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Spinal Cord Leptomeningeal Enhancement as a Marker of Extensive Spinal Cord Involvement in Children With MOGAD

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Abstract

Background and Objectives

Spinal cord leptomeningeal enhancement (LME) can be observed in children with myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD) and with seronegative myelitis. We investigated whether the presence of spinal cord LME in MOGAD and seronegative myelitis is associated with distinct clinical, CSF, and MRI findings.

Methods

Study participants were identified among the 490 children and adolescents recruited to the Canadian Pediatric Demyelinating Disease study following an incident attack of CNS demyelination. Inclusion criteria for this study were: (1) evidence of spinal cord lesions on MRI, (2) available postgadolinium MRI sequences, and (3) available MOG and aquaporin-4 (AQP4) antibody results. None of the AQP4 antibody–positive participants met our inclusion criteria and only 1 participant with multiple sclerosis exhibited LME. We therefore focused the study on children with MOGAD and seronegative myelitis and compared the clinical, CSF, and MRI features between participants with and without LME.

Results

Our cohort included 33 participants with MOGAD (median age 5.9 years, 55% women) and 45 with seronegative myelitis (median age 11.9 years, 33% women). Spinal cord LME was detected in 20/33 (61%) participants with MOGAD and 14/45 (31%) with seronegative myelitis. Among children with MOGAD, those with LME were more likely than those without LME to have longitudinally extensive myelitis ([LETM], 19/20 vs 8/13, $p = 0.024$); H-sign (15/20 vs 5/13, $p = 0.036$), tumefactive cord lesions (10/20 vs 1/13, $p = 0.021$); complete cross-sectional involvement (16/20 vs 5/13, $p = 0.026$); nodular lesional enhancement (7/20 vs 0/13, $p = 0.026$); and more spinal cord lesions ($p = 0.036$). LME in MOGAD was not associated with greater CSF protein content or cell count nor predicted relapse rate or clinical recovery. Children with seronegative myelitis and LME were more likely than those without LME to have tumefactive lesions (6/14 vs 4/31, $p = 0.048$) and complete cross-section involvement (11/14 vs 13/31, $p = 0.028$) but did not differ in terms of H-sign, LETM, lesional enhancement, or number of lesions.

Discussion

The presence of spinal cord LME is associated with more extensive spinal cord abnormalities on MRI in children with MOGAD and to a lesser extent in those with seronegative myelitis. The biological underpinnings of this finding and its clinical implications should be assessed in further studies.

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Canadian Pediatric Demyelinating Disease Network coinvestigators are listed in the Appendix.

Glossary

ADEM = acute disseminated encephalomyelitis; **CPDDS** = Canadian Pediatric Demyelinating Disease Study; **EDSS** = Expanded Disability Status Scale; **IQR** = interquartile range; **LETM** = longitudinally extensive myelitis; **LME** = leptomeningeal enhancement; **MOGAD** = myelin oligodendrocyte glycoprotein antibody–associated disease; **MS** = multiple sclerosis.

Introduction

Myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD) is a recently defined immune-mediated demyelinating disorder of the CNS that causes inflammation in the optic nerves, spinal cord, and brain.[1,2] Leptomeningeal enhancement (LME) of the brain is a relatively common feature of MOGAD, reported in up to 46% of cases, and occurs with substantially greater frequency than in multiple sclerosis ([MS], 4%) and neuromyelitis optica spectrum disorder associated with antibodies to aquaporin 4 (AQP4-Ab + NMOSD, 7%).[3,4] Brain leptomeningeal inflammation has been occasionally reported as the first or sole manifestation of MOGAD,[5,6] and a recent study suggested an association between brain LME in MOGAD and greater frequency of headache, fever, and seizures compared with MOGAD without brain LME.[3] In addition, leptomeningeal inflammation was noted in most brain biopsies from subjects with MOGAD where meninges could be assessed, displaying a topographic relationship with underlying cortical demyelination.[7]

Recent studies have also demonstrated a relatively high prevalence of spinal cord LME (53%–69%) in children with MOGAD-associated myelitis,[8,9] exceeding the prevalence observed in children with MS (7%–14%), AQP4-Ab + NMOSD (0%), and seronegative monophasic myelitis (23%–26%).[8,9] At present, little is known about the clinical features associated with spinal cord LME in MOGAD.

We hypothesized that MRI evidence of spinal cord LME in MOGAD would be a marker of more extensive inflammation and investigated its association with the extent of acute spine abnormalities, presence of brain MRI lesions, increased CSF cellular and protein concentrations, and clinical outcomes including relapse rate. To assess whether these relationships were MOGAD-specific, we also evaluated these features in children with seronegative myelitis.

