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Original article

Status of the neuromyelitis optica spectrum disorder in Latin America

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ABSTRACT

Background: Neuromyelitis optica spectrum disorders (NMOSD) is an increasing diagnostic and therapeutic challenge in Latin America (LATAM). Despite the heterogeneity of this population, ethnic and socioeconomic commonalities exist, and epidemiologic studies from the region have had a limited geographic and population outreach. Identification of some aspects from the entire region are lacking.

Objectives: To determine ethnic, clinical characteristics, and utilization of diagnostic tools and types of therapy for patients with NMOSD in the entire Latin American region.

Methods: The Latin American Committee for Treatment and Research in MS (LACTRIMS) created an exploratory investigational survey addressed by Invitation to NMOSD Latin American experts identified through diverse sources. Data input closed after 30 days from the initial invitation. The questionnaire allowed use of absolute numbers or percentages. Multiple option responses covering 25 themes included definition of type of practice; number of NMOSD cases; ethnicity; utilization of the 2015 International Panel criteria for the diagnosis of Neuromyelitis optica (IPDN); clinical phenotypes; methodology utilized for determination of anti-Aquaporin-4 (anti- AQP4) antibodies serological testing, and if this was performed locally or processed abroad; treatment of relapses, and long-term management were surveyed.

Results: We identified 62 investigators from 21 countries reporting information from 2154 patients (utilizing the IPDN criteria in 93.9% of cases), which were categorized in two geographical regions: North-Central, including the Caribbean (NCC), and South America (SA). Ethnic identification disclosed Mestizos 61.4% as the main group. The most common presenting symptoms were concomitant presence of optic neuritis and transverse myelitis in 31.8% ($p=0.95$); only optic neuritis in 31.4% (more common in SA), $p<0.001$); involvement of the area postrema occurred in 21.5% and brain stem in 8.3%, both were more frequent in the South American cases ($p<0.001$). Anti-AQP4 antibodies were positive in 63.9% and anti-Myelin Oligodendrocyte Glycoprotein (MOG) antibodies in 4.8% of total cases. The specific laboratorial method employed was not known by 23.8% of the investigators. Acute relapses were identified in 81.6% of cases, and were treated in 93.9% of them with intravenous steroids (IVS); 62.1% with plasma exchange (PE), and 40.9% with intravenous immunoglobulin-G (IVIG). Therapy was escalated in some cases due to suboptimal initial response. Respondents favored Rituximab as long-term therapy (86.3%), whereas azathioprine was also utilized on 81.8% of the cases, either agent used indistinctly by the investigators according to treatment accessibility or clinical judgement. There were no differences among the geographic regions.

Conclusions: This is the first study including all countries of LATAM and the largest cohort reported from a multinational specific world area. Ethnic distributions and phenotypic features of the disease in the region, challenges in access to diagnostic tools and therapy were identified. The Latin American neurological community should play a determinant role encouraging and advising local institutions and health officials in the availability of more sensitive and modern diagnostic methodology, in facilitating the the access to licensed medications for NMOSD, and addressing concerns on education, diagnosis and management of the disease in the community.

1. Introduction

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a major immune inflammatory disease of the central nervous system that predominantly affects optic nerves and the spinal cord (Weinshenker & Wingerchuck, 2017). In some cases, there may be associated involvement of other areas of the CNS such as the area postrema, brain stem, diencephalon or cerebrum, all clinically eloquent syndromes manifesting as a complex neurological entity (Bienia & Balabanov, 2013). The immunopathological process initially affects astrocytes conditioning subsequent development of demyelination and neurodegeneration (Kawachi & Lassmann, 2017).

Aquaporin-4 (AQP4), the most abundant water channel in the CNS, largely expressed in the astrocytic processes at the blood-brain barrier, becomes the target of the immunoglobulin G (lgG) antibody. The presence of this antibody constitutes the eminent serologic marker for NMOSD due to its high specificity (Waters et al., 2012). However, even the most advanced methodology is not absolutely sensitive to detect patients clinically diagnosed with this disorder. About 42% of the seronegative population satisfying the 2015 NMOSD diagnostic criteria test positive for anti-myelin oligodendrocyte glycoprotein (MOG)-lgG antibody (Hamid et al., 2017). While anti-MOG syndrome may exhibit some clinical and imaging features resembling NMOSD, these two entities differ in pathology, immunologic mechanism, phenotypic characteristics, management, and even age distribution since anti-MOG syndrome is more common in children.

