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*Review*

# Neuromyelitis Optica Spectrum Disorder in Latin America: State-of-the-Art and Current Challenges

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**Abstract**

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disease of the central nervous system characterized by severe attacks of optic neuritis, myelitis, and/or area postrema. Advances in understanding the pathophysiology of NMOSD have led to improved diagnostic and therapeutic approaches. There has been a notable increase in research efforts worldwide, including in Latin America (LATAM). In recent years, LATAM has witnessed a surge in research on NMOSD, resulting in a growing body of evidence on various aspects such as epidemiology, clinical manifestations, paraclinical features (including AQP4-IgG [Aquaporin-4-immunoglobulin G] and imaging), acute and long-term treatment strategies, as well as accessibility to diagnostic tests. This narrative review aims to present the most relevant findings from different NMOSD cohorts in LATAM, providing a comprehensive overview of the current understanding of the disease in the region, while considering its unique characteristics and challenges. LATAM-focused evidence is crucial for adding valuable information to the international dataset and is therefore summarized in this review.

**Keywords:** NMOSD; Latin America; research

## 1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare immune-inflammatory disease that mainly affects the optic nerves, spinal cord, and area postrema, with potential involvement of other areas of the central nervous system (CNS), leading to complex neurological manifestations [1,2]. Aquaporin-4 (AQP4), a crucial water channel abundantly found in the CNS, particularly in astrocytic processes at the blood-brain barrier, becomes the target of immunoglobulin G (IgG) antibodies [3]. The presence of these antibodies (AQP4-IgG) serves as a highly specific serologic marker for diagnosing NMOSD [3,4].

Advancements in understanding the pathophysiology of NMOSD have led to improved diagnostic and therapeutic approaches for patients [5]. Although NMOSD is classified as a rare disease, there has been a notable increase in research efforts worldwide, including in Latin America (LATAM). LATAM is an extensive geographical area with diverse ethnic and socioeconomic backgrounds (Fig. 1). Comparing characteristics of patients from this region with previously studied populations of Caucasian and Asian ethnicity represents a valuable opportunity to understand variations of the disease, regarding geographical and ethnic background [6,7].

In recent years, there has been a surge in research on NMOSD in LATAM, leading to a growing body of evidence on various aspects such as epidemiology, clinical manifestations, paraclinical features (including AQP4-IgG and imaging), acute and long-term treatment strategies, as well as accessibility to diagnostic tests. This narrative review aims to present the most relevant findings from different NMOSD cohorts in LATAM, providing a comprehensive overview of the current understanding of the disease in the region, while considering its unique characteristics and challenges. By synthesizing the available evidence, this review seeks to provide the most relevant findings found in LATAM cohorts, to better understand what profile of patients we attend in the region, which may differ from patients in other regions of the world.

## 2. Epidemiology and AQP4-ab Frequency

LATAM is a vast region spanning from the northern border of Mexico to the southern part of South America and the Caribbean Islands. It is known for its extensive racial and genetic diversity, resulting from historical interactions among indigenous populations, European colonizers, and African slaves (Fig. 1, Ref. [6]). As of February 20th, 2021, the population of LATAM is reported to be 657,680,320 by


**Fig. 1. Latin America region map extending from Mexico (North) to Argentina (South), including the Caribbean Island [6].**

the United Nations [6,8]. However, beyond these racial and genetic variations, several factors significantly influence the epidemiological records of NMOSD in LATAM. Notable disparities persist regarding access to medical resources and specialized healthcare services throughout the region [9]. The limited availability of diagnostic tools, such as magnetic resonance imaging (MRI), AQP4-IgG (and myelin oligodendrocyte glycoprotein immunoglobulin G antibody [MOG-IgG]) testing, and difficulties in accessing consultations with specialists, inevitably impact the accuracy and comprehensiveness of epidemiological data. Moreover, the absence of national programs dedicated to disease registration further complicates the collection and analysis of comprehensive NMOSD data in LATAM.

The prevalence of NMOSD worldwide ranges from approximately 0.5–4 cases per 100,000 individuals, with potential variations of up to 10 cases per 100,000 in specific racial groups such as Asian and Afro-descendant populations [10]. However, it is important to note that this range is relatively small compared to the prevalence of multiple sclerosis (MS) [11,12]. The relative frequency (RF) of NMOSD in relation to MS was established in different regions of LATAM. For instance, the RF in Martinique, Ecuador, Mexico, and Sao Paulo was reported to be 27%, 15.9%, 6.8%, and 20.5%, respectively [8,10]. A study conducted in cities between latitude 10 degrees north (Caracas, Venezuela) and latitude 34 degrees south (Buenos Aires, Argentina) in South America revealed a decreasing RF along a North-South gradient, with Venezuela having the highest RF of 43.2% and Argentina the lowest at 2.1% [13–17]. In recent years, several studies have been conducted in the LATAM region, showing a wide range of prevalence, which even shows variation within the same country. It is essential to emphasize that these variations may be attributed to factors other than racial components, such as the inclusion of the 2015 NMOSD criteria used in the most recent studies [18–20]. In this context, a 2009 population study of 645,000 individuals with 73% African ancestry in the French Antilles (Martinique and Guadalupe) reported a prevalence of 4.2 cases per 100,000 [14]. Among Mestizos in Mexico City, the estimated prevalence was 1 case per 100,000 [13]. In Volta Redonda city (Rio de Janeiro state, Brazil), the estimated prevalence was 0.37 cases per 100,000 [8], while in Belo Horizonte, it was 4.52

