

Etiologic spectrum and functional outcome of the acute inflammatory myelitis

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Received: 1 June 2016 / Accepted: 29 December 2016 / Published online: 10 January 2017
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Abstract Clinical, neuroimaging, and laboratory features are not specific enough to establish the etiological diagnosis of the acute inflammatory myelitis (AIM). Longitudinally extensive transverse myelitis (LETM) seen on magnetic resonance imaging (MRI) has been associated with a poor functional prognosis. The aim of this study was to assess the functional outcomes of a first AIM event comparing patients with LETM vs. no LETM on MRI and to report the differential diagnosis. Clinical, radiological, biochemical aspects were collected, and Winner–Hughes Functional Disability Scale (WHFDS) was performed after 3 and 6 months. Centromedullary lesions were associated with LETM, lateral lesions with partial lesion (PL), and brain MRI lesions with multiple sclerosis and acute encephalomyelitis disseminated. LETM patients were associated with a worse functional outcome as the need of a wheelchair after 3 and 6 months (OR = 7.61 p = 0.01; OR 4.8 p = 0.04, respectively), a walker or cane (OR = 11.0 p = 0.002, OR = 4.3 p = 0.03, respectively). In addition, we found a correlation between LETM and acute complete transverse myelitis and PL with acute partial transverse myelitis (83.3 and 90.9%, respectively; p < 0.0001). In conclusion, AIM is a heterogeneous syndrome from an etiological point of view and LETM patients had worse functional prognosis compared with PL after 3 and 6 months.

Keywords Partial myelitis · Longitudinally extensive transverse myelitis · Multiple sclerosis · Neuromyelitis optica · Prognosis · South America

Introduction

Acute inflammatory myelitis (AIM) are a heterogeneous group of autoimmune spinal cord disorders characterized by disruption of the ascending and descending pathways with wide differential diagnosis. The most common causes of immune-mediated spinal cord injury are acquired demyelinating diseases, such as multiple sclerosis (MS) and neuromyelitis optica (NMO)/NMO spectrum disorders (NMOSD); or due to systemic autoimmune causes, such as systemic lupus erythematosus (SLE) and Sjögren syndrome [1, 2], postinfective or postvaccinal are causes to consider as differential diagnosis [3]. After a detailed assessment, in almost 15–30% of the cases, no cause is found (idiopathic myelitis) [4, 5]. Magnetic resonance imaging (MRI) of the spinal cord with and without gadolinium enhancement is the initial investigation of choice in the evaluation of acute myelitis (AM) and it is the best noninvasive tool for identifying patients with longitudinally extensive transverse myelitis (LETM), which is more often observed in NMOSD and less in MS [1]. Therefore, differentiating LETM from partial or short lesion (PL) on MRI is very important from a clinical point of view to guide physicians towards the correct etiological diagnosis because of the different prognosis, these diseases have. Early studies reported that up to one-third of patients with a first episode of AIM remained unable to walk [6]. Several clinical factors are associated with a poor functional outcome, including motor involvement at onset, sphincter dysfunction, number of relapses, spinal shock, severe functional

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deficit at onset, and LETM [7, 8]. AIM does not have specific diagnostic criteria; therefore, a systematic and comprehensive assessment could help us to recognize the etiology of the AIM, facilitate therapeutic decision, and provide early accurate treatment to prevent future relapses and disability.

The purpose of this retrospective study is to assess the functional outcome of a consecutive series of patients with a first AIM event (LETM vs. no LETM) through Winner–Hughes Functional Disability Scale (WHFDS) after 3 and 6 months and to establish the etiologic spectrum, clinical presentation, and neuroradiological findings in an Argentinean population.

Materials and methods

All patients diagnosed with isolated AIM that was admitted at the Neurology Department of the Carlos G. Durand Hospital of Buenos Aires, Argentina, from June 2008 to June 2014 and met the inclusion/exclusion criteria (see Table 1) that were included. According to the medical record database, clinical manifestations of spinal cord dysfunction were classified as acute partial transverse myelitis (APTM, incomplete or patchy involvement of at least one spinal segment with mild-to-moderate weakness, asymmetric, or dissociated sensory symptoms and occasionally sphincter dysfunction) and acute complete transverse myelitis (ACTM, acute or subacute symmetric moderate or severe loss of function distal to that level) and motor, sensory, and autonomic dysfunction were collected. Etiological diagnoses were defined by internationally accepted criteria [1, 4, 9–14]. All patients underwent brain and spinal cord MRI with and without gadolinium contrast on T1-weighted images using a 1.5-T scanner for diagnostic workup. Sagittal and axial T1, T2, fluid-attenuated