AQP4-lgG antibody positive NMOSD patients frequently demonstrate association of autoantibodies that target nuclear and cytoplasmic antigens detected in diseases in diseases like systemic lupus erythematosus, Sjogren, and anti-phospholipid antibody syndromes (Adawi et al., 2014), even in the absence of clinical manifestations. The pathophysiological link of this association has not been established.

The prevalence of NMOSD is considered to be low worldwide (Hor et al., 2020), with a consistently disproportionally higher female/male ratio (4-9:1) (Lana-Peixoto & Talim, 2019), or 70%-90% of patients being comprised by women in Latin America (LATAM) (Alonso et al., 2018)

Studying NMOSD in LATAM has been of particular interest considering this large geographical area offers a great ethnic and socioeconomic diversity, comparison to previously studied Caucasian and Asian populations. Epidemiologic studies and reports from LATAM, however, have been based mostly on small national cohorts or series from one or a few countries. There is a prevalence report from Mexico (Rivera et al., 2008), one from Panama (Gracia et al., 2014) and several from the South American area (Soto de Castillo et al., 2020; Correa Diaz et al., 2020; Papais-Alvarenga et al. 2015; Uribe-San Martin et al., 2017).

Despite the great heterogeneity of the Latin American peoples, important ethnic, linguistic and cultural commonalities exist.

The LATAM geopolitical boundaries include countries where the main languages are Spanish and Portuguese. The continental mass extends from 32° North at the northern border of Mexico with the US, to 56° South at the Chilean and Argentinean Patagonia.

The Caribbean Spanish-speaking island countries: Cuba, Puerto Rico and Dominican Republic are also included in the LATAM geographic and cultural concept (Fig. 1). The LATAM population (as per February 20, 2021), is reported by the United Nations as 657,680,320.

Fig. 1. Latin America (LATAM) geographic political map. **Foot Note,** Fig. 1. LATAM zones. North America: Mexico; Central America: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica, Panama; Spanish Caribbean: Cuba, Puerto Rico, Dominican Republic and Aruba. South America: Venezuela, Colombia, Ecuador, Peru, Bolivia, Chile, Paraguay, Argentina, Uruguay, Brazil.

Over the course of five centuries, the blended genetics and cultures of white Caucasians of European ancestry with Native Americans, and with black Africans, has resulted in the modern predominant Latin American ethnic populations: Mestizos, biracial, and multiracial groups. Thus far, an inclusive study of the entire Latin American region is lacking. The aim of this study was to explore diverse aspects of NMOSD in the region, focusing on clinical phenotypes, challenges in access to diagnostic tools, and the therapeutic strategies employed. The Latin American Committee for Treatment and Research in Multiple Sclerosis (LACTRIMS), originated and designed this continental Investigation to identify aspects and areas of need to be targeted in further investigations.

1.1. Data source

Identification of neurologists with expertise in NMOSD was obtained from the LACTRIMS database, and the Central American and Caribbean Forum for Multiple Sclerosis (FOCEM) registry. The NMO International Clinical Consortium of the Guthy- Jackson Charity Foundation provided data from the Latin American membership registry. Sixty nine neurologists were identified.

1.2. Methods

This is an investigational exploratory study. A twenty five-item web-based questionnaire was distributed among a purposive sampling of NMOSO specialists. At least two investigators from each Latin American country were invited, and three to five contributors from areas with larger geographic extension and population, or antecedents of having participated on local or international studies and/or publications on the subject, were included. In some cases, a local coordinator was assigned to sort out contributors. Emphasis was placed on selecting one or two investigators representing an institution or a research group to prevent duplication of data. In order to avoid redundancy with previous studies from the region, it was decided *a priori* not to include in the survey specific inquiries on age and gender of the reported subjects. Each contributor contributed data from their institutional or private practice files. Private information on patients was not utilized hence an informed consent was not required (*Criteria established by the U.S. Deparlment of HHS at 45 CFR parl 46, subparl* A). Information encompassing the last 24 months (October 1, 2018 to October 31, 2020) was requested.