per 100,000 (95% confidence interval [CI] 3.72–5.43) [19]. In Antioquia (Colombia), the prevalence was 4.03 cases per 100,000 inhabitants (95% CI 3.3–4.8), with a predominant Mestizo racial background (81.6%) [20–22]. The estimated crude prevalence of NMOSD in Panama and the Dominican Republic was 1.62 per 100,000 inhabitants and 0.73 per 100,000 inhabitants, respectively [22]. However, it is likely that this rate is underestimated due to the challenging diagnosis of NMOSD, especially in its seronegative form, and the possibility that patients may not have been referred to a specialized tertiary center. It is important to note that while NMOSD is generally considered a rare disease, the reported prevalence rates in Belo Horizonte, Antioquia and Martinique are notably high and they are in line with studies conducted in different populations worldwide with high prevalence of NMOSD, such as Japan and Korea [10]. This is likely due to a higher proportion of Afro-descendant patients included in the Belo Horizonte and Martinique cohorts [10].

In terms of gender, epidemiological studies in LATAM found that most patients were women between the ages of 30 and 40 years, consistent with reports from Europe, North America, Asia, and Australia/New Zealand [10]. However, individuals of all age groups, including children and elderly, were also reported in LATAM. In South America, NMOSD predominantly affects young non-white women and is associated with moderate to severe disability, especially in late-onset ($\geq$50 years) NMOSD patients [8,21]. In a recent study in Central America, which included 186 NMOSD patients, 84% were female (sex ratio of 5.6:1), and the mestizo population constituted 72% of the study group [22], consistent with other epidemiological reports from LATAM [7–21].

The discovery of AQP4-IgG in the serum of NMOSD patients has been a significant breakthrough in understanding the immune mechanisms involved in this disease. In the original study (USA), the antibody was detected in 73% of neuromyelitis optica (NMO) patients [4]. However, the rate of antibody positivity varies in LATAM studies. It is important to note that most LATAM studies used tissue-based indirect immunofluorescence (IIF) to detect AQP4-IgG [8]. A recent multicenter study, which collected data from most LATAM countries, showed that serologic analysis of AQP4-IgG was performed in 95.4% of the sample, with a positivity rate of 63.9%. The highest positivity rate was observed in the North America-Central America-Caribbean region (73.8%). Cell-based assays (CBA) were the most commonly used testing method (accounting for 42.2% of cases), followed by tissue-based IIF, enzyme-linked immunosorbent assay (ELISA), and a combination of CBA in 15.6%, 10.9%, and 6.35% of cases, respectively [6].

The initial study on genetic susceptibility in NMOSD was carried out in 2009 for Western populations [23]. The researchers examined human leukocyte antigen (HLA) alleles in French-Caucasian patients with NMO and found a correlation between NMO and HLA DRB103 alleles [23]. In South America, similar associations were found in Afro-Caribbeans, Afro-Brazilians, white Brazilians, and mestizos [24,25].

Infectious diseases have been suggested as potential environmental factors linked to NMOSD onset or relapse triggering. Some of these factors are more prevalent in Asia and LATAM than in North America and Europe, in line with a greater NMOSD prevalence in those regions [26]. However, there is still a lack of strong evidence to connect any specific infectious agent or vaccination to NMOSD. In this context, NMOSD cases associated with COVID-19 infection have been recently reported in studies conducted in the LATAM population during the COVID-19 pandemic [27–30].

While there is increasing evidence regarding NMOSD epidemiology in LATAM in recent years, many countries (e.g., Argentina) still lack comprehensive data. Understanding the epidemiological characteristics of NMOSD is extremely important for establishing health policies in the countries of this region.