inversion recovery (FLAIR), and short tau inversion recovery (STIR) sequences were carried out routinely. Lesions on spinal cord MRI included extension (sagittal images) classified as PL (only one lesion <2 vertebral segments in length), LETM (extending over ≥ 3 vertebral segments), and multisegmental lesions (MSL, two or more lesions <2 vertebral segments in noncontiguous segment) and distribution (axial images) that were classified as peripherally located (lateral/posterior) and centromedullary located. Axial, coronal, and sagittal brain MRI were analyzed and classified as normal, suggestive of MS [15, 16] and white matter non-specific lesions that were suggestive of NMO (“typical lesions” defined as lesions located at sites of high AQP4 expressions) [17, 18]. Contrast enhancement was classified as present or not present. Oligoclonal bands (OCBs) were analyzed using isoelectric focusing. Aquaporin-4 antibodies (AQP4-ab) were analyzed by indirect immunofluorescence (IIF) assay as described originally by Lennon et al. [19]. Other specific tests were done according to the clinical suspicion of the neurologist. Functional outcome was performed retrospectively at 3 and 6 months after presentation of the symptoms with the WHFDS [19]: 0 = normal, 1 = minor symptoms, 2 = able to walk more than 30 ft without assistance, 3 = able to walk more than 30 ft with assistance, 4 = bed bound/wheelchair bound, and 5 = requires assisted ventilation, 6 = death.

Statistic

Categorical variables were presented as proportions, and continuous variables were presented as means and SDs. Measures of risk, such as ORs, are presented with respective 95% CIs. The statistical significance of the differences observed between the variables was analyzed using Chi-square test or Fisher’s exact test for categorical data. The

Table 1 Inclusion/exclusion criteria for acute inflammatory myelitis

Inclusion	
	Motor or sensory symptoms with or without sphincter dysfunction attributable to the spinal cord
	Progression to nadir between 4 h and 21 days following the onset of symptoms
	Free new-relapses during these period (6 months)
	Spinal cord MRI on a 1.5-T MR scanner
	Spinal cord T2 signal hyperintensity
	Available brain MRI study
	Intravenous methylprednisolone 1 g daily for 5 days during the attack
	Follow-up for at least 6 months with the Winner–Hughes Functional disability scale
Exclusion	
	Extra-axial compressive etiology by neuroimaging
	History of neurological disease or symptoms
	Previous spine irradiation
	No symptoms or signs attributable to involvement other than the spine

significance level was established with $p < 0.05$. Data analysis was performed using the Epi Info 7 software program.

Results

Demographic, clinical, and laboratory findings

A total of 46 patients ($n = 46$) diagnosed as AIM were included. Differential diagnosis, clinical, and paraclinical characteristics are summarized in Table 2. Mean age at

onset was 34.76 (± 11.19) years, and 82.61% (38/46) were female. All our patients had sensory dysfunction in at least one limb at onset. We identified a clear sensory level in 73.91% (34/46), and the most frequently affected localizations were thoracic 70.5% (24/34) followed by cervical 23.53% (8/34) and finally lumbar 5.88% (2/34). Motor system dysfunction was found in 91.30% (42/46), mostly in the lower limbs (LL) (58.70%). Thirty patients (65.22%) had sphincter dysfunction with bladder (retention or urinary urge incontinence) and/or bowel (constipation or fecal urge incontinence) involvement. From a clinical point of view, APTM was observed in 52.17% (24/46) and ACTM