The questionnaire was designed by VMR and subsequently reviewed by FH and FG.

On October 22, 2020, FOCEM distributed the questionnaire by email among the selected neurologists from Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica, Panama, Cuba, Puerto Rico, Dominican Republic and Aruba. This phase of the study was used as pilot test the survey and modify it as required based on the input from this group. On October 27, 2020, the survey was provided to investigators from Argentina, Chile, Paraguay, Uruguay, Bolivia, Ecuador and Peru; on October 28 and 29, 2020, to experts from Brazil, Venezuela and Colombia, and on October 31, 2020, to investigators from Mexico. Data input was closed on November 25, 2020.

Information on the locality, country, and type of professional practice (institutional, private, or both) was requested. The survey included inquiries to each investigator on number of NMOSD cases being followed; patients ethnicity; utilization of the International Panel criteria for the diagnosis of neuromyelitis optica (IPDN) (Wingerchuck et al., 2015); clinical types and phenotypes; associated autoimmune disorders; local access to anti-AQP4 and anti-MOG antibody testing, or utilization of laboratory facilities abroad, and assessment methodology employed. The participants were surveyed on their therapeutic strategies to manage NMOSD relapses and their use of immunosuppressive therapies. The contributors were specifically asked on the actual therapies they utilize, ergo, available and accessible in their ambiance. A theoretical therapeutic consideration was not requested.

Patient's ethnicity was identified through the medical records or by the investigator, by utilizing either their respective traditional national race/ethnicity self-identification criteria, or the national census and statistics department criteria.

The questionnaire allowed use of absolute numbers or percentages, and ability to select several options as answers to each item. The survey was written in Spanish, which did not constitute a comprehension impediment for Portuguese-speaking contributors in view of the common linguistic roots and scientific terminology, and the simplicity of the survey. The official languages of LACTRIMS are Spanish and Portuguese.

1.3. Statistics

All data was compiled in a single dataset, for statistical analysis. Counts and percentages were provided for categorical variables, and continuous variables were expressed as mean (with standard deviation) [SD] or median (with interquartile range [IQR]). Single univariate analysis was performed to compare frequencies among groups using a X2 (with Yates correction), or Fisher's exact test; for continuous variables a T test or U Mann Whitney Test were performed, according to sample size as required.

P values are expressed and considered as significant when <0.05. All statistical analysis were done using SPSS for Macintosh (version 22.0 IBM).

2. Results

A total of 69 Latin American neurologists from twenty one countries were Invited to participate in this study, with 62 (89.8%) contributing to the survey. In 76% of the cases, the group indicated their professional activity was in a government-affiliated institution, while most of the neurologists, 81.8%, held in addition private practices; no significant differences were seen among physician's gender and type of clinical practice ($p=0.47$).

The majority (93.9%) utilized the IPDN for NMO Diagnosis consensus.

Indirect information from 2154 patients is reported. Although every item from a few topics were not addressed by the entirety of the investigators due to their lack of data, these answers were tabulated according to the number of answers provided and their respective percentage.

Each investigator provided data from their own practice, their professional group or their institutional center. There was a wide range of participation from the contributors, some reporting only one case, and some from a few to several dozens or hundreds of cases.

In order to facilitate aspectual comparisons of the reported data in the survey, and anticipated ethnic differences, the patient's data were divided in two main geographic regions: North-Central America-Caribbean (NCC), vs South-America (SA). While Mexico geographically forms part of North America, and it is the second largest country in LATAM, six countries constitute Central America, and for the purpose of this regional classification, the Caribbean islands of Cuba, Puerto Rico, Dominican Republic and Aruba were included in the NCC area. Ten countries comprise the South American region including Brazil, the largest Portuguese-speaking country in the world.