## 3. Clinical Manifestations (Including Prognostic Factors) and Application of the 2015 Criteria

Several studies have investigated the clinical manifestations and prognosis factors of NMOSD in various LATAM cohorts. Most reports indicated that optic neuritis (ON) was the most common initial NMOSD manifestation, with a range of 29% to 57% of cases [18]. A recent large LATAM study (Argentina, Chile, Ecuador, Brazil, Venezuela, and Mexico) compared outcomes of 195 ON-related NMOSD patients and showed that ON-NMOSD was associated with poorer clinical outcomes compared with ON seen in MOG-associated diasease (MOGAD). When ON-NMOSD was associated with myelitis at disease onset, it was found to be a predictor of wheelchair dependency at the last visit [31]. Additionally, older age at disease onset was a predictor of severe visual disability, and a higher number of relapses were predictors of permanent motor disability [31]. Rituximab treatment was a factor protective for developing permanent motor disability. In contrast, a study from Chile (N = 37) reported that the most frequent initial presentation was myelitis (61%), followed by ON (33%), and area postrema syndrome (11%). The age of onset was independently associated with disability measured by Expanded Disability Status Scale (EDSS). Onset before the age of 30 years was a protective factor, while age above 50 represented a risk factor for disability [32]. Furthermore, an Argentinean cohort reported that ON was the initial attack in most AQP4-IgG-positive NMOSD patients, while in AQP4-IgG-negative patients, myelitis was the most frequent manifestation [33]. Several Brazilian studies have also addressed NMOSD symptomatology. In

a study including 153 NMOSD patients, myelitis occurred in 85%, ON in 84.3%, and brainstem syndromes in 29% during follow-up, with no data regarding symptoms at disease onset. The mean EDSS at diagnosis was 4.13 ± 1.89 (range: 1.0 to 8.5) [34]. Other case series from Northeast Brazil, including 91 patients, described isolated myelitis (32.9%) and isolated ON (22.4%) as the most frequent initial clinical syndromes. After conducting multivariate analysis, it was found that ON was linked to slower disease disability accrual, while area postrema involvement was associated with faster disability accrual [35]. Additionally, a study of 37 Brazilian patients revealed that ON or myelitis was the initial clinical event in approximately 60% of patients. Simultaneous ON and myelitis (with an interval of up to one month between each event) occurred in 23.5% of patients, and brainstem syndrome (mainly refractory nausea and vomiting, and protracted hiccups) were observed in 17.6% of patients [36]. Similar proportions were reported in other relevant Brazilian studies [37–40].

In a study from Peru, 58 NMOSD patients (40%) experienced ON as the first clinical event, followed by myelitis in 26%; while during follow-up, the most frequent clinical event was myelitis, which occurred in 79% of the entire cohort [41].

In a Venezuelan study involving 249 NMOSD patients, a high rate of simultaneous ON and myelitis as the first event (51%) was reported, followed by isolated myelitis (22.4%), and ON (21.6%), while 2.4% presented brainstem/cerebral and area postrema syndromes [18].

In a descriptive study of 59 Ecuadorian patients, the most common clinical presentations were ON and the association of ON with myelitis. At disease onset, 37% of the cases presented ON, 37% presented ON associated with myelitis, 8% experienced symptoms in the area postrema, and 17% of patients had symptoms of myelitis [16]. The most frequent clinical manifestations during the disease were motor compromise (84.7%), followed by sensory symptoms (79.7%). At follow-up, ON was observed in 81.4% (35.6% of the cases had unilateral ON involvement and 45.8% had bilateral). The mean EDSS was 4.8 ± 1.8 [16]. Furthermore, AQP4-IgG-negative patients experienced a higher grade of disability than AQP4-IgG-positive patients [16].

A study in Mexico analyzed 58 NMOSD patients and found that ON was the initial clinical presentation in most cases (58.6%), with 31% being bilateral. Myelitis occurred in 26% of patients, and area postrema syndrome in 10.3% [42]. Another study in Mexico, focusing on area postrema syndrome (N = 50), showed a higher incidence in women, with nausea/vomiting as a clinical presentation. This was associated with AQP4-IgG positivity and core clinical characteristics such as ON and myelitis [43]. Interestingly, symptoms of area postrema syndrome were improved after rituximab treatment.

In a study in Central America and the Caribbean, 229 NMOSD patients from various countries showed that the most common clinical manifestation was the combination of ON and myelitis in 42.5% of cases. Isolated myelitis was present in 25.3% and isolated ON in 16.7%. Additionally, 13.97% had ON plus myelitis and area postrema syndrome throughout the disease course [22]. NMOSD can also be associated with systemic autoimmune disorders, reported in approximately one-quarter of patients in LATAM [1,6]. To summarize, clinical manifestations at disease onset o during follow-up are varied and their prevalence depends on many factors of the cohorts studied.

It was found that NMOSD patients can develop the disease after the age of 50 (namely late-onset). Although late-onset NMOSD is relatively uncommon, it has been reported that these patients may have a worse prognosis due to greater severity of symptoms, worse recovery from relapses, and higher occurrence of spinal cord involvement despite early aggressive treatment [44]. In a retrospective study of 140 patients from Argentina, Brazil, and Venezuela, 17.1% experienced late-onset NMOSD. A positive correlation between older age at disease onset and worse EDSS score at last follow-up was found in that cohort. However, this association was not observed in a Mexican cohort [45].

