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Original article

The frequency of longitudinally extensive transverse myelitis in MS: A population-based study

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ABSTRACT

Background: Determining the frequency of longitudinally-extensive transverse myelitis (LETM: T2-lesion ≥3 vertebral segments) in multiple sclerosis (MS) is essential to assess its utility in differentiating from aquaporin-4-IgG (AQP4-IgG) positive neuromyelitis optica spectrum disorder (NMOSD) and myelin-oligodendrocyte-glycoprotein-IgG (MOG-IgG) myelitis. We sought to determine the frequency of LETM in MS during a myelitis attack.
Methods: We identified Olmsted County (MN, USA) residents on 12/31/2011 with inflammatory demyelinating disease. Inclusion criteria were: 1) Clinical myelitis episode accompanied by a new spinal magnetic resonance imaging (MRI) lesion (≤6 weeks from onset); 2) MS diagnosis by 2010 McDonald criteria; 3) Seronegative for AQP4-IgG and MOG-IgG. MRI characteristics were determined.
Results: Sixty-seven patients (median age at myelitis: 41 years [range, 16–65]; 76% females) with 92 myelitis attacks accompanied by a new MRI spinal cord lesion were identified. The frequency of LETM was 0%. The median T2-hyperintense lesion length in vertebral segments was 1.0 (range, 0.5–2.5) and 82/92 (89%) were peripheral in location on axial sequences; 58% had associated gadolinium enhancement. Two patients (2% of attacks) had multiple short lesions resembling LETM on sagittal images but axial sequences confirmed multiple non-contiguous short lesions.
Conclusion: LETM is rare in adult MS myelitis and its presence should prompt evaluation for AQP4-IgG, MOG-IgG or other etiologies. Careful scrutiny of axial images is important as coalescence of multiple short lesions may lead to the artifactual appearance of an LETM.

1. Introduction

Myelitis is a common clinical manifestation of multiple sclerosis (MS) and is typically accompanied by short magnetic resonance imaging (MRI) T2-hyperintense spinal cord lesions. In adults, longitudinally-extensive transverse myelitis (LETM) spanning ≥3 vertebral segments is used to distinguish myelitis associated with neuromyelitis optica spectrum disorder (NMOSD) from that of MS (Flanagan et al., 2015). However, the frequency of LETM in MS has varied widely (Wu et al., 2008; Tartaglino et al., 1995; Matsuoka et al., 2007; Amezcua et al., 2013) with frequencies as high as 32% reported (Matsuoka et al., 2007). These results could be influenced by ethnicity as the frequency was 32% in a Japanese population (Matsuoka et al., 2007) versus 10% in Caucasians (Tartaglino et al., 1995). The recent discovery of serum biomarkers of central nervous system inflammatory demyelinating diseases (IDD's) including aquaporin-4-IgG (AQP4-IgG) and myelin oligodendrocyte glycoprotein-IgG (MOG-IgG) has aided their distinction from MS. Myelitis in AQP4-IgG and MOG-IgG are an LETM in 62–85% (Dubey et al., 2018; Jitprapaikulsan et al., 2018b; Ciron et al., 2019). Studies assessing the frequency of LETM in MS have only occasionally assessed for AQP4-IgG but never MOG-IgG potentially resulting in overestimation of LETM frequency in MS by including patients with AQP4-IgG or MOG-IgG. Furthermore, the prior studies from tertiary referral centers (rather than being population-based) could have overestimated LETM frequency in MS from being impacted by referral bias. In this population-based study we assessed the frequency