Methods

This study included participants to the Canadian Pediatric Demyelinating Disease Study (CPDDS), which enrolled subjects younger than 18 years presenting within 90 days of onset of an incident acquired demyelinating syndrome between 2004 and 2019.[10] Study participants underwent serial clinical evaluation and acquisition of brain MRI scans at presentation, 3, 6, 12 months, and yearly thereafter. MRI of the spinal cord with gadolinium was not a component of the study research protocol but was acquired in a subgroup of

Figure 1 Flowchart of Participant Recruitment

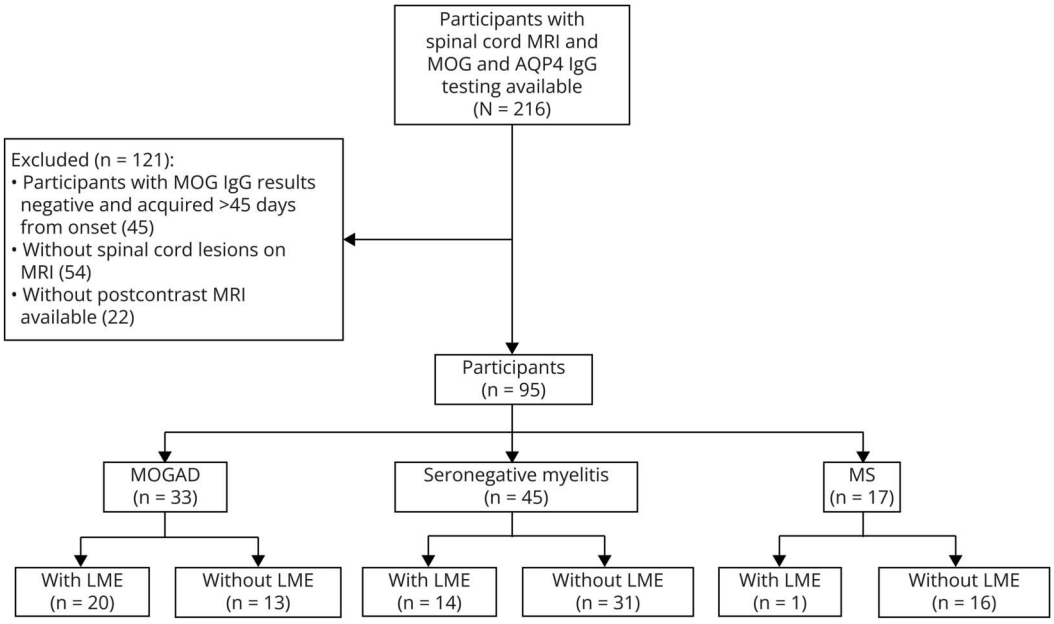

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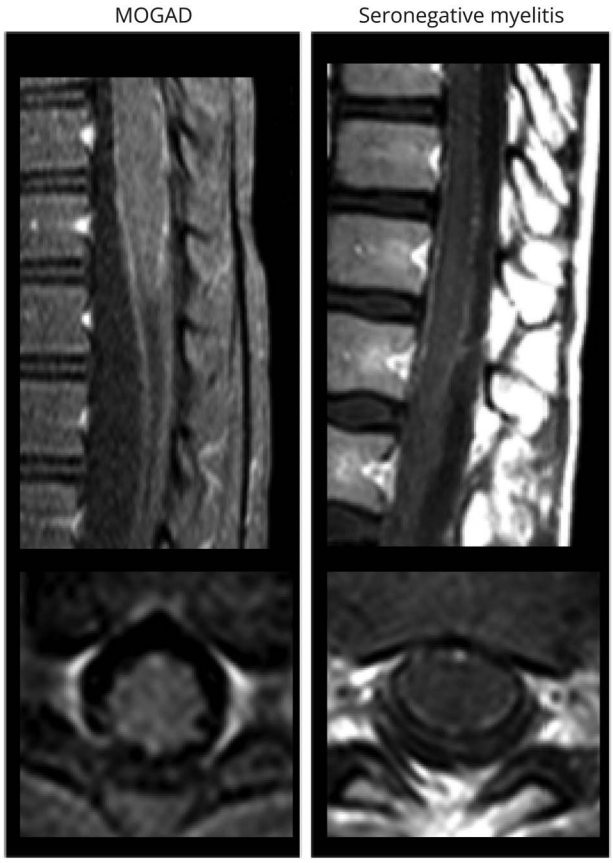
Figure 2 Spinal Cord Leptomeningeal Enhancement



