Clinical characteristics of ultra-longitudinally extensive transverse myelitis in a Peruvian cohort

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KEYWORDS
Anti-MOG antibody; Aquaporin-4 antibody; Longitudinally extensive transverse myelitis; Ultra-longitudinally extensive transverse myelitis; Neuromyelitis optica spectrum disorder

Abstract
Introduction: Ultra-longitudinally extensive transverse myelitis (uLETM) is defined as an inflammatory lesion involving 10 or more spinal cord segments. The aim of our study is to describe the clinical and radiological features of this atypical form of myelitis.

Methods: We conducted a descriptive cross-sectional study of clinical data from 57 patients older than 18 years diagnosed with longitudinally extensive transverse myelitis. Nineteen cases were classified as uLETM.

Results: Twelve of the 19 patients were women, age ranged between 18 and 76 years, and the main aetiology was neuromyelitis optica spectrum disorder (8 patients), followed by anti-MOG antibody myelitis (3 patients). The main region involved was at cervical-thoracic spinal cord. Two patients presented complete spinal cord lesion.

Conclusions: Our results are consistent with previous reports suggesting that neuromyelitis optica spectrum disorder remains the main aetiology in uLETM; however, anti-MOG antibodies should be considered within the differential diagnosis.

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PALABRAS CLAVE
Anticuerpo antiaquaporina-4; Anticuerpo anti MOG; Mielitis longitudinal extensa;

Resumen
Introducción: La mielitis longitudinal ultra extensa se define como el compromiso inflamatorio de 10 o más segmentos menavales. El objetivo de nuestro estudio es describir las características clínicas y radiológicas de esta forma atípica de mielitis.
Mielitis Longitudinal Ultra extensa; Trastorno del espectro de neuromielitis óptica

Métodos: Realizamos un estudio transversal y descriptivo en base a los datos clínicos de 57 pacientes mayores de 18 años con diagnóstico de mielitis longitudinal extensa. Diecinueve pacientes cumplían con la definición de mielitis longitudinal ultra extensa.

Resultados: Doce de los 19 pacientes fueron del sexo femenino, el rango de edad estuvo entre los 18 y 76 años, la principal etiología fue el trastorno del espectro de la neuromielitis óptica (8 pacientes), seguido de la mielitis por anticuerpos anti-MOG (3 pacientes). La principal región comprometida fue a nivel cervicodorsal. Dos pacientes sufrieron una lesión completa del médula espinal.

Conclusiones: Nuestros resultados concuerdan con lo publicado en que el espectro de la neuromielitis óptica sigue siendo la principal etiología en la mielitis longitudinal ultra extensa; sin embargo, el anticuerpo anti MOG debe considerarse dentro del diagnóstico diferencial. © 2024 Sociedad Española de Neurología. Publicado por Elsevier España, S.L.U. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Transverse myelitis is a heterogeneous group of inflammatory disorders of diverse aetiologies; it is most frequently immune-mediated, and can affect any segment of the spinal cord. The extension of the spinal lesion may be informative in determining the aetiology and establishing prognosis. Longitudinally extensive transverse myelitis (LETM) refers to a lesion involving 3 or more spinal cord segments on MRI. The most frequent aetiology is neuromielitis optica spectrum disorder (NMOSD), followed by vascular aetiology (infarction) and infectious myelopathy; other causes include radiation, paraneoplastic syndromes, systemic lupus erythematosus, and vitamin B12 deficiency. Less frequently, it is observed in anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibody syndrome and myelopathies secondary to deficiency diseases or paraneoplastic or traumatic causes. The incidence of LETM is not well studied, although a retrospective study of 339 patients with transverse myelitis reported only 6 cases (2%) of isolated, idiopathic LETM. Cases have also been described of myelitis affecting over 10 spinal cord segments; the term ultra-longitudinally extensive transverse myelitis (uLETM) has been proposed to describe these cases. The main cause of uLETM is NMOSD, although cases have also been reported in patients with arteriovenous fistula, syringomyelia, and Epstein–Barr virus infection. In any case, there is a high likelihood of severe disability if treatment is not started promptly.

The objective of the present study is to describe the clinical, aetiological, and radiological characteristics of uLETM in a series of patients attended at our centre.

Methods

We conducted a descriptive, cross-sectional study of the clinical records of 57 patients hospitalised at the Peruvian National Institute of Neurological Sciences between January 2016 and December 2022 with a diagnosis of myelitis. Inclusion criteria were age over 18 years and having undergone at least one spinal MRI study.