The Argentinean registry of MS and NMOSD (RelevarEM) conducted a study on 137 NMOSD patients to analyze the main prognostic factors of disability. The study revealed that the presence of relapses during follow-up, age at disease onset, and higher EDSS after the first attack were the most significant clinical factors associated with a higher risk of disability [46].

The 2015 NMOSD diagnostic criteria were validated in various cohorts from LATAM. In an Ecuadorian study, 24% of patients were newly classified as having NMOSD when the 2015 criteria were applied, compared with the 2006 NMO criteria. The median time to diagnosis was shorter using the 2015 criteria than when applying the 2006 criteria [16]. Similarly, in a multicenter cohort from Argentina, Venezuela, and Brazil, the application of the 2015 diagnostic criteria led to a 62.5% increase in the rate of diagnosing NMOSD compared with the 2006 NMO criteria, with a shorter median time to diagnosis. The median time taken to fulfill the 2015 NMOSD criteria was 1 month, whereas the median time needed to fulfill the 2006 NMO criteria was 18 months [47]. These results were replicated in several LATAM cohorts, demonstrating that the 2015 NMOSD criteria should be used in the LATAM region in daily clinical practice, as recommended by the LATAM consensus recommendation and in line with results from other cohorts such as Korea and UK [16,18,20,22].

## 4. Cognitive and Neuropsychiatric Disorders, and Health-Related Quality of Life

NMOSD patients may exhibit cognitive impairment at disease onset or during follow-up. It is estimated that over 40% of patients experience cognitive deficits [48,49]. The study of cognition in NMOSD has garnered increasing interest in recent years, emphasizing the necessity for a comprehensive understanding of the disorder beyond its classic clinical presentation [49,50]. Cognitive symptoms in NMOSD encompass a wide range of deficits, including difficulties with attention and concentration, executive dysfunction, processing speed impairment, and memory problems [51]. These symptoms can significantly impact daily functioning and quality of life (QoL) [52]. There is limited data in LATAM regarding the cognitive profile of NMOSD patients, specifically from studies that include comprehensive neuropsychological assessments [51]. The cognitive profile is similar to that of patients with MS, although NMOSD patients from LATAM exhibited lower performance in tasks related to verbal fluency, attention, and working memory.

One study conducted by a collaborative group from Argentina, Colombia, and Chile performed neuropsychological evaluations in 10 patients with NMOSD, along with an assessment of the action-sentence compatibility effect (ACE) paradigm, which induces a contextual coupling of motor actions and verbal processing [53]. Patients with NMOSD showed cognitive impairment in short-term memory, information processing speed, and executive functions, consistent with results reported in other parts of the world [49,50]. However, no differences were found in ACE when compared with controls, demonstrating preserved motor-language processing. Additionally, the same research group investigated facial emotion recognition in these patients, controlling for relevant cognitive factors [54]. Researchers reported that NMOSD patients experienced difficulty recognizing negative emotions (disgust, anger, and fear) compared with healthy controls. These deficits were not explained by other cognitive aspects and may be related to potential damage in brain regions underlying emotional networks, including the anterior cingulate cortex, amygdala, and medial prefrontal cortex, as reported recently in multicenter studies from Europe [49,50].

Psychiatric symptoms often coexist with other clinical manifestations of NMOSD. These can range from mood disorders, such as depression and anxiety, to cases of psychosis. Understanding and addressing psychiatric symptomatology in NMOSD is crucial for achieving better disease outcomes.

Regional data shows a high prevalence of mood symptoms in patients with NMOSD [52,55]. An Argentinian study using the MINI (Mini International Neuropsychiatric Interview) found that 45% of 20 included NMOSD patients had psychiatric illness [55]. This study compared the performance of NMOSD patients with MS patients and found a higher presence of impairment in those with NMOSD. The most common disorders were recurrent major depressive disorder, past manic episodes, dysthymia, lifetime psychotic disorder, and bulimia nervosa.

Other studies have used self-report questionnaires to investigate cognitive symptoms in NMOSD. One study found a 43% prevalence of depressive symptoms, assessed using the Beck Depression Inventory-II (BDI-II) [56]. This symptomatology was associated with poorer performance in working memory tasks. Another Argentine study, which evaluated 18 NMOSD patients, reported a 22% prevalence of mild depression, 11% of moderate depression, and 22% of severe depression. This research also showed that patients with moderate and severe symptomatology experienced significantly lower health-related QoL [52].