Sagittal and axial gadolinium-enhanced T1-weighted MRI of the spine demonstrating leptomeningeal enhancement in a child with MOGAD (left) and a child with seronegative myelitis (right). MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease.

participants based on clinical indication, either due to myelitis symptoms or as part of the diagnostic evaluation for demyelinating disease. Serum MOG and AQP4 antibody analyses were conducted in a batched fashion at the University of Oxford using a live cell–based assay, blinded to clinical details.[11]

The inclusion criteria for this study were: (1) demonstration of spinal cord lesions on MRI scans obtained at the first attack, (2) acquisition of postgadolinium spine MRI studies, and (3) MOG and AQP4 antibody test results available at the time of presentation. To avoid including participants in the MOG-seronegative group who were initially MOG antibody–positive and underwent early conversion to seronegative status, we excluded participants with negative MOG antibody results whose first sample was obtained more than 45 days from onset of symptoms.

All spine MRI studies, including T2-weighted images in both axial and sagittal planes, unenhanced and gadolinium-enhanced T1-weighted sequences, were evaluated by a neuroradiologist (C.A.A.) and a neurologist with expertise in neuroimaging (G.F.) by applying an MRI scoring tool, blinded to the clinical diagnosis and to brain MRI findings, with a third neuroradiologist consulted in case of disagreement, as previously described.[8] The spinal cord MRI features assessed included: number of spinal cord lesions, presence of longitudinally extensive lesion (a single spinal cord lesion extending 3 vertebral segments or more), number of spinal vertebral body segments spanned by longitudinally extensive lesions, involvement of complete cross-section (defined as involvement of all gray matter and most of white matter in at least 1 slice), tumefactive appearance (defined by the increase of the diameter of the lesioned spinal cord compared to the adjacent segments), presence of H-sign (defined as predominant T2 hyperintensity in the gray matter of the spinal cord assessed on axial views), snake-eyes sign (bilaterally symmetric circular or ovoid foci of high T2-weighted signals in the anterior horns of the spinal cord gray matter), bright spot (parenchymal T2 hyperintensity greater than the surrounding CSF), lesional nodular enhancement (increased signal intensity on T1-weighted contrast-enhanced images aligned with an area of hyperintensity on T2-weighted images), root, and LME. Spinal cord lesion resolution was reported in case of complete resolution of spine abnormalities on serial MRI exams and computed among participants with at least 1 month of MRI follow-up. The presence of MRI lesions on paired brain MRI was evaluated blinded to antibody results and spine MRI findings.

Demographic characteristics (age, sex assigned at birth, and ethnicity), phenotype, occurrence of clinical attacks, and any exposure to immunotherapy were collected on all participants. The presenting clinical phenotypes were defined based on published consensus definitions and included acute disseminated encephalomyelitis ([ADEM], defined by with multifocal neurologic symptoms with encephalopathy),[12] myelitis,[13] optic neuritis,[14] ADEM with myelitis (simultaneous occurrences of the clinical and radiologic features of ADEM and myelitis), and myelitis with optic neuritis (simultaneous occurrence of symptoms of optic neuritis and myelitis). Disability score at presentation and over follow-up was mapped to Expanded Disability Status Scale (EDSS), as previously described.[15] CSF analyses were performed when clinically indicated and results on cell count, protein concentration, and CSF-restricted oligoclonal bands were included in the analyses whenever available.

Statistical Analyses

The clinical, CSF, and MRI characteristics were compared between children with MOGAD and seronegative myelitis with and without LME on spine MRI. The comparisons were performed using Mann-Whitney *U* test for continuous variables and Fisher exact test or 2-sided χ^2 test for categorical variables. A p value < 0.05 was considered statistically significant. The effect size of these comparisons was computed as standardized difference scores. The statistical analyses were performed using SPSS (Statistical Package for Social Science).

Standard Protocol Approvals, Registrations, and Patient Consents

Informed consent for participation in the study was obtained from all participants or parents/guardians with assent by

