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ORIGINAL COMMUNICATION

Clinical features and prognosis of late-onset neuromyelitis optica spectrum disorders in a Latin American cohort

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Abstract

Background We aimed to assess the clinical, paraclinical, imaging and prognostic features of patients with late-onset neuromyelitis optica spectrum disorder (LO-NMOSD; ≥ 50 years at disease onset) LO-NMOSD, compared with early onset-NMOSD (EO-NMOSD, ≤ 49 years at disease onset), in Latin American (LATAM).

Methods We retrospectively reviewed the medical records of patients with NMOSD, as defined using the 2015 validated diagnostic criteria. We included patients from Argentina, Brazil and Venezuela. They were divided into: LO-NMOSD and EO-NMOSD and comparison among the groups were performed.

Results Among these 140 NMOSD patients, 24 (17.1%) were LO-NMOSD; 64% were positive for aquaporin-4 antibodies; and 41.5% of this population cohort was non-Caucasian. Severe disability [expanded disability status scale (EDSS) ≥ 6] at the last follow-up and presence of comorbidities were significantly associated with LO-NMOSD, compared with EO-NMOSD. LO-NMOSD patients had a shorter median time to EDSS ≥ 4 than EO-NMOSD patients (46 vs. 60 months; log-rank test $p = 0.0006$). Furthermore, we observed a positive correlation between age at onset and EDSS score at the last follow-up (Spearman $r = 0.34$, $p < 0.0001$).

Conclusion LO-NMOSD patients from LATAM developed early severe disability, compared with EO-NMOSD. Therefore, age at onset could have important implications for the long-term prognosis of NMOSD patients.

Keywords Late-onset NMOSD · Neuromyelitis optica spectrum disorder · Prognosis · Disability · Latin america

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disease of central nervous system. It is identified as an astrocytopathy that affects mainly the spinal cord, optic nerves and area postrema, and is often characterized by devastating neurological sequelae [1–3].

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NMOSD patients were classically categorized as a subtype of multiple sclerosis (MS) until aquaporin-4 antibodies (AQP4-Ab) were first identified in 2004 [4]. Currently, the 2015 NMOSD criteria are based on this determination or serostatus [3]. Although presence of AQP4-Ab is not an absolute criterion for diagnosing NMOSD, these antibodies are frequently found (in around 80% of the cases) when cell-based assays (CBAs) are performed on patients who fulfill the 2015 NMOSD criteria, as has previously been reported from different large cohorts worldwide [1–7]. In addition, other antigenic targets such as anti-myelin glycoprotein autoantibodies (MOG-Ab) have also been found to be involved in NMOSD, particularly among patients who are negative for AQP4-Ab [8, 9].

While the typical onset of NMOSD is between the third and fourth decades of life, the initial symptoms and signs may occur later [1, 4, 10]. These patients are considered to present late-onset NMOSD (LO-NMOSD), given that their age at initial presentation is greater than 50 years [10–14]. Although LO-NMOSD is infrequent, its occurrence has been reported to be associated with a lower female-to-male ratio and worse prognosis due to higher frequency of spinal cord lesions, greater severity of symptoms and rapid disease progression, despite early aggressive immunosuppressive treatment [14, 15].

Few studies on the epidemiological and clinical aspects and prognostic factors of LO-NMOSD have been published worldwide, and no multicenter Latin American (LATAM) populations have been investigated [16–19]. Therefore, the objective of this study was to assess the clinical, paraclinical, imaging features and prognostic factors of LO-NMOSD patients, compared with early onset NMOSD (EO-NMOSD; age at onset of first symptoms ≤ 49 years) patients, in a LATAM population.

Methods

We retrospectively reviewed the medical records of patients with at least one core clinical characteristic of NMOSD at onset or during follow-up. Patients diagnosed with NMOSD ($n = 140$) according to the 2015 validated diagnostic criteria for NMOSD [4] in Argentina (EO-NMOSD = 60; LO-NMOSD = 17), Brazil (EO-NMOSD = 41; LO-NMOSD = 5) and Venezuela (EO-NMOSD = 15; LO-NMOSD = 2) were included. They were divided into two groups: LO-NMOSD and EO-NMOSD. LO-NMOSD patients were defined as those with an age at onset of first symptoms ≥ 50 years; and EO-NMOSD patients were classified as those with an age at onset of first symptoms ≤ 49 years, as described previously [10–19].