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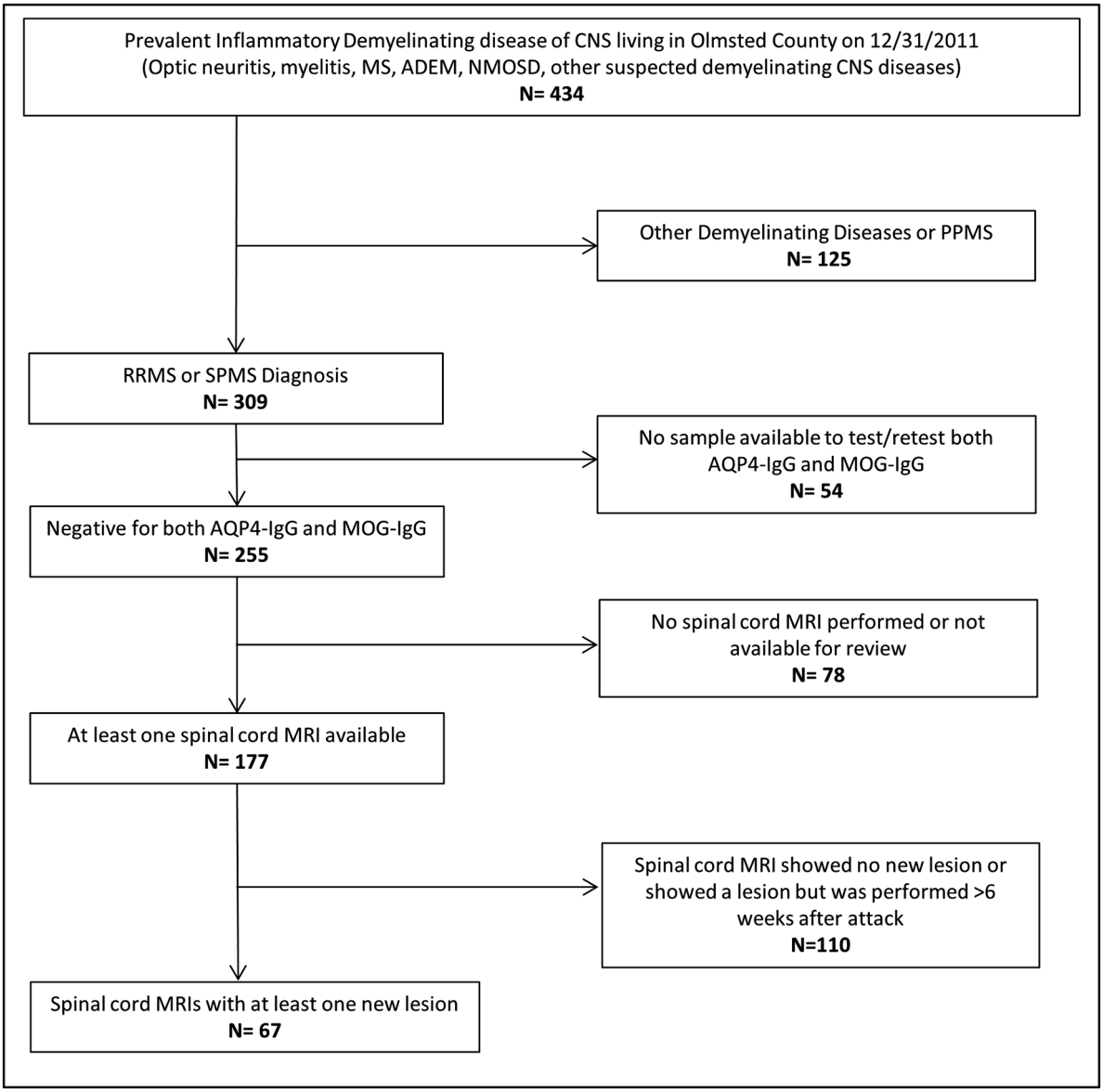

Fig. 1. Flowchart illustrating the inclusion process of the study.
Abbreviations: ADEM, acute disseminated encephalomyelitis; AQP4-IgG, aquaporin-4-IgG; MOG-IgG, myelin-oligodendrocyte glycoprotein-IgG; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

of LETM in MS patients confirmed negative for AQP4-IgG and MOG-IgG.

2. Methods

2.1. Standard protocol approvals, registrations, and patient consents

The study protocol was approved by the Mayo Clinic Institutional Review Board. All patients consented to the use of their medical records for research purposes.

2.2. Identification of patients

We identified patients through a population-based sero-prevalence biorepository of IDD's established in Olmsted County (MN, USA) on 12/31/2011 (Fig. 1). (Flanagan et al., 2016) Inclusion criteria: 1) Myelitis episode with accompanying new MRI spinal cord lesion (within 6 weeks of onset) with images available; 2) MS diagnosis by 2010 Revised McDonald criteria; 3) Seronegative for AQP4-IgG and MOG-IgG. We excluded patients who lacked either a new lesion accompanying their myelitis (n = 25) or a serum sample available (n = 54) (Fig. 1). Of the 54 patients without a serum sample available, 37 had an MRI spine available and none had a longitudinally extensive T2-hyperintense lesion.