Table 1 Demographic and Clinical Features of Children With MOGAD

	Spine LME present (n = 20)	Spine LME absent (n = 13)	*p* Value	Standardized difference
Age, yrs (median [IQR])	6.71 [4.01–11.25)	5.59 (3.27–11.84)	0.84	0.19
Female n (%)	10 (50)	8 (61.5)	0.51	−0.23
Ancestry, n (%)				
African	1 (5)	1 (8)	1	−0.11
Asian	0	1 (8)	0.39	−0.41
European	16 (80)	8 (61)	0.42	0.41
Other and mixed	3 (15)	3 (23)	0.65	−0.21
Phenotype, n (%)				
Myelitis	6 (30)	4 (31)	1	−0.02
ADEM	1 (5)	6 (46)	0.012	−1.07
ADEM + myelitis	7 (35)	2 (15)	0.23	0.46
Optic neuritis	1 (5)	1 (8)	1	−0.11
Optic neuritis + myelitis	3 (15)	0	0.24	0.59
Other	2 (10)	0	0.51	0.47
Onset EDSS (median [IQR])	7 (5–8)	6.5 (3.75–7.75)	0.57	0.19
Days from onset to spine MRI (median [IQR])[a]	7.5 (1–17.7)	8 (5.5–19.5)	0.29	−0.04
Days from onset to brain MRI acquisition (median [IQR])	10.5 (3.5–17.0)	8.5 (5.8–20.3)	0.37	0.19
Steroid exposure before spine MRI acquisition, n (%)[b]	1 (5)	0 (0)	>0.99	0.32

Abbreviations: ADEM = acute disseminated encephalomyelitis; EDSS = Expanded Disability Status Scale; IQR = interquartile range, LME = leptomeningeal enhancement.
[a] The spinal cord was imaged in full for 21/23 participants, while 2 participants had only images of the cervical segment available.
[b] Only 1 participant with MOGAD was ever treated with chronic immunotherapy.

participants for younger children. The institutional review boards of all the participating institutions approved this study.

Data Availability

Anonymized derived data used for this article will be made available by request from qualified investigators.

Results

Participants

Of 490 children enrolled in the CPDDS (Figure 1), 216 had available spine MRI and MOG antibody test results. Of them, 45 participants were excluded because their first MOG testing was performed more than 45 days from symptom onset with negative results; 54 participants were excluded as they did not exhibit spinal cord lesions, and 22 participants were excluded because their spine MRI was acquired without administration of gadolinium. Therefore, the final cohort included 95 participants with gadolinium-enhanced spinal imaging and MOG testing results (33 with MOGAD, 17 with MS, 45 with seronegative myelitis, and none with AQP4 antibodies).

Spinal cord LME was observed in 20/33 MOGAD participants (61%) and in 14/45 (31%) participants with seronegative myelitis (Figure 2). Only one of the participants with MS displayed LME (1/17, 6%), and therefore, this group was not included further in the analyses.

MOGAD Cohort

The clinical and demographic features of the 33 MOGAD participants included in the study are presented in Table 1. No significant differences were observed in the age at MRI scan, sex assigned at birth, and ethnicity between participants with and without LME. The time elapsed from symptom onset to MRI acquisition was similar between participants with and without LME (median 7.5 vs 8 days, $p = 0.29$).

Spinal Cord MRI Findings in Children With MOGAD

Almost all children with MOGAD and spinal cord LME presented with longitudinally extensive transverse myelitis (LETM) (19/20, 95%) vs 61% (8/13) of those without LME ($p = 0.024$). In addition, 42% more children with LME had tumefactive spinal cord lesions (10/20 [50%] vs 1/13 [8%], $p = 0.021$), 42% more

Table 2 Onset MRI and CSF Findings and Clinical and Imaging Evolution in MOGAD Children With and Without Spine LME

	Spine LME present (n = 20)	Spine LME absent (n = 13)	*p* Value	Standardized difference
H sign, n (%)	15/20 (75)	5/13 (38)	0.036	2.10
LETM, n (%)	19/20 (95)	8/13 (61)	0.024	2.44
LETM length[a] (median [IQR])	11 (6–11)	11 (6.5–11)	0.815	0.00
Snake eyes, n(%)	2/20 (10)	4/13 (31)	0.182	−1.51
Bright spot sign, n (%)	0/20	0/13	1	—
Tumefactive, n (%)	10/20 (50)	1/13 (8)	0.021	2.52
Complete cross-section, n (%)	16/20 (80)	5/13 (38)	0.026	2.42
Nodular enhancement, n (%)	7/20 (35)	0/13 (0)	0.026	2.40
Root enhancement, n (%)	9/20 (45)	2/13 (15)	0.13	1.76
Number of spinal cord lesions (median, IQR)	2 (1–2)	1 (1–1)	0.036	1.26
Lesion resolution, n (%)	11/16 (69)	2/5 (40)	0.325	1.16
Brain lesions present, n (%)	14/18 (78)	11/12 (92)	0.62	−1.00
CSF WBC count (median, [IQR])	36 (11–167)	33 (13–50)	0.49	0.05
CSF RBC count (median, [IQR])	1 (0–60)	0 (0–4)	0.4	0.09
CSF protein concentration (median, [IQR])	0.46 (0.25–0.69)	0.30 (0.2–0.5)	0.13	0.91
CSF-restricted OCB, n (%)	3/14 (21)	1/8 (13)	>0.99	0.52
Length of clinical follow-up (y median [IQR])	8.06 (4.1–8.24)	6.63 (4.7–10)	0.65	0.56
Acute treatment with IVIg, n (%)	5 (25)	2 (15)	0.13	0.66
Acute treatment with PLEX, n (%)	0 (0)	0 (0)	>0.99	—
Relapses, n (%)[b]	5/20 (25)	0/13 (0)	0.13	1.96
Last EDSS (median [IQR])[c]	1 (0–1.5)	0 (0–1)	0.20	1.10