The core clinical characteristics of NMOSD were defined as follows [4]: acute transverse myelitis (ATM), optic neuritis (ON), area postrema syndrome (APS), brainstem syndrome (BSS), narcolepsy or diencephalic syndrome (DS) and cerebral syndrome (CS). Combinations at presentation were also documented as simultaneous ON/ATM, simultaneous ON/AP, simultaneous ATM/AP, simultaneous ON/AP/ATM or simultaneous ATM/AP. A relapse was defined as an acute event of neurological symptoms lasting 24 h or more that presented at least 30 days after the previous attack [4]. The clinical course at follow-up was defined as monophasic (e.g. isolated event of ON or LETM or APS that was positive for AQP4-Ab) or recurrent. Disability was measured using the expanded disability status scale (EDSS) [20] at the last follow-up visit.

Ethnicity was determined based on a direct genealogical interview that recorded the place of birth of antecessors as far back as the great-grandparents, along with the paternal and/or maternal surnames as culturally-transmitted markers, to confirm ancestry origin. It was categorized as follows [21]: Caucasian (individuals of European descent); mestizo (people of mixed European and Amerindian ancestry living in the Latin American region); Afro-American (individuals of mixed Amerindian and African descent); Asian (individuals whose ancestry was among any of the original peoples of the Far East, Southeast Asia or Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, Philippines, Thailand or Vietnam); or Aboriginal (unmixed native American ancestry).

Serum AQP4-Ab levels were tested by means of CBA [7] or were based on tissue-based indirect immunofluorescence (IIF) assays, using a substrate consisting of a composite cryosection of normal adult monkey cerebellum, as described previously by Lennon et al. [5]. NMOSD patients were classified as follows [4]: positive for AQP4-Ab (P-NMOSD), negative for AQP4-Ab (N-NMOSD) and unknown status of AQP4-Ab (U-NMOSD).

Antinuclear antibodies (ANA) were tested by means of IIF assays using Hep-2 cell culture and situations of positivity were defined as $\geq 1/160$. Oligoclonal bands (OCB) were investigated by means of isoelectric focusing on cerebrospinal fluid (CSF) and presence of a type II pattern was defined as a positive result.

NMOSD-typical lesions [4, 22] on brain MRI were classified as follows: optic nerve lesions (extending over 50% of the optic nerve length or presenting bilaterally increased T2 signal or involving optic chiasm); brainstem/cerebellum lesions (periependymal surfaces of the fourth ventricle and cerebellar peduncle); area postrema lesions (dorsal medulla or contiguous with an upper cervical spinal cord lesion); diencephalic lesions (hypothalamus and/or thalamus or periependymal surfaces of the third ventricle); periependymal lesions surrounding the lateral ventricles (at least 50% of the length of the corpus callosum); corticospinal tract

lesions; or hemispheric white matter lesions (> 3 cm in largest diameter).

Spinal cord MRI abnormalities were classified as follows [23]: LETM (lesions ≥ 3 spinal segments); STM (only one lesion < 3 spinal segments); or multisegmental (MSL, two or more lesions ≤ 2 and/or ≥ 3 spinal segments in noncontiguous segments). In addition, patients with MRI lesions were classified as gadolinium-positive (Gd+) or gadolinium-negative (Gd−) according to the contrast enhancement.

This study was approved by the local ethics committee of each participating center, and written informed consent was obtained from all participants.

Statistical analyses

Statistical analyses were performed using the GraphPad Prism 6 and SPSS v 22 software. The results were presented as percentages, means and standard deviations (SD) and medians. Continuous data for the comparisons among groups were evaluated using Student's *t* test or the Mann–Whitney *U* test; and categorical data were evaluated using the chi-square test or Fisher's exact test, as appropriate. The Kolmogorov–Smirnov test was performed to evaluate the distribution of the variables. Kaplan–Meier (KM) analysis was performed to estimate the median time taken to reach EDSS ≥ 4 (poor prognosis) for both LO-NMOSD and EO-NMOSD patients. KM survival curves were compared using the log-rank test. The Spearman correlation between disability and age at disease onset was also analyzed. For all the analyses, the significance level was established as $p < 0.05$.