Table 2 Demographic, clinical, and paraclinical characteristics

Characteristics	Total ($n = 46$)	MS ($n = 20$)	NMO ($n = 10$)	Idiopathic ($n = 7$)	SLE ($n = 6$)	ADEM ($n = 3$)
Mean age at onset (years)	35.9	36.4	36.2	38.7	25.3	27
Female (%)	28 (60.86)	18 (90)	8 (80)	4 (57.1)	6 (100)	2 (66.6)
First myelitis no (%)						
APTM	24 (52.17)	19	2	1	1	1
ACTM	22 (47.83)	1	8	6	5	2
Sensory level no (%)						
Cervical	8 (17.39)	7	–	–	–	1
Thoracic	24 (52.18)	5	6	5	6	2
Lumbosacral	2 (4.35)	–	1	1	–	–
No	12 (26.08)	8	3	1	–	–
Motor dysfunction no (%)						
UULL	7 (15.21)	–	1	–	5	1
LLLL	22 (47.83)	12	6	3	1	–
4 LL	13 (28.27)	4	3	4	–	2
No	4 (8.69)	4	–	–	–	–
Sphincter dysfunction no (%)						
Yes	30 (65.22)	8	8	6	5	3
No	16 (34.78)	12	2	1	1	–
OCB no (%)						
Positive	12 (26.10)	11	1	0	–	–
Negative	20 (43.47)	–	9	6	2	3
Not Performed	14 (30.43)	9	–	1	4	–
AQP4-ab no (%)						
Positive	6 (13.05)	–	6	–	–	–
Negative	19 (41.30)	4	4	7	3	1
Not Performed	21 (45.65)	16	–	–	3	2
Functional outcome at 6 months						
WHFDS <3	26	15	5	1	2	3
WHFDS 3	8	2	4	1	1	–
WHFDS ≥ 4	12	3	1	5	3	–
WHFDS mean (\pm SD)	1.76 (± 1.47)	1.10 (± 1.41)	1.70 (± 0.82)	3.42 (± 0.77)	2.66 (± 1.50)	0.66 (± 0.57)

MS multiple sclerosis, NMO neuromyelitis optica, ADEM acute demyelinating encephalomyelitis, SLE systemic lupus erythematosus, ACTM acute complete transverse myelitis, APTM acute partial transverse myelitis, UULL upper limbs, LLLL lower limbs, LL limbs, OCB oligoclonal bands, AQP4-ab aquaporin-4 antibodies, WHFDS Winner–Hughes Functional Disability Scale

in 47.83% (22/46) of the cases, at onset. OCBs were performed in 66% of patients (32/46), and positive results were obtained in 12 subjects (37.5%). MS patients had 100% positive OCBs (not performed $n = 9$), while only 10% (1/10) NMO patients had positive results. All idiopathic myelitis patients included in this study were both OCBs and AQP4-ab negative at presentation. Data about AQP4-ab were available in 54.34% being positive in only 13.05%; all these patients were diagnosed as NMO/NMOSD.

Differential diagnosis of AIM

All our patients had symptomatic spinal cord and MRI lesions at onset. After 6 months of follow-up, we identified the following causes: MS = 43.47% (20/46), NMOSD 21.73% (10/46) (AQP4-ab positive or negative patients fulfilled the Wingerchuk revised criteria for NMO: 8 and AIM AQP4-ab positive: 2), idiopathic = 15.21% (7/46), SLE-related myelitis = 13.04% (6/46), and acute encephalomyelitis disseminated (ADEM) = 6.51% (3/46) (see Table 2). None of these patients had relapses during this follow-up period.

MRI lesion characteristics

In spinal cord MRI, we observed that 47.83% (22/46) patients corresponded to LETM, 41.30% (19/46) to MSL, and 10.87% (5/46) to PL. LETM lesions expanded for a mean of 8.04 (± 4.56) spinal segments. Centromedullary lesions were associated with LETM (19/22), whereas lateral and/or posterior lesions were associated with PL and MSL (24/24). In addition, we found correlation between LETM and ACTM; and PL or MSL with APTM (83.3 and 90.9%, respectively; $p < 0.0001$). Contrast enhancement lesions were found in 54.34% of the patients (25/46) at presentation. Brain MRI lesions were associated with MS and ADEM, and non-specific T2-hyperintensities and normal findings were observed in the rest of the differential diagnosis. MRI characteristics of spinal cord and brain lesions are summarized in Table 3.

Treatment

All our patients received high-dose intravenous (i.v.) methylprednisolone, 1 g daily for 5 days. MS patients were also treated with Interferon or Glatiramer acetate at onset; NMO/NMOSD (AQP4-ab seropositive) patients were treated with azathioprine (with or without oral corticosteroids) and 50% of SLE-related myelitis patients with iv cyclophosphamide at presentation. Idiopathic myelitis and ADEM did not receive the long-term therapy during this period.

Functional outcome

When we compared between LETM vs. no LETM (PL and MSL) patients after 3 months, we found that ≥ 4 WHFDS score (bed bound/wheelchair bound) was seen in 40.91% for LETM vs. 8.33% no LETM (CI 95% OR = 7.61, $p = 0.01$) patients. In addition, WHFDS ≥ 3 (able to walk with assistance) was associated with LETM (OR = 11.0, $p = 0.002$) patients. In addition, WHFDS score at 6 months ≥ 3 and ≥ 4 score was associated with LETM (OR = 4.3, $p = 0.03$ for ≥ 3 and OR 4.8, $p = 0.04$ for ≥ 4). Thus, LETM correlates with a worse functional prognosis compared with PL/MSL after 6 months (see Table 4). In our sample, we identified a WHFDS ≥ 4 score in MS (15%, 3/20), idiopathic (71.42%, 5/7) and SLE-related myelitis (50%, 3/6). Differential diagnosis and WHFDS are summarized in Table 2.