Abbreviations: EDSS = Expanded Disability Status Scale; IQR = interquartile range; LETM = longitudinally extensive transverse myelitis; LME = leptomeningeal enhancement; OCB = oligoclonal bands; PLEX = plasma exchange; RBC = red blood cells; WBC = white blood cells.
[a] LETM length indicates the number of vertebral segments spanned by the longitudinally extensive lesion.
[b] Of the 5 MOGAD participants experiencing clinical relapses, one had a relapse with myelitis phenotype and another had ADEM phenotype with clinical evidence of spinal cord involvement.
[c] Only 1 of the MOGAD participants manifested residual sphincter dysfunction (mild) at the last follow-up.

showed involvement of the complete spinal cord cross-sectional area at one or more cord levels (16/20 [80%] vs 5/13 [38%], p = 0.026), and 37% more displayed an H-sign on axial views (15/20 [75%] vs 5/13 [38%], p = 0.036) (Table 2).

Moreover, the presence of LME was associated with a higher prevalence of lesional nodular enhancement (35% [7/20] vs 0% [0/13] p = 0.026) and 3 times greater frequency of root enhancement, although this latter was not statistically significant (45% [9/20] vs 15% [2/13], p = 0.132). Participants with LME displayed a higher number of spine lesions compared with those without enhancement (median = 2 [interquartile range {IQR} 1–2] vs median = 1 [IQR 1-1], p = 0.036), but overall similar number of vertebral segments spanned by LETM, when present.

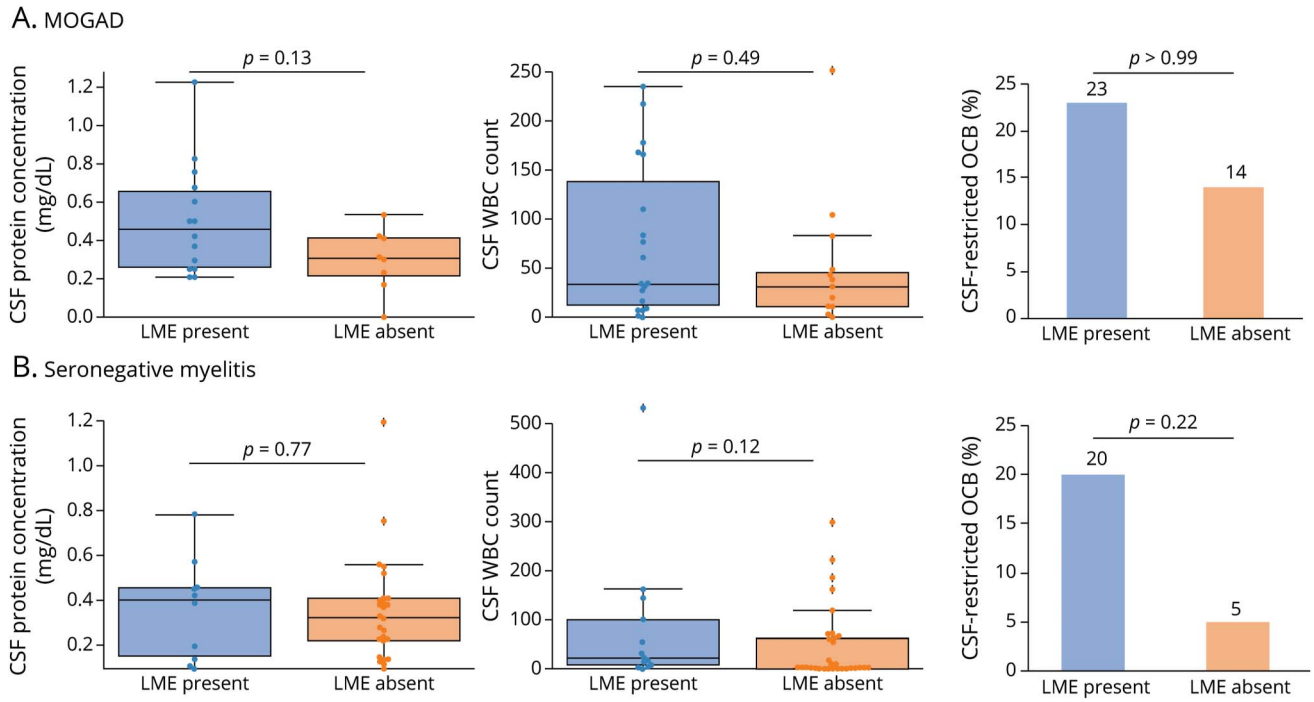
Among the 21 participants with follow-up spine MRI examinations acquired more than 1 month from baseline scan (median 816 days, IQR 184–1,414), complete lesion resolution was observed in 11/16 (69%) patients with LME (median follow-up 931 days, IQR 184–1,414) vs 2/5 (40%) without LME (p = 0.325, median follow-up 779 days, IQR 261–2,365). Spinal cord LME resolved in 13/14 of the participants with initial LME and available postcontrast MRI at follow-up but was again detected in 1 participant during a subsequent myelitis and was transiently persistent for 2.5 months in 2 children presenting with ADEM.

