |
| Female, n (%)                              | 8 (44.4)                           | 15 (53.5)                         | 0.76**   |
| Hispanic, n (%)                            | 16 (88.8)                          | 19 (67.8)                         | 0.15**   |
| His White, n (%)                           | 8 (44.4)                           | 13 (46.4)                         | 0.99**   |

** Initial Diagnosis
| DDNOS (%)                                  | 12 (66.6)                          | 13 (46.4)                         | 0.26***  |
| RRMS (%)                                   | 4 (22.2)                           | 7 (25.0)                          |          |
| CIS (%)                                    | 0 (0)                              | 5 (17.8)                          |          |
| CIS (%)                                    | 2 (11.1)                           | 2 (7.1)                           |          |
| CIS (%)                                    | 0 (0)                              | 1 (3.5)                           |          |

** Event Severity
| Mild, x (%)                                | 1 (5.55)                           | 0 (0)                             | 0.55***  |
| Moderate, x (%)                            | 1 (5.55)                           | 7 (25.0)                          |          |
| Severe, x (%)                              | 16 (88.8)                          | 21 (75.0)                         |          |

** Baseline CSF
| Presence of oligoclonal bands, x/n (%)    | 4/13 (30.7)                        | 3/13 (23.0)                       | 0.90**   |
| WBC ≥50 cells/µl, x/n (%)                 | 8/18 (44.4)                        | 8/26 (30.7)                       | 0.52**   |
| Protein ≥45.3 mg/dL, x/n (%)              | 3/17 (17.6)                        | 10/24 (41.6)                      | 0.17**   |

** Baseline Brain MRI
| Presence of T2-hyperintense foci, x/n (%) | 16/18 (88.9)                       | 21/28 (75.0)                      | 0.44**   |
| Proportion of patients with enhancing foci, x/n (%) | 9/16 (56.3)                       | 14/21 (66.7)                      | 0.73**   |

** Baseline Optic Nerve Involvement on MRI
| Presence of T2- hyperintense foci, x/n (%) | 9/12 (66.7)                        | 11/18 (61.1)                      | 0.69**   |
| Proportion of patients with enhancing foci, x/n (%) | 8/9 (88.9)                        | 11/11 (100)                       | 0.45**   |

** Baseline Spinal Cord MRI
| Presence of T2- hyperintense foci, x/n (%) | 6/18 (33.3)                        | 8/28 (28.5)                       | 0.75**   |
| Proportion of patients with enhancing foci, x/n (%) | 3/6 (50.0)                        | 4/8 (50.0)                        | 0.99**   |
| Proportion of patients with LETM (≥3 vertebral segments), x/n (%) | 1/6 (16.6)                        | 3/8 (37.5)                        | 0.58**   |

** Disease Course
| ARR, median (IQR)                          | 0.15 (0.6)                         | 0.36 (0.7)                        | 0.45*    |
| Receiving chronic treatment, x/n (%)       | 11/18 (61.1)                       | 19/28 (67.8)                      | 0.75*    |

* Mann Whitney test.
** Fisher’s exact test.
*** Chi-squared test for trend.