The array of symptoms in NMOSD significantly impacts patients' daily lives, affecting their QoL [57,58]. Numerous studies worldwide have reported poorer health-related QoL in NMOSD patients, with limited studies from LATAM populations [52,59]. An Argentinean study compared the health-related QoL of NMOSD patients, MS patients, and healthy controls, and found that NMOSD patients had worse health-related QoL, as assessed by the Argentinean validation of the 36-Item Short Form Health Survey (SF-36) [59]. NMOSD patients differed from healthy controls mainly in areas related to physical functioning, emotional well-being, and social functioning. When comparing health-related QoL with MS patients, NMOSD patients experienced lower scores specifically in the bodily pain domain, which has been reported as one of the most debilitating symptoms in NMOSD [60]. Another study examined the relationship between health-related QoL, mood, and cognitive symptomatology [52]. The authors found that NMOSD patients with moderate and severe depressive symptomatology had poorer performance on the vitality and social functioning subscales of the SF-36. Furthermore, when comparing health-related QoL between patients with cognitive impairment and those without, it was found that cognitively impaired patients had lower scores in all the areas evaluated of the SF-36.

Assessing the health-related QoL is extremely important for addressing the implications of the disease and improving treatment approaches for patients facing high levels of disability. While many international studies are focusing on the health-related QoL of patients with NMOSD, more data from LATAM are needed to better understand typical aspects of this population. Data on cognitive and psychiatric disorders are generally limited, but there has been a notable increase in interest of these aspects in recent years. Updating LATAM data and conducting multicenter studies would be beneficial in advancing knowledge in this area.

## 5. Imaging

MRI plays a crucial role in the diagnosis of NMOSD and in ruling out other possible differential diagnoses. It is

particularly helpful in confirming the diagnosis of NMOSD when the serologic status of AQP4-IgG is unknown or seronegative, evaluating new inflammatory lesions, confirming relapses, and monitoring the side effects of immunosuppressant therapies during follow-up (e.g., opportunistic infections) [61,62].

Although brain lesions were not initially reported in the original description of NMO [63], recent evidence suggests that brain abnormalities are actually quite common (71.2%–81%) even at disease onset [35,36,44,64]. In a multicenter study from Brazil, Argentina, and Venezuela (N = 94), the mean number of reported lesions was 8.4 $\pm$ 21.8 [65].

The understanding of brain MRI findings in NMOSD patients from LATAM is limited due to the scarcity of descriptive studies and incomplete reporting of brain MRI lesions [6,34,41,66,67]. Nevertheless, a LATAM multicenter cohort (Argentina, Brazil, and Venezuela, N = 79) found brain MRI lesions in 81.02% of NMOSD patients at disease onset, and 53.1% of patients (N = 42) showed typical-NMOSD lesions. These results are consistent with other cohorts from Asia and Europe [68,69]. The most frequent findings in brain MRI were nonspecific lesions (62.03%), followed by lesions affecting the brainstem/cerebellum (32.9%). No significant differences were detected regarding the frequency of brain lesions between seropositive and seronegative patients. Furthermore, brain MRI lesions were found in 71.2% of patients in a Northeast-Brazilian cohort [35]. Most lesions in that cohort were periventricular (17.8%), followed by those located in the area postrema (16.4%) and cerebellum (13.7%). Other LATAM studies from Venezuela, Mexico, Chile, Ecuador, and Colombia, including Central America and the Caribbean (CAC), have shown a frequency of brain lesions ranging from 25.7% to 65.5% [16,18,22,32,42,70]. In general, non-specific lesions are most frequently observed in clinical practice, and no differences in serostatus were reported, consistent with other large cohorts worldwide [36,44,61,62].

Researchers from the Argentinean registry recently reported a high frequency of new asymptomatic brain and spinal cord MRI lesions during follow-up (19%) and relapses (48%), which contrasts with observational studies conducted in the United States, Asia, and Europe where these findings were less frequent. The most frequent silent MRI lesions were those affecting optic nerves, followed by short-transverse myelitis (STM) [71–74].

Additionally, longitudinal brain volume changes during follow-up were analyzed in a LATAM multicenter cohort (N = 39), and no longitudinal changes or differences between seropositive and seronegative patients were found, consistent with data from a study carried out in the United Kingdom [73,75].

In a recently published LATAM cohort, fluffy (poorly demarcated) infratentorial lesions, which have been described mainly in MOGAD patients [76], were observed in up to 6% of NMOSD patients [77].

It is important to highlight that some differences among LATAM cohorts have been found, probably because of the lack of standardized brain MRI protocols to evaluate these patients. Although the majority of studies used 1.5- or 3.0-Tesla scanners, the absence of standardized brain MRI protocols does not allow specific comparisons between them. Furthermore, factors such as ethnicity, population, and differences in study designs contribute even more to this problem. New recommendations have been made on this matter in a recently published LATAM consensus [7].