Data regarding paired brain and spinal MRI examinations were available for 30/33 children (18 with and 12 without LME). Within this group, no differences were observed in the frequency of presence of brain lesions (as opposed to normal brain MRI) between children with and without spinal cord LME (14/18 [78%] vs 11/12 [92%], p = 0.62).

CSF Findings in Children With MOGAD

CSF samples were obtained from 30 participants with MOGAD, with white blood cell counts available for all samples,

Figure 3 CSF Findings



CSF findings in participants with MOG antibody associated disease (A) and seronegative myelitis (B) with and without LME. LME = leptomeningeal enhancement.

and protein count and paired CSF and serum oligoclonal bands results available for a subgroup of 22 children (Table 2).

The white blood cell counts and protein levels showed greater variability, and median values were higher in participants with LME compared with those without LME (Figure 3), but these differences were not statistically significant. Oligoclonal bands were detected in a similar minority of participants from both groups. Nine of 19 (47%) participants with spinal cord LME had CSF pleocytosis greater than 50 cells/mm^3 vs 3/11 (27%) without LME (p = 0.44). The proportion of participants with protein count greater than 45 mg/dL was 7/14 (50%) among those with spinal cord LME vs 2/8 (25%) among participants without LME (p = 0.38).

Clinical Outcomes in Children With MOGAD

Both participants with and without enhancement had an overall excellent recovery, without statistically significant differences in EDSS at the last available follow-up (median 1 with LME vs 0 without LME, p = 0.20, computed after a median of 8.06 and 6.63 years, respectively).

Clinical relapses were adjudicated over a median of 6.3 years of observation, which was similar between the groups with and without LME (median 8.06 [4.1–8.24] with LME vs 6.63 [4.7–10] without LME). Only 5 (25%) participants with MOGAD experienced relapses during the observation period. While all relapsing participants belonged to the group with LME, the difference in relapse risk compared with LME negative MOGAD participants was not statistically significant (p = 0.13).

Seronegative Myelitis Cohort

The clinical and demographic features of the 45 participants with seronegative myelitis are presented in Table 3. All participants in this group had a monophasic disease course.

Among the 45 participants with seronegative myelitis (14 with LME, 31 without LME), the presence of LME was associated with a higher prevalence of tumefactive lesions (6/14 [40%] vs 4/31 [13%], p = 0.048) and complete cross-section involvement (11/14 [79%] vs 13/31 [42%], p = 0.028). However, no significant differences were observed in the occurrence of the "H" sign, nodular enhancement, and number of spine lesions between children with and without LME (Table 3). All 13 participants with LME at baseline and follow-up available had resolution of LME during follow-up, with transient persistence for 0.5–1.5 months detected in 2 participants presenting with ADEM.

The EDSS at the last follow-up was higher among children with seronegative myelitis without LME compared with those with LME (median 1.25 vs 0, p = 0.005).

Table 3 Demographic, Clinical Features, MRI, and CSF Findings of Children With Seronegative Myelitis