The larger ethnic group was identified as Mestizos (61.4%) distributed in the entire Latin America area but with differences between the NCC and SA regions, more prevalent in the latter ($p=0.005$). White Caucasian ethnicity was reported in 406 patients (18.8%, $p<0.001$), mainly in the NCC region. The Afro-American group (10.5%) did not have a significant difference in regional distribution, while Native-American patients (4.0%) were significantly prevalent in the NCC ($p<0.001$) compared to SA (Table 1).

Most common concomitant autoimmune conditions were systemic lupus erythematosus in 6.3%, Sjogren's syndrome in 3.3%, antiphospholipid syndrome in 2.7%, and rheumatoid arthritis in 0.6% of cases; other associated autoimmune conditions were rare (less than 0.1%), listed in Table 2.

Presenting clinical picture at diagnosis mainly included Optic Neuritis (ON) without associated transverse myelitis (TM) in 677 cases

Table 1
General Characteristics of NMOSD patients by Latin American geographic regions.

	North America-Central America, Caribbean n=792 (%)	South-America n=1362 (%)	Total N=2154 (%)	p value
Ethnicity				
Caucasian	188 (23.7)	218 (16.1)	406 (18.8)	<0.001
Mestizo	456 (57.6)	867 (63.6)	1323 (61.4)	0.005
Afroamerican	92 (11.7)	134 (9.8)	226 (10.5)	<0.19
Native-American	50 (6.3)	36 (2.6)	86 (4.0)	<0.001
Asian	0	7 (0.5)	7 (0.3)	0.03
No Information	6 (0.7	100 (7.41}	106 (4.9}	<0.00
Main associated Autoimmune conditions				1
SLE	63 (7.9)	73 (5.3)	136 (6.3)	0.03
Sj6gren	20 (2.5)	51 (3.7)	71 (3.3)	0.09
APS	30 (3.8)	29 (2.1)	59 (2.7)	0.04
RA	7 (0.8)	6 (0.4)	13 (0.6)	0.22
Clinical symptoms				
ON	97 (12.2)	406 (29.8)	677 (31.4)	<0.001
TM	221 (27.9)	352 (25.8)	573 (26.6)	0.23
ON+TM	263 (33.2)	423 (31.0)	686 (31.8)	0.95
Area Postrema syndrome	133 (16.8)	330 (24.2)	463 (21.5)	<0.001
Brain stem syndrome	21 (2.6)	159(11.7)	180 (8.3)	<0.001
Dyencephalic syndrome	6 (0.7)	23 (1.7)	29 (1.3)	0.08
Symptomatic encephalic syndrome	19(2.4)	116(8.5)	135 6.2)	<0.00 1
Antibodies profile				
Anti-Aquaporin 4 +	585 (73.8)	793 (58.2)	1378 (63.9)	<0.00 1
Anti-MOG +	24 (3.0)	81 (5.9)	105 (4.8)	0.002
Clinical Course				
Relapsing	618(78.1)	1130 (82.9)	1748 (81.6)	0.004
Monophasic	174(21.9)	232 (17.0)	406 (18.4)	<0.001

NMOSD: neuromyelitis optica spectrum disorder; SLE: systemic lupus erythematosus; APS: anti-phospholipid syndrome; RA: rheumathoid arthritis; ON: optic neuritis; TM: transverse myelitis; MOG: myelin oligodendrocite glycoprotein.

Table 2
Other associated autoimmune disorders to NMOSD in Latin America

	(N=)
Autoimmune thyroid disease	15
Rheumatoid Arthritis*	11
Myasthenia Gravis	5
Antinuclear Antibody positive**	5
Paraneoplastic polyneuropathy	2
Pernicious anemia	2
Scleroderma	2
Autoimmune epilepsy	1
Chron's disease	1
Immune Thrombocytopenic Purpura	1
Mixed connective tissue disorder	1
Primary biliary cirrhosis	1
Psoriasis	1
Vitiligo	1

* Serological tests for Rheumatoid factor were positive in 10 patients; one had clinical manifestations.