Regarding optic nerve MRI lesions, a recent publication included a large multicenter NMOSD cohort from Argentina (N = 72), Chile (N = 21), Ecuador (N = 31), Brazil (N = 30), Venezuela (N = 10), and Mexico (N = 82) [78,79]. The study found that bilateral (42%) and longitudinally extensive optic nerve (40%) lesions were frequently observed. Additionally, chiasmatic lesions (31.7%) were significantly more frequent in NMOSD than in MOGAD. These optic nerve lesions were described in the 2015 NMOSD criteria as "typical" or suggestive of NMOSD [2,69]. Furthermore, a positive correlation was observed between poor visual scores and these three types of lesions. At disease onset, MRI optic nerve lesions were reported in 76.7% of patients with a first-ever NMOSD-related ON [79]. Different frequencies were reported in Chile (4%), Colombia (61%), and Peru (74.2%), and no further data from other LATAM countries were reported. A recent study from Brazil (25 AQP4-IgG-positive NMOSD) found that 50% of patients experienced bilateral lesions with a mean of segments involved of 3.7 $\pm$ 2.8. The most frequently affected segments were canalicular/pre-chiasmatic (92.8%), followed by intraorbital (85.7%), chiasmatic (57.1%), and optic tracts (50%). Notably, 64.3% had longitudinally extensive optic nerve affectation [64].

Regarding spinal cord lesions, longitudinally extensive transverse myelitis (LETM), defined as a lesion compromising 3 or more vertebral segments and involving at least 50% in the axial plane, is a hallmark of NMOSD.

In a recent LATAM cohort study (Colombia, Venezuela, Mexico, and CAC), the occurrence of spinal cord lesions ranged from 60% to 81%. No differentiation between LETM and STM was made. Another study reported LETM lesions in 51.7% (Peru), 69.4% (Argentina), 75% (Chile), 78.5% (Brazil), 91% (Ecuador), and 94.4% (Northeast Brazil) of cases. Cervicothoracic was the most frequent localization (38.5%) in a study conducted in Ecuador [16]. In contrast, cervical lesions were more common in studies conducted in Brazil and other LATAM countries, ranging from 38.5% to 94.4%.

A multicenter study from Brazil reported a mean segment extension of 7.6 $\pm$ 4.7 for the spinal cord lesions, which is similar to another study from Argentina where the mean extension was 7.3 $\pm$ 3.9 [80]. Interestingly, 61%

of patients showed bright spotty lesions, defined as intramedullary, markedly hyperintense lesions on axial T2-weighted images [64]. Although lesions affecting upper cervical segments with extension to the brainstem suggest NMOSD, this description was not found in the evaluated LATAM studies. In addition to LETM, STM may also be observed, even at disease onset. STM was reported from 5.2% (Peru) to 29.6% (Argentina) of NMOSD patients. Thus, STM does not rule out NMOSD, which is consistent with studies from the USA and Asia [80–83]. STM usually involves the central gray matter in NMOSD patients, as seen on the axial plane (61.1%), and subsequent myelitis episodes are LETM in 92% of a cohort of American patients; however, these results were not reported in LATAM studies.

It is crucial to recognize NMOSD-typical MRI lesions and symptoms and attend to relevant regional particularities to achieve an early and accurate diagnosis of NMOSD [84].

## 6. Acute and Long-Term Treatment Strategies

In NMOSD, disability typically accumulates after each clinical attack, resulting in long-term motor and/or visual impairment, as well as other neurological manifestations [2]. Acute relapse treatment is critical to minimize disability accumulation. Therefore, it should be started early and aggressively [7]. The objectives of acute treatment include suppressing acute inflammatory attacks, restricting CNS damage, and improving long-term neurological function. In addition, long-term relapse prevention treatment is recommended in all patients diagnosed with NMOSD as soon as possible to avoid permanent neurologic disability [7].

## 7. Acute Treatment for NMOSD Relapses

The significance of acute relapse treatment was assessed in an Argentinean population [33]. Recovery levels were compared after analyzing 262 acute attacks in 120 NMOSD patients (75 were AQP4-IgG-positive and 45 AQP4-IgG-negative). Significant differences in remission rates were found between ON and myelitis in the AQP4-ab-negative group. Patients with ON showed complete recovery (CR) in 82% of cases, while only 61% of patients with myelitis achieved this level of improvement. In the AQP4-IgG-positive group, a similar pattern was observed; patients with ON had CR in 88% of the cases, whereas for myelitis the CR rate was of 63%. Furthermore, the CR rate after the first NMOSD attack treated with high-dose intravenous methylprednisolone (IVMP) was 72% with a significant decrease in CR rate in subsequent relapses (7%–30.6%), indicating that disability accumulates after each clinical attack as reported in different cohorts worldwide.

A recent LATAM consensus recommendation emphasizes the utmost importance of therapies for acute relapses and the need for early initiation [7]. Although there are no large-scale, randomized, controlled trials regarding treatment of acute relapses, it is widely recommended that NMOSD patients should receive 1 g of IVMP for 3–5 consecutive days. In addition, after a qualitative analysis, some panel members have also suggested treatment for up to 7 days [85]. Importantly, timing is crucial [86].