2.3. Clinical and radiologic data

Clinical and laboratory data were abstracted from the electronic medical record or paper records as applicable. We collected demographic and clinical details including: ethnicity; age at MS myelitis onset; MS duration at time of myelitis; MS subtype (relapsing remitting, primary or secondary progressive); frequency of disease modifying treatment use; clinical symptoms at myelitis onset; and disability at last follow up. A myelitis episode was defined as an episode in which the symptoms and signs were felt by the treating clinician to be consistent with myelitis. Cerebrospinal fluid findings were assessed for cell count,

protein, oligoclonal bands and IgG index. All available spinal cord MRI studies were reviewed by a neuroradiologist (P.P.M) and a neurologist (E.P.F) to assess for the presence of LETM. The neuroradiologist reported the additional features of the spinal cord lesions including their exact length, level, axial location, and gadolinium enhancement. Sagittal and axial T2-weighted fast spin echo (FSE) were used to determine the length, the axial location, and lesion level. Sagittal short inversion time inversion recovery (STIR) sequences were also used to better visualize subtle lesions, but not to determine lesion length. Sagittal and axial T1-post gadolinium sequences were used to determine the presence of gadolinium enhancement. LETM was defined as clinical myelitis accompanied by a T2-hyperintense lesion extending ≥3 vertebral segments on sagittal T2-weighted FSE sequences and confirmed as a single lesion on axial FSE sequences. When multiple lesions were present, we included the longest lesion for our analysis.

2.4. Autoantibody testing

AQP4–IgG and MOG-IgG testing were performed in the Mayo Clinic Neuroimmunology Laboratory by technicians blinded to diagnosis. Both AQP4–IgG and MOG-IgG were tested using a clinically validated fluorescence activated cell sorting (FACS) live cell based assay, as previously described (Jitprapaikulsan et al., 2018a).

2.5. Statistical analysis

Summary statistics were reported as median (range) and percentages, as appropriate (IBM SPSS 23 software).

2.6. Data availability statement

Anonymized data used for this study are available from the corresponding authors on reasonable request.

3. Results

3.1. Demographics and clinical characteristics

Ninety two attack MRI's with new lesions from 67 patients with one or more myelitis episodes were analyzed and their demographics, clinical and MRI brain features are summarized in Table 1. None of the attack MRI's from these were performed within the first 48 h but all were undertaken within 6 weeks of onset as per the inclusion criteria.

Table 1
Demographics, clinical characteristics and Brain MRI details of included MS patients.

Myelitis episode as initial manifestation of MS	24 of 92 (26%)
Median MS disease duration in years at time of myelitis	4 (0–28)
Patients receiving disease modifying medications or immunosuppressant's at the time of myelitis[a]	25 of 67 (37%)
Patients receiving disease modifying medications or immunosuppressant's at the time of antibody testing[b]	33 of 67 (49%)
MS subtype at last follow up	
Secondary progressive MS	7 of 67 (10%)
Relapsing remitting MS	60 of 67 (90%)
Median time to progression onset in those with secondary progressive MS	8 years (range, 4–15)
Median (range) duration of follow up in years	10 (0–38)
Median (range) EDSS at last follow up	1 (0–8)
Fulfill Barkhof MRI criteria	37 of 66 (56%)

Abbreviation: EDSS, expanded disability status scale score; MRI, magnetic resonance imaging; MS, multiple sclerosis.

[a] Medications used included one or more of: Interferon beta; glatiramer acetate; or dimethyl fumarate.

[b] Medications used included one or more of; Interferon-beta; glatiramer acetate; natalizumab, methotrexate; or fingolimod.

Median age at myelitis attack (range) was 41 years (range, 16–65); just one patient (1.5%) was a child at the time of their myelitis. Fifty one patients were of female sex (76%). Ethnicity was documented as Caucasian in all patients (100%). The clinical features accompanying the myelopathy included: numbness, 87/92 (95%); sensory ataxia/imbalance, 35/92 (38%); motor deficit, 30/92 (33%); bowel/bladder dysfunction, 16/92 (17%); and lhermitte's phenomenon, 12/92 (13%). At myelitis nadir the frequency of disability was as follows: no gait aid, 82/92 (89%); cane, 5/92 (5%); walker, 4/92 (4%); and wheelchair, 1/92 (1%). Cerebrospinal fluid analysis revealed and elevated white blood cell count (> 5/μL) in 23/37 (62%) with a median of 9/μL (range, 1–150: 90% lymphocytic predominant; 8% neutrophil predominant); in 21/23 (91%) the white blood cell count was < 50/μL. CSF oligoclonal band positivity occurred in 31/39 (79%) and an increased IgG index (≥0.85) was found in 24/38 (63%). An elevated protein (> 35 mg/dL) was noted in 24/36 (67%).