Results

We included 140 NMOSD patients from three LATAM countries and 24 (17.1%) of them were classified as LO-NMOSD. In the entire cohort, the NMOSD patients had a mean age of 38.2 years (± 13.8) at disease onset with predominance of females (86.4%; ratio 6.3:1), and they had a mean length of follow-up of 60 months. Unilateral or bilateral ON was the most frequent symptom at disease onset; a recurrent course was observed in 86.4%; and 41.5% of the population included comprised non-Caucasian patients (ethnic contribution from each country is summarized in Supplementary Table 1). The clinical and demographic features are summarized in Tables 1 and 2.

No statistically significant differences in NMOSD duration, ethnicity, clinical course, symptoms at disease onset, length of follow-up or type of acute and preventive NMOSD treatment were observed between LO-NMOSD and EO-NMOSD patients. However, both severe disability (EDSS ≥ 6) at presentation and higher EDSS score at the last follow-up, along with presence of comorbidities, were significantly associated with LO-NMOSD, in comparison with EO-NMOSD. Hypertension was the most commonly observed comorbidity, followed by diabetes.

As shown in Fig. 1a, the entire cohort of LO-NMOSD patients took a shorter median time to reach EDSS ≥ 4 than the EO-NMOSD patients (46 vs. 60 months; log-rank test $p = 0.0006$), as observed at the last follow-up. Furthermore, AQP4-Ab-positive LO-NMOSD patients took a shorter median time to reach EDSS ≥ 4 than EO-NMOSD patients (48 vs. 60 months; log-rank test $p = 0.01$), as observed at the last follow-up, as illustrated in Fig. 1b. In addition, we observed that there was a positive correlation between age at onset and EDSS score at the last follow-up, both in the entire cohort (Spearman $r = 0.34$, $p < 0.0001$) and in the non-Caucasian population (Spearman $r = 0.34$, $p = 0.0008$) (Fig. 2).

Among the entire sample of NMOSD patients, 63.6% were found to be AQP4-Ab-positive (71.1% of the serum samples evaluated) and 26.9% presented unknown status. No statistically significant differences in serum and CSF results, brain MRI topography of typical NMOSD lesions or spinal cord lesions were found. However, nonspecific white matter lesions were significantly more frequent in LO-NMOSD than in EO-NMOSD patients ($p = 0.01$). Lastly, when we evaluated only AQP4-Ab-positive NMOSD patients, we found that the presence of comorbidities and higher EDSS at the last follow-up was associated with LO-NMOSD, in comparison with EO-NMOSD. No statistical differences were observed in the remaining comparisons (Table 3).

Discussion

There are no LATAM studies comparing LO-NMOSD and EO-NMOSD patients with different serostatus and with nearly 50% of the cohort included comprising non-Caucasian patients. In the present study, 17.1% (24 out of 140) of the LATAM NMOSD patients (from Argentina, Brazil and Venezuela) experienced their first symptom after reaching the age of 50 years (LO-NMOSD).

In multicenter studies on NMOSD cohorts that were conducted in Europe and Asia, the prevalence of LO-NMOSD was reported to be up to 29% and 41.5%, respectively [10–14, 16, 17]. On the other hand, in a recent report on 37 LO-NMOSD patients in Brazil, no data relating to the overall population or any EO-NMOSD patients were informed [15]. Nonetheless, in that descriptive study, the LO-NMOSD patients experienced significantly worsened disability over a short time. This worsened prognosis among those patients was not specifically associated with positivity for AQP4-Ab, which was consistent with other reports from Europe and Asia [16–18, 23]. In particular, a multicenter Korean study reported that AQP4-Ab-seropositive LO-NMOSD