According to the aforementioned experts' panel, after IVMP treatment, a gradual tapering course of oral steroids (with 1 mg/kg/day dose, followed by a gradual decrement for 2–8 weeks, depending on the severity of the attack) should be implemented. Although there is a lack of controlled trials, oral steroids are used as a bridge, once NMOSD diagnosis has been confirmed, until a steroid-sparing therapy reaches full efficacy [7].

The current approach suggests that patients with severe NMOSD relapses and those who do not respond to IVMP treatment may benefit from 5–7 plasmapheresis (PLEX) procedures (approximately 1.5 plasma volumes every other day, over two weeks) [7]. A Mexican study evaluated the impact of PLEX on 89 patients with NMOSD relapses, as an add-on therapy to IVMP. The reported response rate was 39.3% and the mean decline in EDSS was 0.7 points after comparing baseline and post-PLEX scores [87]. Additionally, a Colombian study including 119 NMOSD attacks (N = 78, 87.2% AQP4-IgG-positive), assessed PLEX as first-line therapy in combination with IVMP vs. IVMP alone [88]. The study showed that PLEX was associated with a better chance of complete improvement and demonstrated that delaying PLEX initiation beyond seven days, especially in severe attacks, may decrease the probability of full recovery. Furthermore, PLEX was also associated with increased time to upcoming attacks. The independent factors associated with a successful outcome after PLEX were: PLEX + IVMP as a first-line treatment, AQP4-IgG positivity, low basal EDSS score, and a small number of previous attacks. Due to its higher efficacy, some authors suggest that PLEX should be considered an initial treatment approach in severe relapses, in patients with myelitis, when a good response with this intervention has been observed in previous relapses or in those patients who had a regular-to-poor response to IVMP, particularly in older patients [89]. These statements are based on robust data coming from Europe and USA [89]. However, this is difficult to extrapolate to daily practice in LATAM, because of access/availability limitations. In this regard, IVMP use seems to be equally distributed in different regions within LATAM, while PLEX is more widely spread among South American countries as compared to Mexico, Central American and Caribbean countries [90]. Probably, the recommendation in the LATAM region is to continue using IVMP as the first line of treatment for relapses, and then consider a rapid use of PLEX (±IVMP) if no improvement is observed. Retrospective studies comparing the effectiveness of PLEX and immune absorption (IA) on NMOSD relapses have found no significant differences between these two in-

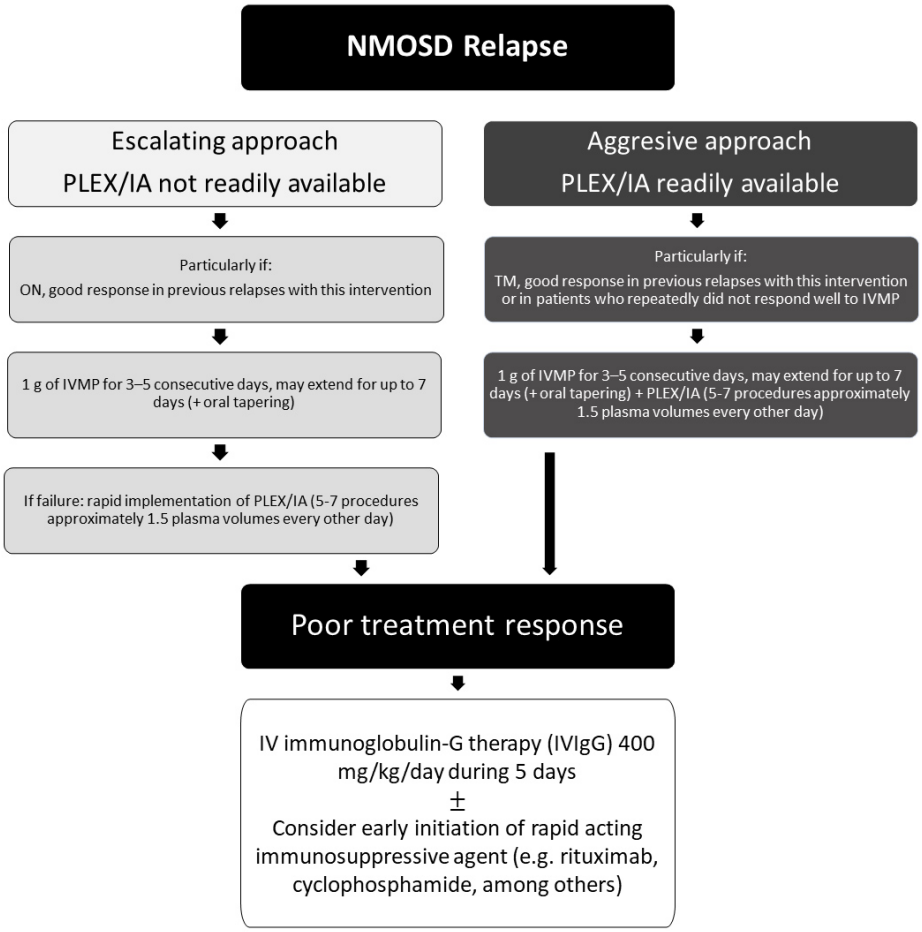


**Fig. 2. Proposed algorithm for the treatment of neuromyelitis optica spectrum disorder (NMOSD) relapses.** ON, optic neuritis; TM, transverse myelitis; PLEX, plasmapheresis; IA, immunoadsorption; IVMP, intravenous methylprednisolone; IV, intravenous; IgG, immunoglobulin G.