** ANA was positive in five patients without an associated clinical syndrome.

(31.4%); the combination of ON and TM in 686 (31.8%), and TM without ON in 573 patients (26.6%). Interestingly, area postrema syndrome affected 21.5% of cases, with more cases (24.6%) in the SA region (p<0.001). Brain stem involvement was also significantly reported in SA with 11.7% (p<0.001). No significant differences were seen on those cases with spinal cord involvement among groups (alone or in combination with ON) (Table 1).

The number of patients reported as having relapses was 1758 (81.6%), and 396 (18.47%) of cases were reported as exhibiting a monophasic clinical course. Long-term follow-up was not part of this investigation. No cases of neuroendocrinopathy or Reversible Posterior Leukoencephalopathy were reported.

In terms of serologic analysis for NMOSD cases, anti-AQP4 antibodies were performed on 95.4% of this sample with a 63.9% positivity, reported mainly from the NCC region (73.8%, p<0.001). Anti-MOG antibodies were assessed in 50.7% NMO- seronegative patients, proving positive in 105 cases (4.8%, mainly in SA [5.9%, p=0.002]). Local laboratory facilities were utilized in 55.2% of the samples to determine anti-AQP4, and in 38.8% assessing anti-MOG antibodies; practitioners in countries with no facilities to perform antibody testing, sent samples to laboratories abroad for processing. No serological testing was performed in 4.6% of patients.

Most tests were performed using cell-based assay or CBA (42.2%); the second most employed methodology was tissue-based indirect immunofluorescence or IIF (15.6%), then the enzyme-linked immunoabsorbent assay or ELISA (10.9%) and combination of CBA and ELISA (6.35%).

Therapeutic approaches were evaluated according to the survey's responses, as no individual data regarding the type of therapy for each single case was recorded. The investigators responded that acute relapses were treated mainly with intravenous steroids (IVS) in 93.9% of the cases, plasma exchange (PE) in 62.1%, and Intravenous gamma globulin (IVIG) in 40.9%. While these modalities were utilized indistinctly, in 6.06% of the cases the investigators reported therapies were escalated treating a single episode in case of a suboptimal initial response, or due to the severity of the clinical situation. Regarding use of immunosuppressive therapies as long-term management, the investigators responded as using mostly and indistinctly, either rituximab infusions (86.3%), or oral azathioprine (81.8%) as the favored treatments. Their utilization depended on accessibility to the therapy, or clinical judgement if both were available. No differences among the Latin American regions were noted. Other therapies are displayed on Table 3. Management with other monoclonal antibodies were reported only in 5 responses (eculizumab 1, inelizumab 1, and tocilizumab 3 cases).

Table 3
Therapy utilization according to survey responders (n=66).

	North-America, Central- America, Caribbean n=28 (%)	South-America n=38 (%)	Total N=66 (%)	P value
Therapy for acute relapses				
IV steroids	26 (92.8)	36 (94.7)	62 (93.9)	0,98
IV Gammaglobulin	13 (46.4)	14 (36.8)	27 (40.9)	0,45
PE	11 (39.2)	30 (78.9)	41 (62.1)	0,002
Disease Modifying Therapy				
Azathioprine	23 (82.1)	31 (81.5)	54 (81.8)	0,97
Methotrexate	1 (3.5)	3 (7.9)	4 (6.0)	0,63
Cyclophosphamide	6 (21.4)	8 (21.0)	14 (21.2)	0,98
Micophenolate	9 (32.1)	19 (50.0)	28 (42.4)	0,2
Rituximab	24 (85.7)	33 (86.8)	57 (86.3)	0,98

IV: intravenous; PE: plasma exchange.

3. Discussion

This study was designed by LACTRIMS as an exploratory informational activity and purposeful sampling to identify areas of need, and of further interests to be approached regarding NMOSD issues in the Latin American regions. This is the first study of its kind, engaging all continental areas of LATAM and the Caribbean and providing data from 2154 patients, the largest regional series reported. The NMOSD prevalence in the Latin American region has been estimated from 0.37 to 4.2/100,000 (Alvarenga et al., 2017), however, a recent study reports the highest frequency rate as 4.52/100,000 inhabitants in Belo Horizonte, Brazil (Lana-Peixoto et al., 2021).