3.2. MRI features

All 92 myelitis attacks were accompanied by a short lesion (Fig. 2, B) and thus we found a frequency of LETM of 0%. The radiologic characteristics are summarized in the Table 2. Notably, in 2 patients, coalescence of multiple short lesions resembled LETM on sagittal sequences but axial images confirmed multiple non-contiguous short lesions (Fig. 2, A).

4. Discussion

In this study, we found no cases of LETM among 92 myelitis attacks in MS patients. However, in 2% of MS myelitis the coalescence of multiple short lesions mimicked LETM. The presence of a true LETM should prompt a search for alternative etiologies including testing for AQP4-IgG, MOG-IgG and other etiologies of long lesions prior to attributing it to MS.

This frequency of LETM in MS we report is considerably less than in previous studies. A wide range of frequencies of LETM in MS were previously reported, including in Japanese (32% of conventional MS patients) (Matsuoka et al., 2007), Hispanic (19%), (Amezcua et al., 2013) and western Australian cohorts (3.4%) (Wu et al., 2008). A 1995 United States study reported three of 68 (4%) MS myelitis patients with LETM, but preceded AQP4-IgG and MOG-IgG discovery (Tartaglino et al., 1995).

A number of possible explanations exist for the lower frequency that we found. Our study analyzed LETM frequency during the myelitis episode while others assessed at any time during the disease course (Tartaglino et al., 1995; Matsuoka et al., 2007). The utility of LETM in distinguishing the different CNS demyelinating diseases outside of a myelitis attack is uncertain as LETM in AQP4-IgG and MOG-IgG positive patients will usually resolve between attacks (Flanagan and Weinshenker, 2017; Cobo-Calvo et al., 2016). Furthermore, chronic MS without disease activity may have hazy T2-hyperintensities throughout the cord that can appear longitudinally-extensive. Confirmation of AQP4-IgG/MOG-IgG seronegativity reduced the risk of inclusion of non-MS patients in our study. While AQP4-IgG testing has been incorporated into some of the prior studies (Wu et al., 2008; Matsuoka et al., 2007), none have assessed MOG-IgG. Also, our study was population-based which helped eliminate referral bias. Other factors leading to the contrasting results that we found compared to other studies include ethnicity differences, the optico-spinal phenotype in Asian countries and variations in the MS diagnostic criteria utilized.

Our study had limitations including a large number of patients were excluded due to lack of MRI availability or sample unavailability for testing AQP4-IgG/MOG-IgG. There were few children with MS in our population limiting the generalizability of findings to children where frequency of LETM in MS was reported to be higher (Banwell et al., 2008). The patients that met inclusion criteria from our population