Discussion

In the present study, we retrospectively reviewed 46 consecutive patients diagnosed as AIM and found several clinical and MRI features with different functional prognosis. The mean age at presentation was 34.76 (± 11.19) years, and females were more commonly affected, in line with other studies [13, 19, 20].

Scott et al. [5] reviewed the utility of distinguishing ACTM from APTM in determining the etiology of AIM, identifying that APTM initially converted to MS in 10.3% of the cases, whereas ACTM suggests a transition to MS in 0–2% of the patients (most commonly observed in NMOSD). In our series, we found that 95% of MS patients and 20% of NMOSD subjects had the initial APTM. ACTM was found in NMO/NMOSD (80%), idiopathic myelitis (85%), SLE-related myelitis (83%), ADEM (66%), and only one MS patient (5%) at presentation. In addition, LETM was seen on ACTM (83.3%) and PL or MSL with APTM (90.9%) at onset on MRI. Regarding to etiological causes, demyelinating diseases (MS 43% and NMOSD 21%) and idiopathic myelitis (15%) were the most frequently found. Thus, during this follow-up period, idiopathic myelitis patients had no history of infection/vaccine and did not fulfill MS/NMO criteria and no systemic inflammatory diseases were found. However, a percentage of these patients may remain undiagnosed (and idiopathic) because of the short follow-up period. Interestingly, we observed a high percentage of SLE-related myelitis (13.04%) cases, but we believe that our results might be biased due the fact that our hospital is a national reference center for the study of SLE.

In recent years, the discovery of AQP4-ab has significantly changed the initial evaluation of AIM [19, 21, 22].

Table 3 MRI characteristics of spinal cord and brain lesions

	Total (n = 46)	MS (n = 20)	NMO (n = 10)	Idiopathic (n = 7)	SLE (n = 6)	ADEM (n = 3)
Segmentos medulares no (%)						
Multisegment lesions	19 (41.30)	18	–	–	1	–
LETM	22 (47.82)	1	10	6	2	2
Partial lesion	5 (10.86)	1	–	1	3	1
Localization no (%)						
Cervical	7 (15.21)	6	–	1	–	–
Thoracic	10 (22.71)	5	–	2	2	1
Cervical and thoracic	19 (34.78)	8	6	2	2	1
Thoracic and lumbar	9 (19.56)	1	4	2	2	–
Cervical, thoracic and lumbar	1 (4.60)	–	–	–	–	1
Enhancement present	25 (54.34)	11	8	3	2	1
Axial Topography no (%)						
Central	19 (41.30)	1	10	5	2	1
Lateral and/or posterior	27 (58.70)	19	–	2	4	2
Brain MRI no (%)						
Normal	17 (36.96)	–	5	5	6	1
Suggestive of MS (DIS)	19 (41.30)	19	–	–	–	–
Non-specific WM lesions	8 (17.39)	1	3	2	–	2
Suggestive of NMO	2 (4.34)	–	2	–	–	–

MS multiple sclerosis, NMO Neuromyelitis Optica, ADEM acute demyelinating encephalomyelitis, SLE systemic lupus erythematosus, DIS dissemination in space (demonstrated by ≥ 1 T2 Lesion in at least 2 of 4 areas of the CNS: Periventricular, Juxtacortical, Infratentorial, Spinal cord), NMO neuromyelitis óptica (“typical” was definite as brain lesions usually corresponded with structures such as area postrema, hypothalamic and periaqueductal grey lesions)

Table 4 Comparison of functional outcome between partial lesions and longitudinally extensive lesions

	PL and MSL	LETM	OR (IC 95%)	p value
No (%)	24 (52.17)	22 (47.83)		
WHFDS ≥ 3 at 3 months	2 (8.3%)	18 (80.6%)	11	0.002
WHFDS ≥ 4 at 3 months	2 (8.3%)	9 (40.9%)	7.6	0.01
WHFDS ≥ 3 at 6 months	6 (25%)	13 (59.09%)	4.3	0.03
WHFDS ≥ 4 at 6 months	3 (12.5%)	9 (40.9%)	4.8	0.04