	Spine LME present n = 14 (31%)	Spine LME absent n = 31 (69%)	*p* Value	Standardized difference
Age (median [IQR])	8.34 (5.1–12.4)	11.3 (7.04–13.4)	0.309	0.58
Female n (%)	6 (43)	9 (29)	0.36	0.29
Ancestry, n (%)				
African	0	1 (3.5)	1	0.26
Asian	2 (17)	5 (18)	0.9	0.05
European	7 (58)	16 (57)	0.5	0.03
Other and mixed	3 (25)	6 (21.5)	0.8	0.05
Phenotype, n (%)				
Transverse myelitis	9 (64)	26 (84)	0.24	0.45
ADEM	3 (21)	2 (6)	0.16	0.43
ADEM + TM	1 (7)	2 (6)	1	0.03
Optic neuritis	1 (7)	0	0.31	0.39
ON + TM	0	1 (3)	1	0.26
Onset EDSS (median [IQR])	7.5 (6.4–8.5)	7.5 (5–8)	1	0.00
Steroid exposure before MRI, n (%)[a]	2 (14)	5 (16)	>0.99	0.05
Acute treatment with IVIg, n (%)	4 (29)	5 (16)	0.43	0.30
Acute treatment with PLEX, n (%)	2 (14)	3 (10)	0.64	0.14
Days from onset to spine MRI (median [IQR])[b]	4 (1.75–7.25)	2 (1–5)	0.042	0.56
Days from onset to brain MRI (median [IQR])	7.0 (4.5–16.0)	3.0 (1.0–7.3)	0.027	0.58
H sign, n (%)	7/14 (50)	13/31 (42)	0.74	0.15
LETM, n (%)	10/14 (71)	19/31 (61)	0.73	0.22
Snake eyes, n (%)	3/11 (21)	6/25 (19)	1	0.08
Tumefactive, n (%)	6/14 (40)	4/31 (13)	0.048	0.71
Complete cross-section, n (%)	11/14 (79)	13/31 (42)	0.028	0.74
Nodular enhancement, n (%)	2/12 (14)	3/28 (10)	0.64	0.17
Root enhancement, n (%)	3/11 (21)	3/31 (10)	0.35	0.45
Number of spinal cord lesions (median [IQR])	1 (1–1.25)	1 (1–2)	0.64	0.00
Brain lesions present, n (%)	7/13 (54)	10/28 (36)	0.27	0.37
CSF WBC count (median [IQR])[c]	22 (5–123.5)	2 (1–67)	0.12	0.28
CSF protein concentration (median [IQR])	0.4 (0.13–0.49)	0.32 (0.2–0.4)	0.77	0.37
CSF OCB present, n (%)	2/10 (20)	1/22 (5)	0.22	0.47
Length of clinical follow-up (y median [IQR])	5.53 (3.74–9.02)	5.32 (4.1–7.03)	0.695	0.07
Last EDSS (median [IQR])	0 (0–1)	1.25 (1–3)	0.005	1.07

Abbreviations: ADEM = acute disseminated encephalomyelitis; EDSS = Expanded Disability Status Scale; IQR = interquartile range; IVIG = IV immunoglobulin; LETM = longitudinally extensive transverse myelitis; LME = leptomeningeal enhancement; OCB = oligoclonal bands; ON = optic neuritis; PLEX = plasma exchange; TM = transverse myelitis; WBC = white blood cells.
[a] None of the participants with seronegative myelitis was ever treated with chronic immunotherapy.
[b] The spinal cord was imaged in full for all participants except two, who had only images of the cervical segments and of cervical and lumbar segments available, respectively.
[c] CSF samples were obtained from 44/45 participants, with white blood cell counts available for all samples, and protein count and paired CSF and serum oligoclonal bands results available for a subgroup of 36 and 32 children, respectively.

Direct comparison between participants with spinal cord LME and either MOGAD and seronegative myelitis is presented in eTable 1.

Discussion

We investigated the clinical, imaging, and CSF features associated with the presence of spinal cord LME in children with MOGAD and seronegative myelitis. In children with MOGAD, we observed several MRI features indicative of pronounced spinal cord inflammation associated with the presence of LME, including higher frequency of multiple and longitudinally extensive lesions, involvement of the complete spinal cord cross-section, tumefactive lesion appearance, presence of an "H-sign," and nodular enhancement.

Similar to our previous findings,[8] we found that the proportion of children with spinal cord LME was substantially lower in MS compared with MOGAD and other seronegative myelitis.

The association between LME and MRI features suggestive of pronounced inflammation was in part shared with seronegative forms of myelitis, where tumefactive lesions and involvement of complete spinal cord cross-sectional area were also more frequently detected among children with spinal cord LME.

LME is often considered an imaging correlate of meningeal inflammation and meningeal-blood barrier disruption. It could be speculated that disruption of this barrier may allow inflammatory factors to diffuse into the CNS parenchyma through the pial-glial basement membranes,[16,17] potentially leading to subsequent disruption of the blood-brain barrier within the spinal cord parenchyma, contributing to more extensive spinal cord lesions. Alternatively, leptomeningeal inflammation could result from the spillover of inflammation from within the cord to its surface. In animal models, tracers introduced into the CSF can enter the brain by travelling along the pial-glial basement membranes located on the outer aspects of cerebral arteries.[17] Based on this assumption, we anticipated that the CSF of children with LME would also exhibit more pronounced inflammatory abnormalities. However, although we observed greater variability and overall higher cell counts and protein concentration in children with MOGAD and LME compared with those without LME, none of these differences reached statistical significance. It is important to interpret these findings in the context of the study's limitations, particularly the small number of participants contributing to this analysis, as CSF samples were acquired only in a subgroup of participants, based on clinical indication.