Latin American studies have addressed demographic data (including age and gender), and epidemiologic aspects from several areas: Argentina, Brazil, Cuba, Chile, Ecuador, Mexico, Paraguay and Venezuela (Cabrera Gomez, et al., 2009; Carnero Contentti et al.,2020; Correa Diaz et al., 2020; Lana-Peixoto et al., 2021; Papais-Alvarenga et al., 2015; Rivera et al., 2008; Soto de Castillo et al., 2020; Uribe-San Martin et al., 2017). Contributors to the present study also collaborated to the referenced previous reports. The majority of the Latin American neurologists participating in this survey had a private practice in addition to a staff position in a governmental health institution. Utilization of third-party carrier insurance is rare in LATAM. The principal source of national care in all countries in LATAM is provided by their respective Health Ministry or Secretariat utilizing public clinics, public hospitals, and national Social Security Institutes (SSI) (Rivera et al., 2014). This combination of professional institutional and private practice gainful activities represents a common medical and societal reality in LATAM where, due to economic reasons, physicians tend to hold a hospital institutional post (often with an academic affiliation) as well as a private office. The greater proportion of the NMOSD cases reported in this study were extracted from institutional hospitals.

A major challenge posed to people with NMOSD living in rural areas in LATAM, or to economically disadvantaged persons in these regions, is access to adequate medical care including appropriate diagnostic tools and management.

The racial and ethnic composition of LATAM is quite heterogeneous due to complex racial and ethnic admixtures developing over the course of five centuries . In this study, the responses to ethnic identification of patients with NMOSD reflected the peoples fabric of LATAM (Table 1). A majority, was constituted by Mestizos, the most representative population of the Latin American regions reflecting the typical racial blend of white Caucasians of European ancestry with Native American peoples, and black groups of Sub-Saharan and west Africa ancestry, in the Americas.

Prevalence studies from LATAM have shown all patients from a cohort in Mexico City (34 subjects) were Mestizos (Rivera et al., 2008). White Caucasians of European ancestry were the second reported group (18.8%) in our study. Caucasian populations are prominent throughout LATAM particularly in Argentina, Brazil, Uruguay, Costa Rica, northern and western Mexico. In some European studies (Asgari et al., 2011; Jacob et al., 2013), Caucasians constituted the totality of the NMOSD cohorts.

Population-based studies in people of European descent show NMOSD seems to be more common in these groups than earlier believed (Johnson et al., 2019). Groups of African-descent reported on 10.5% in our survey, while having a demographic presence in most areas of LATAM, the larger proportions were reported from the Caribbean, most Central American countries, and Venezuela, Colombia, Ecuador and Brazil. NMOSD represents 11.8% of all "Idiopathic inflammatory demyelinating diseases" in South America (Papais-Alvarenga et al., 2015). This study reported the highest frequency occurring among African Brazilian young women, the disease causing moderate to severe disability as measured by EDSS, as compared to Multiple Sclerosis (MS) cases in South American countries.

A morbidity/mortality comparison study in Brazil (Bichuetti et al., 2013) among NMOSD and relapsing-remitting MS patients, disclosed the former to have a more severe disease course and higher risk of dying from a demyelinating disease.

A salient feature of our Latin American study was the reported proportion (4.0%) of patients identified as Native Americans from Mexico, Guatemala, Venezuela, Peru, Colombia, Bolivia and Argentina. Although non-mixed indigenous populations in the Americas have dwindled due to historical and pervasive sociological factors, large segments inhabiting these countries reside mostly in rural and remote locations but some tend to immigrate to the outskirts of urban areas. The common Latin American American observation that MS is rare among Native Americans (Rivera, 2017), does not apply to NMOSD candidacy. Early reports (Mirsattari et al., 2001) described Canadian Algonkians diagnosed with "MS", whom, however, had clinical, MRI and autopsy features of NMO.