Table 1 General demographic and clinical features

	NMOSD	LO-NMOSD	EO-NMOSD	*p* value
Number, no	140	24	116	
Mean age at onset, years (±SD)	38.2 (±13.8)	59.8 (±6.8)	33.8 (±10.1)	0.0001
NMOSD duration, months (±SD)	60.0 (±44.2)	52.0 (±31.7)	61.7 (±46.1)	0.22
Female, no (%)	121 (86.4)	20 (83.3)	101 (87.0)	0.74
Ratio, F:M	6.3:1	5:1	6.7:1	
Ethnicity, no (%)				
Caucasian	82 (58.5)	13 (54.1)	69 (59.4)	0.65
Afro-American	17 (12.1)	2 (8.3)	15 (12.9)	0.73
Mestizo	39 (27.8)	9 (37.5)	30 (25.8)	0.31
Aboriginal	1 (0.7)	0 (0)	1 (0.8)	1
Asian	1 (0.7)	0 (0)	1 (0.8)	1
Clinical course at the last follow-up, no (%)				
Recurrent	121 (86.4)	20 (83.3)	101 (87.0)	0.74
Monophasic	19 (13.6)	4 (16.7)	15 (12.9)	
Relapses after presentation attack, no (±SD)	3.6 (±2.6)	3.3 (±2.0)	3.7 (±2.7)	0.41
Time to first relapse, months (±SD)	15.8 (±17.9)	16.2 (±16.0)	15.7 (±18.2)	0.90
Symptoms at onset no (%)[A]				
Uni or bilateral ON[a]	80 (57.1)	17 (70.8)	63 (54.3)	0.17
ATM[b]	65 (46.4)	11 (45.8)	54 (46.5)	1
AP syndrome[c]	12 (8.5)	1 (4.1)	11 (9.4)	0.69
Brainstem	6 (4.2)	1 (4.1)	5 (4.3)	1
Diencephalic	2 (1.4)	0	2 (1.7)	1
Cerebral syndrome	3 (2.1)	0	3 (2.5)	1
Mean length of follow-up, months (±SD)	60.0 (±44.2)	52.1 (±31.7)	61.7 (±46.4)	0.22
Other autoimmune diseases	33 (23.5)	8 (33.3)	25 (21.5)	0.28
Comorbidities	29 (20.7)	14 (58.3)	15 (12.9)	0.0001
Outcome at the last follow-up, no (%)				
EDSS score ≤ 3	55 (39.2)	3 (12.5)	52 (44.8)	0.002
EDSS score 3.5–5.5	53 (37.8)	9 (37.5)	44 (37.9)	1
EDSS score ≥ 6 (severe disability)	32 (62.5)	12 (50.0)	20 (17.2)	0.001
EDSS score at the last follow-up, no (±SD)	4.34 (±3)	5.2 (±2.2)	3.2 (±2.3)	0.0006
Time take to reach EDSS score ≥ 4, months (±SD)	29.4 (±32.1)	29.1 (±27.3)	30.7 (±37.1)	0.83
Acute treatment, no (%)				
Received plasma exchange	50 (36.7)	11 (45.8)	39 (34.8)	0.35
Preventive medication at diagnosis, no (%)				
Time elapsed between onset and start of IST start, months (±SD)	9.9 (±17.0)	7.5 (±7.0)	10.4 (±18.4)	0.22
Azathioprine	91 (65.2)	19 (79.1)	72 (62.0)	0.15
Mycophenolate mofetil	10 (8.6)	1 (4.1)	9 (7.7)	0.36
Rituximab	39 (27.8)	4 (16.6)	35 (30.1)	0.21

EDSS ≥ 6 (severe disability) was defined as the need for intermittent or unilateral assistance (braces, canes or crutches) to walk 100 m, with or without resting

F female, *M* male, *ON* optic neuritis, *ATM* acute transverse myelitis, *AP* area postrema, *IST* immunosuppressant therapy

[A]Symptoms at disease onset were in isolation or in combination

[a]ON in isolation was observed in 11 (45.8%) of the LO-NMOSD patients and in 43 (37.0%) of the EO-NMOSD patients. The remaining cases of ON were in combination with ATM ($n=6$, 25%) in LO-NMOSD patients and in combination with AP ($n=4$, 3.5%), BS ($n=1$, 0.8%) and ATM ($n=16$, 13.7%) in EO-NMOSD patients