PL partial lesion, MSL multisegmental lesions, LETM longitudinally extensive transverse myelitis, WHFDS Winner–Hughes Functional Disability Scale

AQP4-ab is present in one-third to one-half of LETM, and seropositive patients are at risk of subsequent optic neuritis or recurrent myelitis [23]. In addition, the Mayo clinic group found that 14% of NMOSD had short lesions on MRI at the first myelitis episode and the authors observed that 92% of these patients presented LETM lesions in subsequent AIM episodes [24]. Therefore, short lesions on MRI do not revoke the need of testing AQP4-ab, or exclude NMOSD diagnosis [24]. In our series, AQP4-ab was performed in 54.34% and positive status was observed in 60% of NMO patients (this technique became available in our hospital in 2010) and 100% of these patients had LETM at presentation. Idiopathic myelitis often shows a spinal cord pattern on MRI that is similar to NMOSD, as seen in the

current study [25, 26]. All idiopathic myelitis patients were tested for AQP4-ab, and negative results were found.

Brain MRI is a useful diagnostic tool for the initial evaluation of AIM. In our sample, NMOSD patients had normal brain MRI in 50% of the cases, 30% of patients had non-specific results, and 20% were suggestive of NMOSD (periaqueductal and area postrema lesions). However, a recently published consensus showed a 50–85% incidence of brain MRI lesions using the revised NMO diagnostic criteria (2006), and also has been observed in 51–89% of seropositive patients [17, 18]. In contrast, normal brain MRI is associated with a 19% risk of developing MS, while having two or more lesions (typical MS lesions) means up to 88% risk of developing MS after 5 and 20 years of

follow-up [27]. In line with these data, 95% of our MS patients had suggestive MS lesions at onset.

As regards prognosis, case series have estimated that approximately 33% of patients with a first episode of AIM remained unable to walk. Others studies disclosed similar poor functional recovery rates, ranging from 11 to 35.8% [6, 8, 28]. When we compared LETM vs. no LETM (PL and MSL) patients, applying the WHFDS at 3 and 6 months, we observed that bed bound/wheelchair bound (≥ 4 score) was associated with LETM at onset ($p = 0.01$ at 3 months and $p = 0.04$ at 6 months). In addition, when we analyze the ability to walk more than 30 ft with assistance (≥ 3 score), we found that LETM was associated with LETM at presentation ($p = 0.002$ at 3 months and $p = 0.03$ at 6 months). Therefore, LETM has a worse functional prognosis compared with PL after 3 and 6 months. However, a multicenter study (Europe) found that LETM is associated with a higher number of relapses but not to a worse functional prognosis [19]. In our sample, the leading causes with ≥ 4 WHFDS score were idiopathic (71.42%) and SLE-related myelitis (50%). Therefore, these patients may constitute a critical subgroup with a different prognosis and other treatment needs.

We acknowledge several limitations in our study. This is a retrospective study design with failure to obtain OCBs and AQP4-ab in the whole sample, potential recruitment bias due to small population and short-term follow-up. However, OCBs (6/7) and AQP4-ab were performed in all patients for diagnosis of idiopathic myelitis. In addition, we performed IIF to assess AQP4-ab and some idiopathic myelitis patients could have had positive tests for AQP4-ab if more sensitive methods were used (e.g., cell-based assays) [29]. These data serve to increase the international casuistry, as it can be compared with previously published results from Europe and North America.

In conclusion, MS followed by NMOSD were the most frequent causes of AIM. LETM and AQP4-ab helped us to diagnose NMOSD, whereas the OCBs, brain, and PL MRI lesions were associated with MS according to what has been available in other series from different countries. ACTM at onset was associated with LETM on MRI, and these patients had a worse functional prognosis compared with PL after 3 and 6 months. Finally, we believe that functional scales are important in the clinical practice for a better follow-up of these patients and for promoting early specific treatment to improve their quality of life. Future prospective studies with bigger samples are needed to better assess the functional prognosis of these populations.

Acknowledgements We thank Dr. Carmen Lessa and Edson Chiganer (Immunology and Histocompatibility Unit, Hospital Carlos G. Durand, Buenos Aires, Argentina) for their valuable recommendations in the clinical practice. In addition, we thank Dr. Florencia Ocariz and Adrian Rubstein for his critical reading of the manuscript.

Compliance with ethical standards

Conflict of interest None of the authors has any potential financial conflict of interest related to this manuscript.

Ethical standards The study was approved by the Hospital Ethics Committee.

Informed consent Prior to study entry, they provided their informed consent.

Funding This research received no specific Grant.

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