Seven individuals were reported in our Latin American survey of "Asian origin" (0.3%), but not other racial or ethnic group was identified. During the 19th and early 20th centuries, a large East, Central and Southeast Asian migration took place particularly to northern Mexico, Panama, Peru, Brazil and Venezuela. Despite increasing intermixing, large segments of Asian groups in LATAM remain non-mixed. East Asians appear to have a higher prevalence of NMOSD (around 3.5/100,000) as compared to Caucasians and other racial groups (Houzen et al., 2017). Japanese and Chinese share the same HLA risk genes for NMOSD, namely HLA-DPB1*05:01 and HLA-DRB1*16:02 (Matsushita et al., 2009). Latin American studies (Alonso et al., 2018; Papais-Alvarenga, et al., 2021) disclose HLA-DRB1*03:01 and HLA-DRB1*10 alleles as a significant genetic association with NMOSD. Latin American studies have shown 80%-82.7% of the patients were women (Alonso et al., 2018; Soto de Castillo et al., 2020, Uribe-San Martin et al., 2017). The mean age of cohorts in LATAM is reported as 43.3 years.

The presence of ON and TM in 38.8% of subjects in this Latin American survey, sequential or simultaneous, confirms the principal syndromic duality of this disease. The report in this survey of 21.5% cases affecting the area postrema (AP) however, constitutes an uncommon clinical feature of these Latin American cohorts, in view that large international series (Kim et al., 2018) show AP syndrome is the inaugural event in only 10% of the cases, and in 15% develop during the course of the disease. This study involved 603 patients from six intercontinental centers including Asians, Caucasians and Afro-European/Afro-Americans.

Clinical manifestations or positive serology for several autoimmune diseases, including, among others, systemic lupus erythematosus, antiphospholipid antibody and Sjogren's syndromes, were reported in our study in a higher association than described in general reviews (Shahmohammadi et al., 2017).

Despite magnetic resonance imaging (MRI) is widely available in the region, diversity in protocols and equipment but more importantly lack of access to MRI studies or to serological testing, may impact accurate diagnosis considering the challenge of differential diagnosis in the region with infectious, parasitic and nutritional disorders (Rivera & Macias, 2017). Nevertheless, this surveyed group showed a high index of clinical suspicion of NMOSD reflected in the determination of NMO-lgG antibodies in 95.4% of cases, the majority utilizing the CBA method. The sensitivity of CBA is reported as higher as 92% than those of IIF (78%), and ELISA (60%) (Prain et al., 2019). The fact that 38% of serological samples from this Latin American group were processed in laboratory facilities outside the country indicate a substantial need of access to appropriate and regulated laboratory technology in many localities.

Another aspect for further consideration is that almost a quarter of the contributing investigators did not have knowledge of the diagnostic methodology employed in the determination of the serological testing they requested. Also, while 94% of the surveyed neurologists utilized the 2015 IPDN for NMOSD, still some elements of the updated criteria have not yet been fully validated in the diverse Latin American populations. Nevertheless, a multicenter study from Argentinian, Venezuelan and Brazilian cohorts (Carnero Contentti et al., 2018) utilizing the 2016 IPDN, reported improving diagnostic rate and reducing time to diagnosis ($p<0001$). These issues require further exploration in LATAM.

Most Latin American countries remain in the phase of economic development resulting in limitation of access to adequate diagnostic

technology and therapy for NMOSD. The high cost of some drugs, not just the ones specifically licensed for treatment of the disease by international health agencies, but also the ones frequently utilized off-label, add to challenges of adequate and accessible management of the disease in the region.

The debate of qualifying for NMOSD therapy despite seronegativity or absent testing, and access to licensed therapy, are issues remaining to be explored in LATAM.

Typically, in the Latin American regions, contrasting circumstances occur in one same locality: well-prepared neurologists and well-equipped health facilities in one side, and the disparity of the public system with scant resources for the same professional in the other. The results of this study exhibiting this sociological/professional dichotomy, underline the difficulties encountered in the identification and treatment of NMOSD in LATAM. In our survey, therapies implemented for the management of acute relapses are similar to other series (Kleiter et al., 2016).