All patients admitted to the institution with a diagnosis of myelitis are studied with blood analysis (vitamin B12, VDRL study, HTLV, HIV, ANA, ANCA) and determination of anti–aquaporin-4 (anti-AQP4) and anti-MOG antibodies, as necessary. We also perform CSF analysis and chest, abdomen, and pelvis CT (to rule out occult primary tumours, where needed). In some cases, it was not possible to complete this battery of complementary studies. Determination of anti-AQP4 and anti-MOG IgG antibodies (8 patients and 4 patients, respectively) was performed using cell-based assays; in 8 cases, anti-AQP4 antibodies were determined using an enzyme immunoassay method. MRI studies (T1, contrast-enhanced T1, T2, FLAIR, and proton density-weighted sequences) were performed in a 3 T Philips MRI scanner. We selected all cases presenting MRI alterations in 3 or more spinal cord segments (LETM); uLETM was defined as a lesion affecting 10 segments or more.

The variables analysed were: sex; age; disease progression time; presence of motor, sensory, and autonomic symptoms; number of spinal cord segments affected; aetiological diagnosis; and CSF characteristics.

Data were anonymised and analysed with the Stata software, version 16. Categorical variables are expressed as frequencies and percentages. Continuous variables were tested for normality with the Shapiro–Wilk test; normally distributed variables are expressed as means and standard deviations (SD), and non-normally distributed variables as medians and interquartile ranges (IQR).

This study complies with the ethical principles of the Declaration of Helsinki (2013 revision) and was approved by our centre’s research ethics committee.

Results

We reviewed the records of 57 patients with LETM. The majority (63.15%) were women; all patients were of mixed race; age ranged from 18 to 79 years; all patients presented motor and sensory impairment, but only 42 (73.68%) presented sphincter dysfunction. CSF analysis revealed lymphocytic pleocytosis in 19 patients (33.33%) and elevated protein levels in 22 (38.59%). Nineteen patients (33.33%) met diagnostic criteria for uLETM (≥10 spinal segments affected); Table 1 compares data from this group against the remaining patients with lesions involving 3–9 segments (non-uLETM).
Of the 19 patients with uLETM, 12 (63.15%) were women; age ranged from 18 to 76 years (median, 36; IQR, 31) and disease progression time ranged from 3 to 720 days (median, 60; IQR, 255). Eight patients met diagnostic criteria for NMOSD (4 definite and 4 probable), 3 tested positive for anti-MOG antibodies, 2 were diagnosed with viral myelitis (HIV in one and HTLV-1 in the other), and 1 was diagnosed with syringomyelia; aetiology was undetermined in 5 patients. By spinal region, involvement was cervical-thoracic in 14 patients and thoracic in 3; 2 presented complete spinal cord lesion (1 patient with NMOSD and 1 with anti-MOG syndrome). CSF analysis was performed in 14 patients, revealing elevated protein levels in 8 and predominantly mononuclear pleocytosis in 9.

During the acute phase, 11 patients received methylprednisolone pulse therapy (1 g per day for 5 days), and 4 received methylprednisolone pulse therapy plus 5 sessions of plasma exchange. Rituximab was prescribed to 2 patients and azathioprine to 4 as maintenance immunomodulatory treatment.

**Discussion**

The main aetiologies of uLETM in our sample were autoimmune, with NMOSD and anti-MOG syndrome accounting for 42.10% and 15.78% of cases, respectively. The syndrome presents a wide age range, and predominantly affects women.

Other Latin American series of LETM include patients with lesions involving more than 10 spinal segments, with NMOSD and systemic lupus erythematosus being the most frequent causes; however, no specific description is given of this subgroup of patients with uLETM. Therefore, ours is the first study performed in the region to describe a cohort of patients with uLETM; worldwide, it is the second largest cohort of patients with uLETM reported to date, after the study by Zhang et al., which included 33 patients. Our patients’ clinical characteristics coincide with those reported in that study, in terms of female predominance, age range, and diagnosis of NMOSD as the main aetiology. Fourteen patients (73.68%) presented cervical-thoracic involvement and 2 presented complete spinal cord lesion, whereas in the study by Zhang et al., 95.20% (20 patients) presented cervical-thoracic involvement, with complete spinal cord lesion in 15 patients. LETM is not merely a feature of NMOSD, but rather it is included in the diagnostic criteria for the disease.

LETM is the second most common phenotype in anti-MOG–associated disease; some studies have addressed LETM and anti-MOG antibodies but do not specify how many patients presented involvement of ≥10 spinal cord segments; rather, they report the range. For instance, one study of 47 patients, in which 37 (79%) were positive for anti-MOG antibodies, reported that lesions involved between 1 and 15 segments; another study, including 56 patients, reported that 13 (23.20%) were positive for anti-MOG antibodies, with lesions affecting 3–20 spinal cord segments. In our study, 3 patients met criteria for anti-MOG–associated disease; however, given the current lack of research, we cannot conclude that this represents a high percentage of patients with uLETM.