A potential connection between the presence of spinal cord LME and the severity of spinal cord involvement was raised by previous observations in subjects with AQP4-Ab + NMOSD.[18] Like our findings, LME in the spinal cord of patients with AQP4-Ab + NMOSD was associated with greater frequency of LETM and parenchymal enhancement. Although in AQP4-seropositive myelitis LME was also associated with resistance to corticosteroid therapy,[18] in our MOGAD cohort, we observed only a tendency for higher EDSS values at the last follow-up among children with LME, but the overall excellent clinical outcome of our study participants may have limited the power to detect small differences between groups.

Notably, all 5 patients who experienced further relapses during follow-up had spinal cord LME at presentation. Another small study in 21 children with MOGAD reported that children with LME were 50% more likely to experience relapses compared with those without, with the difference not reaching statistical significance.[6] These observations from small cohorts do not allow to draw firm conclusions but raise questions about the potential mechanisms underlying a relapsing disease course and may warrant further investigation in larger studies.

While pathology studies in MOGAD are limited and might be biased toward the inclusion of cases with more aggressive course, evidence from these studies suggests frequent presence of meningeal inflammation and cortical demyelination, including in a subpial pattern similar to the one typically seen in MS.[7,19] Several differences exist in the characteristics of leptomeningeal inflammation in MS compared with MOGAD, including the detection on pathology specimens from MS brain of inflammatory infiltrates organized in tertiary lymphoid clusters,[20] and the rarity of overt LME detected in clinical scans. Furthermore, chronic leptomeningeal inflammation and cortical demyelination in MS have been linked to disease progression independent from clinical attacks, which is considered not a feature of MOGAD clinical course.[21,22] Therefore, the specific components of the meningeal infiltrates that drive subpial cortical pathology are likely to differ between the 2 diseases.

A limitation of this study is the relatively small sample size, and particularly the very small number of participants experiencing a relapsing course. In addition, spine MRI acquisition followed clinical indication (e.g., clinical findings localizing to the spinal cord or need of additional workup to define the extent of CNS involvement) and thus was not systematically acquired, limiting our ability to comment on the frequency of spinal cord LME among children with demyelinating syndromes, including those without clinical symptoms of myelitis. Some children in the seronegative myelitis group, particularly those with more pronounced residual deficits, might have experienced acute flaccid myelitis, although this diagnostic label was not commonly applied at the time of study enrollment. Because of the heterogenicity of this group, caution should be applied in the translation of our findings to all forms of seronegative myelitis.

Given the very small number of children with AQP4-Ab + NMOSD recruited in our study, a comparison with this relevant

group of patients was not possible. However, we emphasize comparison to other etiologies of spinal cord inflammation that are relatively more frequent in pediatric populations.

In summary, this study characterizes the clinical, imaging, and biological features of myelitis associated with spinal cord LME in children MOGAD and seronegative myelitis. We observed that children with MOGAD-associated myelitis and LME are more likely to exhibit MRI features of pronounced spinal cord inflammation, suggesting that spinal cord LME in this context may reflect distinct pathogenic mechanisms, potentially contributing to the clinical variability of this disease. In addition, certain features associated with the presence of spinal cord LME in MOGAD were also more frequently observed in children with seronegative myelitis and spinal cord LME compared with those without, suggesting that these associations are not strictly disease-specific. Future studies will evaluate the simultaneous presence of LME in the brain and spinal cord and whether this is associated with distinct clinical manifestations.

Author Contributions

S. Bartiromo: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. C. Alves: drafting/revision of the manuscript for content, including medical writing for content. J. O'Mahony: drafting/revision of the manuscript for content, including medical writing for content. E.A. Yeh: drafting/revision of the manuscript for content, including medical writing for content. R.A. Marrie: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Narayanan: drafting/revision of the manuscript for content, including medical writing for content. P.J. Waters: drafting/revision of the manuscript for content, including medical writing for content. A. Gajofatto: drafting/revision of the manuscript for content, including medical writing for content. A. Bar-Or: drafting/revision of the manuscript for content, including medical writing for content. B.L. Banwell: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. G. Fadda: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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Continued

Appendix *(continued)*

Name	Location	Role	Contribution
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