While IVS therapies are more accessible and less expensive, it is noted that PE, a more technologically demanding procedure, was the second selected treatment or utilized as rescue acute therapy modality. lmmunosuppressing agents are commonly used in the long-term management of NMOSD (Lana-Peixoto & Talim, 2019). Rituximab and azathioprine were the principal immunotherapies utilized by the investigators in our survey. Other immunosuppressive therapies were also reported: micophenolate mofetil (40% of cases), cyclophosphamide (20%), mitoxantrone and methotrexate (both less than 10%). South American studies have addressed therapies in the area. An Ecuadoran observational study (Correa-Dias et al., 2021) showed rituximab significantly reduced the annualized relapse rate and the mean EDSS. A Brazilian study reported cyclophosphamide pulses lacking therapeutic effect in NMOSD (Bichuetti et al., 2012).

The immunotherapies reported in our study lack either phase 3 randomized-controlled trials, or studies have been underpowered (Tahara et al., 2020), and remain as off- label, unapproved therapies. Insufficient economic health resources in most countries in LATAM, and perhaps lack of information of health officials, appear to influence prompt availability and access to the recently approved monoclonal antibodies for NMOSD.

Our survey disclosed only two patients treated with the licensed medications for NMOSD in the entire Latin American region: eculizumab (a terminal complement inhibitor), and inebilizumab (anti-CD19 inhibitor); there were no patients treated with satralizumab (interleukin-6 receptor-antagonist). In our study, Tocilizumab was utilized in 3 cases. This monoclonal antibody, also an IL-6 receptor antagonist, is available in the pharmacy formularies of some institutions in LATAM for the treatment of rheumatoid disorders, and following some reports of positive effects as second-line, rescue-therapy in NMOSD (Araki et al.,2014; Carreon Guarnizo et al., 2019), it has been used off-label in Central America and Caribbean clinics. In our study, more than 35% of patients tested AQP4-antibody negative, hence, theoretically, would not qualify (per approved label) for the currently licensed immunotherapies.

Our study was not intended to be an epidemiological survey, and the results should be Interpreted cautiously. There are several limitations to our study. The cross-sectional design did not allow to obtain longitudinal information. Also, the use of an online survey to collect data may induce recall bias; however, to minimize this concern, neurologists responding to the survey were NMOSD experts. The use of a questionnaire in Spanish did not affect the Portuguese-speaking investigators' contributions given the simplicity of the questionnaire and the commonality of linguistic terminology. The frequency of NMOSD in LATAM is low but it has demonstrated to carry a substantial disability and socioeconomic burden.

4. Conclusions

LACTRIMS designed this study to explore specific aspects on the status of NMOSD in LATAM. Previously not identified phenotypic features of the disease in Latin Americans were found, as well as challenges in access to adequate diagnostic tools and therapy. These concerns will be addressed in further actionable and remediable regional projects. Latin American neurologists should play a determining role in education on NMOSD in LATAM, and in advising and encouraging health officials and institutions on acquisition of updated diagnostic technology, and on the access to approved medications for treatment of the disease. Addressing NMOSD care in the Americas calls for a comprehensive professional and community effort.

Credit authors

VMR, FH and FG conceived and planned the survey; VMR coordinated and wrote the manuscript. VR, JIR, DBB and AMV contributed to segments of the manuscript. CCZ, JC, VS, ECC, EPCD, and RA, provided critical feedback. VDM, AS, BB, ITF, LG, JQ, DR, EC, MLP, ER, LZ, EA, JB. AB, EL, AD, CVF, GP, OM, ER, DS, IS, JVC, AB, PM, AC, DT, AP, BSP, ADF, CB, MKG, AC, OGG, JVR, LCR, NER, LO, ES, LIP, APC, RW, VS, RFC, EAC, MH, JCDQ, LAG, COC, JM, PAH, contributed with data and bibliography, reviewed and approved the manuscript.

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Declaration of Competing Interest

None.

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