[b]ATM in isolation was observed in 5 (20.8%) of the LO-NMOSD patients and in 32 (27.5%) of the EO-NMOSD patients. The remaining cases of ATM were in combination with ON ($n=16$, 13.7%), AP ($n=5$, 4.3%) and BS ($n=1$, 0.8%) in EO-NMOSD patients

[c]AP in isolation was observed in 1 (4.7%) of the LO-NMOSD patients and in 7 (6.0%) of the EO-NMOSD patients. The remaining cases of AP were in combination with ON ($n=16$, 13.7%) and ATM ($n=16$, 13.7%) in EO-NMOSD patients

Table 2 Paraclinical features

	NMOSD ($N=140$)	LO-NMOSD ($N=24$)	EO-NMOSD ($N=116$)	p value
Serum and CSF features at onset, no (%)				
Aquaporin-4 antibodies				
Positive	89 (63.6)	16 (66.7)	73 (62.9)	0.43*
Unknown	16 (26.9)	4 (16.6)	12 (10.3)	
Antinuclear antibodies				
Positive	37 (54.9)	7 (29.1)	30 (25.8)	0.80*
Unknown	9 (11.6)	1 (4.7)	8 (6.9)	
Oligoclonal bands				
Positive	20 (17.1)	3 (12.5)	17 (14.6)	0.38*
Unknown	52 (64.6)	6 (25.0)	46 (39.6)	
Brain MRI at onset, no (%)				
Typical lesions	97 (69.2)	19 (79.1)	78 (67.2)	0.33
Optic nerve	38 (39.1)	8 (42.1)	30 (38.4)	0.79
Area postrema	12 (12.3)	1 (5.2)	11 (14.1)	0.45
Brainstem/cerebellum	18 (18.5)	4 (21.0)	14 (17.9)	0.74
Corticospinal tract	3 (3.0)	0	3 (3.8)	1
Thalamus/hypothalamus	6 (6.1)	0	6 (7.6)	0.59
Hemispheric white matter	8 (8.2)	2 (10.5)	6 (7.6)	0.65
Periependymal LV	12 (12.3)	4 (21.0)	8 (10.2)	0.23
Non-typical lesions[a]	44 (31.4)	12 (50.0)	32 (27.5)	0.01
Normal	29 (20.7)	3 (12.5)	26 (22.4)	0.40
Spinal cord MRI at onset, no (%)				
LETM	67 (47.8)	11 (45.8)	56 (48.2)	1
STM	27 (19.2)	5 (20.8)	22 (18.9)	0.78
MSL	8 (5.7)	2 (8.3)	6 (5.1)	0.62
Normal	40 (27.1)	6 (25.0)	32 (27.5)	1
Gadolinium-positive	50 (35.7)	8 (33.3)	42 (36.2)	1

AQP4-Ab status was measured using the indirect immunofluorescence (IIF) assay in 29% and cell-based assay (CBA) in 71%. From this, 35 NMOSD patients were found to be AQP4-Ab-negative (10 out of 35 were measured using IIF)

Spinal cord MRI abnormalities were classified as follows: LETM (lesions ≥ 3 spinal segments), STM (only one lesion < 3 spinal segments) and multisegmental (MSL, two or more lesions < 3 and/or ≥ 3 spinal segments in noncontiguous segments)

*Positive vs. negative results were compared

[a]Nonspecific white matter lesions

patients experienced a lower rate of relapse, subsequent risk of myelitis attacks and a trend towards higher risk of severe disability (EDSS 6.0) [18].

However, in a recently published study from Catalunya, it was reported that APQ4-Ab seropositivity among LO-NMOSD patients was associated with both severe disability and higher last EDSS score [19]. Furthermore, age at disease onset, serostatus and worse recovery from the first relapse were independent factors related to presenting ambulatory disability among LO-NMOSD patients [19]. In addition, it was reported that double seronegative (MOG-Ab and AQP4-Ab) LO-NMOSD patients had even worse outcomes than did those who were AQP4-Ab-positive, thus emphasizing the importance of the serostatus [19].