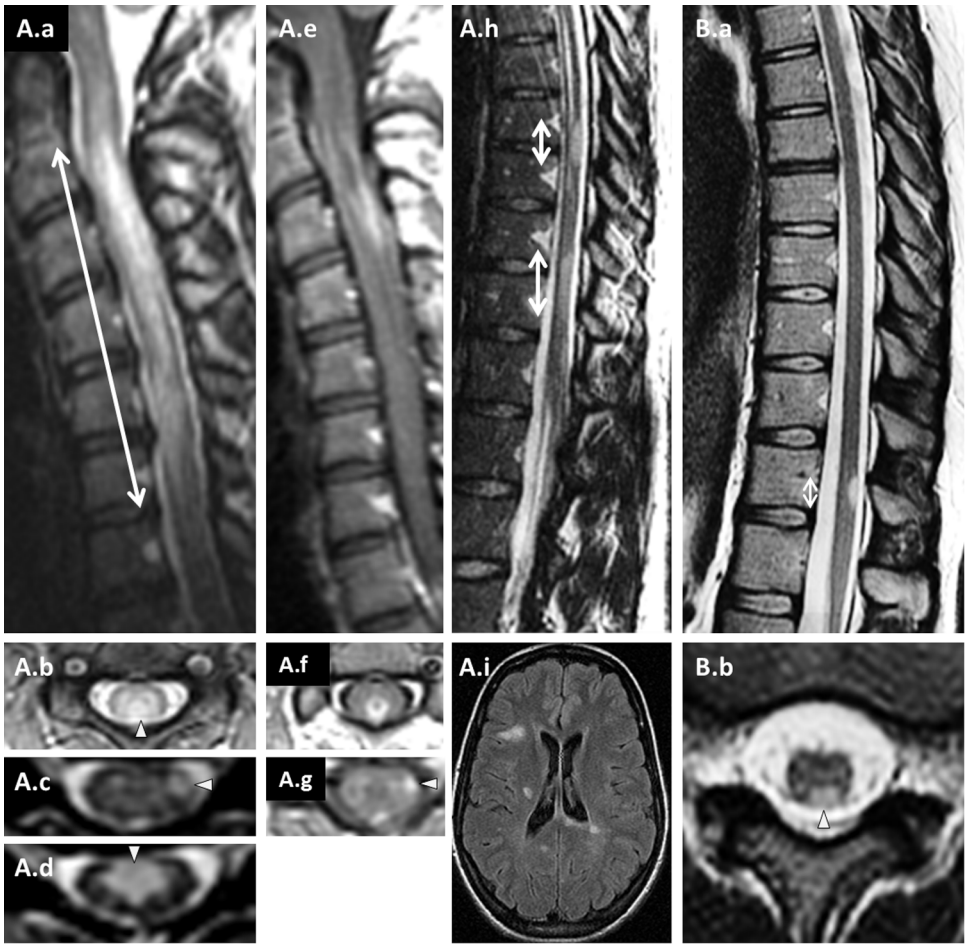

Fig. 2. Examples of short transverse myelitis lesions in MS showing that some can mimic longitudinally extensive lesions.
(A) A patient with artifactual LETM. Sagittal T2-weighted MRI shows a longitudinally extensive cervical T2-hyperintensity, spanning 5.5 vertebral segments (A.a, arrow); axial MRI at three different vertebral levels shows that the long lesion is actually coalescence of multiple non-contiguous peripheral short lesions (A.b-d, arrowheads) giving the artifactual appearance of a longitudinally extensive lesion on sagittal sequences; gadolinium enhancement is seen on the sagittal and axial T1-post gadolinium sequences (A.e-g); Sagittal T2-weighted MRI of the thoracic spine in the same patient shows two short lesions (A.h, arrows) and brain MRI of this patient shows multiple characteristic T2 hyperintensities on axial FLAIR sequence throughout the periventricular and subcortical white matter of both cerebral hemispheres (A.i). (B) A patient with a typical short MS spinal cord lesion. Sagittal and axial T2-weighted thoracic MRI reveal a short and dorsally located T2 signal hyperintensity at the level of T12 vertebra (B.a, B.b, arrow and arrowhead).

Table 2
Summary of spine MRI characteristics .

Frequency of LETM	0/92 (0%)
Coalescence of multiple short lesions mimicking LETM	2/92 (2%)
Median lesion length in vertebral segments (range)	1.0 (0.5–2.5)
Less than 1	16/92 (17%)
1–1.9	57/92 (62%)
2–2.9	19/92 (21%)
3 or more	0/92 (0%)
Lesions involving cervical cord	75/92 (82%)
Peripheral location axially	82/92 (89%)
Gadolinium enhancement	53/92 (58%)

Abbreviation: LETM, longitudinally extensive transverse myelitis.

were exclusively Caucasian and thus our results are not applicable to other ethnicities.

The coalescence of multiple short MS spinal cord lesions occasionally mimicked LETM, similar to a prior study (Matsuoka et al., 2007). Careful scrutiny of axial images is recommended prior to determining a MS myelitis lesion is longitudinally-extensive.

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Declaration of Competing Interest

Drs. Asnafi, Morris, Palace, Messina, and Sechi report no conflict of interest. Dr. Pittock holds patents that relate to functional AQP4/NMO-IgG assays and NMO-IgG as a cancer marker; has a patent pending for MPA1B Ab as a marker of neurological autoimmunity and paraneoplastic disorders; consulted for Alexion and Medimmune; and received research support from Grifols, Medimmune, and Alexion. All compensation for consulting activities is paid directly to Mayo Clinic. Dr.Weinshenker receives royalties from RSR Ltd, Oxford University, Hospices Civil de Lyon, and MVZ Labor PD Dr. Volkmann und Kollegen GbR for a patent of NMO-IgG as a diagnostic test for NMO and related disorders. He serves as a member of an adjudication committee for clinical trials in NMO being conducted by MedImmune and Alexion pharmaceutical companies. He is a consultant for Caladrius Biosciences, Brainstorm Therapeutics, Roivant Sciences and Chugai Pharma regarding potential clinical trials for NMO. He serves as a member of a data safety monitoring committee for clinical trials conducted by Novartis. Dr. Flanagan is a site principal investigator in a randomized placebo-controlled clinical trial of Inebilizumab (A CD19 inhibitor) in neuromyelitis optica spectrum disorders funded by MedImmune/Viela Bio and has served on its advisory board.

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