Comparison between the uLETM and non-uLETM groups revealed no differences in age, sex (both groups displayed a female predominance), or disease progression time; sphincter dysfunction was observed in fewer than half of patients in the non-uLETM group and practically all patients in the uLETM group. However, this symptom was reported in 93.9% of a sample of 66 patients with LETM from India and in 75% of the patients in our study.

**Table 1** Clinical characteristics of patients with and without ultra-longitudinally extensive transverse myelitis.

<table>
<thead>
<tr>
<th></th>
<th>Non-uLETM (3–9 segments)</th>
<th>uLETM (≥10 segments)</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>n = 38</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age, median (IQR)</td>
<td>40 (30)</td>
<td>36 (31)</td>
<td>.364 *</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>24 (63.16)</td>
<td>12 (63.15)</td>
<td>1.00 **</td>
</tr>
<tr>
<td>Progression time in days, median (IQR)</td>
<td>26 (172)</td>
<td>60 (255)</td>
<td>.411 *</td>
</tr>
<tr>
<td>Spinal region, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>15 (39.47)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Thoracic</td>
<td>11 (28.95)</td>
<td>3 (15.79)</td>
<td></td>
</tr>
<tr>
<td>Cervical-thoracic</td>
<td>9 (23.68)</td>
<td>14 (73.68)</td>
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<tr>
<td>Thoracic-lumbar</td>
<td>3 (7.9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>2 (10.53)</td>
<td></td>
</tr>
<tr>
<td>Sphincter dysfunction, n (%)</td>
<td>25 (65.78)</td>
<td>17 (89.47)</td>
<td>.056 **</td>
</tr>
<tr>
<td>Aetiological diagnosis, n (%)</td>
<td></td>
<td></td>
<td>.177 ***</td>
</tr>
<tr>
<td>Definite NMOSD</td>
<td>14 (36.84)</td>
<td>6 (31.58)</td>
<td></td>
</tr>
<tr>
<td>Probable NMOSD</td>
<td>8 (21.05)</td>
<td>2 (10.53)</td>
<td></td>
</tr>
<tr>
<td>Anti-MOG</td>
<td>1 (2.63)</td>
<td>3 (15.78)</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>1 (2.63)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Viral myelitis</td>
<td>2 (5.26)</td>
<td>2 (10.53)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>12 (31.58)</td>
<td>6 (31.58)</td>
<td></td>
</tr>
</tbody>
</table>

IQR: interquartile range; NMOSD: neuromyelitis optica spectrum disorder; uLETM: ultra-longitudinally extensive transverse myelitis.

* Mann–Whitney U test.

** Chi-square test.

Fisher exact test.
of a cohort of 35 patients with LETM associated with systemic lupus erythematosus. Our patients with uLETM predominantly displayed cervical-thoracic involvement, whereas the non-uLETM group mainly showed cervical involvement; the Indian study also reported that the cervical-thoracic region was most frequently affected in patients with LETM, whereas other authors mention the thoracic region only. As mentioned above, NMOSD is the most frequent cause of uLETM; it was also the most frequent diagnosis in our non-uLETM group. However, it should be noted that the most frequent aetiology in other series of LETM was idiopathic myelitis, with NMOSD being the second most frequent cause.

Some of the cases reported in this study were not immune-mediated; however, they were included to highlight the need to consider other aetiologies in the differential diagnosis of patients with MRI findings revealing lesions involving 10 or more spinal cord segments. One case was caused by HTLV-1 infection, with chronic symptoms of spinal cord involvement (19 segments in the cervical-thoracic region), which did not respond to methylprednisolone. Our literature search identified a single report of a patient in Japan who presented subacute HTLV-1–associated myelopathy with a complete spinal cord lesion, which initially improved with corticosteroids.

This study presents certain methodological limitations due to its retrospective approach. Some complementary studies were not performed in all patients, particularly the virus and antibody studies; this explains the high number of patients with uLETM of undetermined aetiology.

In conclusion, NMOSD is the leading cause of uLETM, whereas anti-MOG antibody syndrome, among other aetiologies, must be considered in the remaining cases. Future studies should include larger samples and should follow up patients to confirm our findings and evaluate such other variables as treatment response and residual disability.

Funding
This study has received no specific funding from any public, commercial, or non-profit organisation.

Informed consent
Informed consent was not obtained because the study is based on clinical records, rather than direct study of patients. Data collection was approved by the local ethics committee.

Ethical considerations
This study complies with the ethical principles of the Declaration of Helsinki (2013 revision) and was approved by our centre’s research ethics committee.

Declaration of competing interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurop.2024.100161.

References