In this LATAM cohort, AQP4-Ab-positive LO-NMOSD patients had higher EDSS scores than EO-NMOSD patients [5.1 (± 2.1) vs. 2.1 (± 1.3)], and age at onset was significantly correlated with worse disability, as measured through the EDSS score, both in the entire cohort (Spearman $r=0.34$, $p<0.0001$) and in a subanalysis on the non-Caucasian population (Spearman $r=0.34$, $p=0.0008$). In this study, MOG-Ab was not evaluated among AQP4-Ab-negative NMOSD patients.

Given that a progressive course is rare in cases of NMOSD [4, 24], one explication for the worse prognosis among LO-NMOSD patients, which has been proposed in different publications, may be that the majority of LO-NMOSD patients have myelitis (LETM on spinal cord MRI)

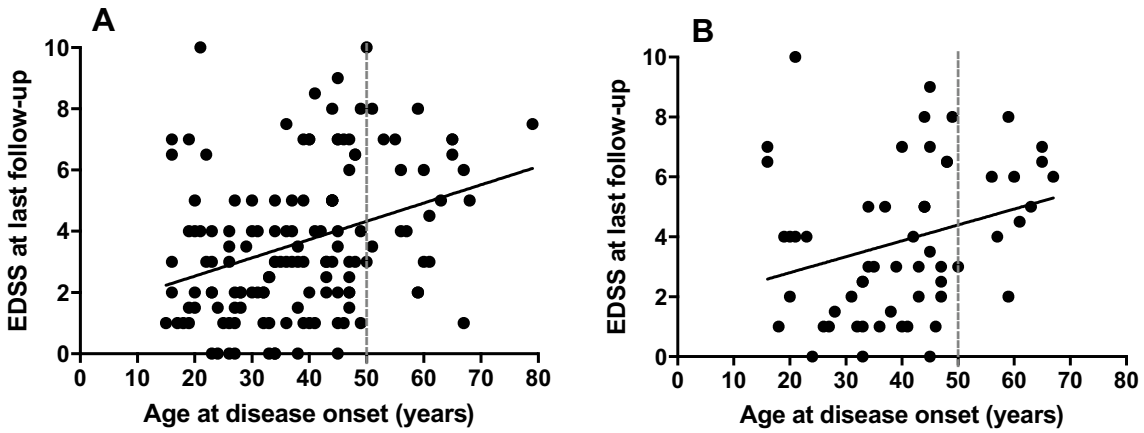

Fig. 1 Correlation between age at disease onset and disability. **a** The entire cohort. Spearman $r=0.3453$, 95% confidence interval 0.1855 to 0.4873, $p<0.0001$. **b** Non-Caucasian population: Spearman $r=0.3436$, 95% confidence interval 0.08582–0.5582, $p=0.0008$

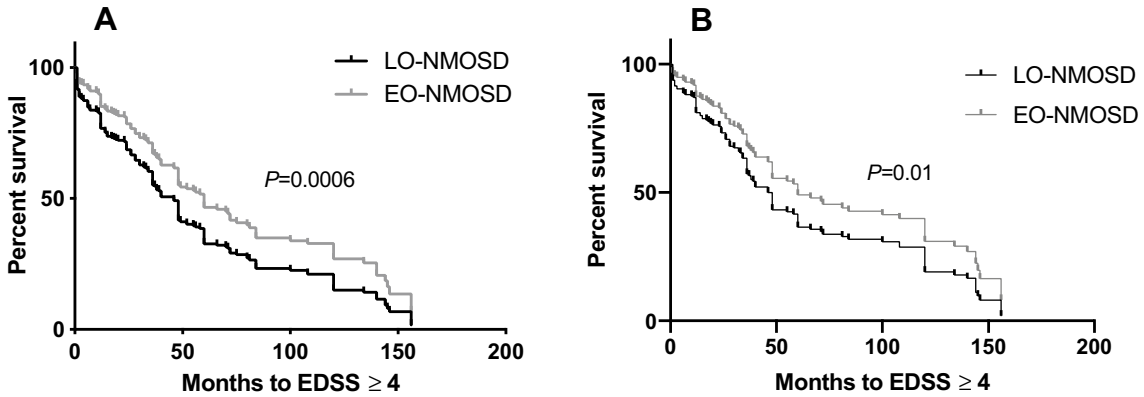

Fig. 2 **a** Overall NMOSD patients (positive, negative and unknown serostatus). LO-NMOSD: late-onset NMOSD; EO-NMOSD: early onset NMOSD; median: 46 vs. 60 months; log-rank (Mantel-Cox) test $p=0.0006$. **b** AQP4-Ab-positive LO-NMOSD and EO-NMOSD. Median: 48 vs. 60 months; log-rank (Mantel-Cox) test $p=0.01$

at presentation [10–19, 23–26]. This is likely to be related to the low rate of improvement over time and to the death of some patients at the end of the follow-up, as previously reported in some cohorts evaluated in Asia and Europe [14, 17, 18].

In addition, mortality and reaching EDSS ≥ 4 have been predicted by older age at onset [14, 17], as observed in our cohort. Along these lines, an European LO-NMOSD cohort had final EDSS scores of between 5.5 and 6.0 after 4.6 ± 4 years of follow-up [14]. In another Asian LO-NMOSD cohort [18], an EDSS score of 3.0 (IQR 2.0–5.0) was reported after 4.0 ± 3.8 years of follow-up.

In the present study, we observed that LO-NMOSD patients had an EDSS score of 5.2 ± 2.2 at the last follow-up. In addition, these patients took a shorter median time to reach EDSS ≥ 4, compared with EO-NMOSD patients, which was similar to what was reported from a Chinese population [17]. While 14 deaths were reported among LO-NMOSD patients in a study conducted in Europe [14] and one death in a study in Asia [18], no death was observed in our cohort during the follow-up.

LO-NMOSD patients are probably more susceptible to disability because of their lower immune tolerance and diminished repair pathways. These factors are usually exacerbated by the comorbidities that are seen more frequently among elderly people [27], and this situation leads to an abnormal anti-inflammatory and restorative process [14]. In addition, older patients may have a less positive response to immunosuppressive treatment (IST) and may have more adverse effects, as was reported in an European study in which 43% of the LO-NMOSD patients died due to severe opportunistic infections [14].

In contrast to previous studies conducted in other regions [11–19], we found that ON was more frequently observed at

Table 3 General features of AQP4-Ab-positive NMOSD patients

	LO-NMOSD	EO-NMOSD	*p* value
Number, no	16	73	
Mean age at onset, years (± SD)	60.5 (± 7.7)	29.8 (± 8.7)	0.0001
NMOSD duration, months (± SD)	53.5 (± 35.8)	48.7 (± 30.1)	0.68
Female, no (%)	15 (93.7)	64 (87.6)	0.68
Ethnicity, no (%)			
Caucasian	11 (68.7)	47 (64.3)	1
Non-Caucasian	5 (31.3)	26 (38.7)	
Clinical course at the last follow-up, no (%)			
Recurrent	12 (75.0)	64 (87.6)	0.23
Relapses after presentation attack, no (± SD)	3.5 (± 2.3)	2.8 (± 1.7)	0.30
Time to first relapse, months (± SD)	15.6 (± 16.0)	15.1 (± 18.6)	0.92
Symptoms at onset, no (%)			
Uni or bilateral ON[a]	11 (68.7)	42 (55.5)	0.57
ATM[b]	8 (50.0)	36 (49.3)	1
AP syndrome[c]	0	7 (9.5)	0.34
Mean length of follow-up, months (± SD)	53.5 (± 35.8)	48.7 (± 30.1)	0.68
Other autoimmune diseases	6 (37.5)	19 (26.0)	0.36
Comorbidities	10 (62.5)	9 (12.3)	0.0001
Outcome at the last follow-up, no (%)			
EDSS score ≤ 3	2 (12.5)	35 (47.9)	0.01
EDSS score 3.5–5.5	7 (43.7)	25 (34.2)	0.56
EDSS score ≥ 6 (severe disability)	7 (43.7)	13 (17.8)	0.04
EDSS score at the last follow-up, no (± SD)	5.1 (± 2.1)	2.1 (± 1.3)	0.0009
Time taken to reach EDSS score ≥ 4, months (± SD)	28.1 (± 18.4)	46.2 (± 50.3)	0.25
Brain MRI at onset, no (%)			
Typical lesions	12 (75.0)	46 (63.0)	0.56
Normal	4 (25.0)	19 (26.0)	1
Spinal cord MRI at onset, no (%)			
LETM	7 (43.7)	37 (50.6)	0.78
Normal	7 (58.0)	37 (61.7)	1
Presence of OCB	2/9 (18.1)	12/34 (26.0)	0.71
Presence of ANA	5/10 (33.3)	23/47 (32.8)	1
Acute treatment, no (%)			
Received plasma exchange	7 (43.7)	22 (31.8)	0.39
Preventive medication at diagnosis, no (%)			
Time elapsed between onset and start of IST, months (± SD)	7.1 (± 6.6)	10.2 (± 17.6)	0.28
Azathioprine	11 (68.1)	45 (64.2)	1
Mycophenolate mofetil	2 (12.5)	4 (5.4)	0.29
Rituximab	3 (16.6)	24 (30.1)	0.37

disease onset than was ATM (in isolation or in combination with other symptoms). This was in line with the findings from a Chinese cohort, in which similar onset frequencies between ON and LETM were observed [17].

Differences among cohorts may relate to ethnicity or to clinical, paraclinical and methodological factors, along with the use of specific IST and its timing, as previously reported in a study in which Japanese populations were shown to have greater severity of disease, compared with United Kingdom (UK) populations [11]. However, a recently published study from the UK, United States, Japan and Martinique found that the disability is often because of relapses and not the onset, thus highlighting the importance of starting treatment soon after the first clinical attack [10]. Nonetheless, in another recent study, it was reported that age and worse recovery from the first relapse were the main predictive factors for disability [19].

Although we observed first relapses of greater severity in the LATAM LO-NMOSD group, similar mean numbers of relapses were found in both groups (3.3 in LO-NMOSD

vs. 3.7 in EO-NMOSD), after a median disease duration of 5 years. In addition, similar use of plasmapheresis and preventive NMOSD treatment (azathioprine, mycophenolate and rituximab) were observed in the two groups, including in the subanalysis on AQP4-Ab-positive patients. Furthermore, the time that elapsed between NMOSD onset and the start of IST was also similar in the two groups.

In line with the findings from a Chinese cohort [17], non-typical lesions (microangiopathic white matter lesions) were more frequently observed on brain MRI in the LO-NMOSD patients than in the EO-NMOSD patients. This can be explained in terms of the greater number of comorbidities, such as hypertension and diabetes, in the LO-NMOSD group. NMOSD-typical lesions were reported in 53.3% of another LATAM series at disease onset [22]. The high number of typical brain MRI lesions in this cohort (69.2%) can be explained in terms of the high number of patients with ON (39.1% with typical optic nerve lesions), as was also found in a Caucasian cohort [12].

The present study had several limitations. One of them was its retrospective design. However, careful data collection and patient follow-up were developed in each center to decrease the possibility of potential information bias. It is important to mention that there was a possibility of unintentional selection bias and relatively small numbers of patients included in the different subgroups. Thus, we were unable to perform some multiple comparisons between the groups or to undertake multivariate regression analysis. Lastly, although several studies have recommended that AQP4-Ab-negative NMOSD patients should be tested for MOG-Ab, this test is not available in all centers. Only NMOSD patients with private insurance have access to this test, which is not covered or reimbursed by the public healthcare systems in Argentina, Brazil and Venezuela, and therefore no results from this test were evaluated [6, 8, 9].

In conclusion, the LO-NMOSD patients of this multicenter study conducted in LATAM developed early and severe disability, compared with EO-NMOSD. This finding was in line with data from other large NMOSD cohorts studied in other regions. As was shown in the present study, age at onset could have important implications for the long-term prognosis for NMOSD patients. These findings add information to the international data set, for comparison with previously published results from Asia, North America and Europe. Patients in LATAM would be expected to present differences in comparison with patients in these other regions.

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Compliance with ethical standards

Conflicts of interest None of the authors have any potential financial conflict of interest relating to this manuscript.

Ethical standards This study was approved by the local ethics committee of each participating center.

Informed consent Informed consent was obtained from all participants.

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