terventions [58]. Due to the short half-life of IVMP (15 minutes) [90,91], infusions of IVMP may be performed immediately after PLEX sessions or every other day between PLEX to avoid its clearance through apheresis. There is no robust evidence for the use of intravenous IgG as an acute treatment of NMOSD attacks; however, this intervention could be used if other treatments are not effective.

In summary, a combination of IVMP and PLEX/IA (immunoadsorption) may be an important and relevant therapeutic strategy for the first and subsequent NMOSD relapses. However, this combination should be evaluated in a randomized clinical trial. Fig. 2 displays a possible relapse acute treatment algorithm considering accessibility and current clinical practice in LATAM.

Several new treatments to improve the management and recovery of relapses in NMOSD are currently under investigation, including bevacizumab, ublituximab, and HBM9161 [92]. To date, there has been no experience with these drugs in LATAM, and further information is expected before they are included in acute treatment algorithms.

## 8. NMOSD Long-Term Treatment

Long-term treatment is recommended for all patients diagnosed with NMOSD to prevent severe neurological disability related to relapses [7]. Until 2019, the choice of long-term NMOSD treatment was based on retrospective data and observational studies. The most frequently used drugs in long-term treatments of NMOSD (in different regions, including LATAM) are azathioprine (AZA), mycophenolate mofetil (MMF), and rituximab [5,9]. MMF and AZA have demonstrated effectiveness in numerous observational studies, showing a significant decrease in relapse rate and even stabilization or improvement of EDSS scores in some instances [93,94]. Additionally, NMOSD patients treated with rituximab have exhibited reductions in relapse rate and stabilization of disability in both retrospective and prospective studies, as well as in meta-analyses. Recently, rituximab was also assessed in a Japanese placebo-controlled trial (RIN-1) with positive outcomes in terms of efficacy and safety [95]. Rituximab and

MMF have been proven to be more effective than AZA in comparative observational studies regarding prevention of NMOSD attacks [96,97].

A recent large survey-based study, involving 62 expert neurologists from LATAM, revealed that rituximab (86.3%) and AZA (81.8%) are the most commonly used first-line therapies. Neurologists indicated that the choice of treatment depends mainly on accessibility and clinical judgment if both drugs are available [6].

In a Brazilian study of 150 NMOSD patients on AZA, 69% showed no increase in disability after a 5-year follow-up; however, various adverse events leading to medication discontinuation were reported [98].

Furthermore, AZA, oral corticosteroids, or a combination of both were reported as the most frequently used initial treatments in NMOSD patients from Brazil. This is likely due to their lower cost, extensive experience, and widespread availability across the country [34]. In a retrospective cohort from Chile [32], 17 out of 36 NMOSD patients required more than one preventive treatment to stabilize inflammatory activity (at disease onset or during follow-up). In Ecuador, rituximab was found to significantly reduce relapse rate and mean EDSS in 23 treated patients [16]. Additionally, this study noted that the most common adverse events with rituximab were infections, which were present in 65.2% of cases.

The use of cyclophosphamide, mitoxantrone, and methotrexate was reported in a lower proportion of patients in LATAM [6]. Tocilizumab has been linked to clinical stabilization in NMOSD patients who did not respond to one or more treatments [99], proving to be more effective than AZA in the Chinese population [9,100], but there are few reports of its use in our region.

In terms of treatment accessibility, the main challenge is the cost of medications [9,100]. Regarding health coverage, half of the countries partially covered treatments, while the other half covered the entire cost of these treatments [100].

From 2019 to date, four randomized clinical trials have resulted in the approval of new drugs for the treatment of AQP4-IgG-positive NMOSD patients [100–104]. These new treatments are all monoclonal antibodies with different specific targets based on the pathophysiology of NMOSD: (1) interleukin-6 receptor ([IL-6R]; satralizumab) [101,102], (2) B cells that express CD19 (inebilizumab) [103] and (3) C5, the final fraction of complement (eculizumab) [104]. They have all demonstrated a significant reduction in relapse rate compared with placebo in phase III studies, with a good safety profile. To date, there are few series that describe the use of these new drugs in our region.

## 9. Access and Utilization of NMOSD Care and Miscellaneous

Treatment options for NMOSD have expanded, with the introduction of highly effective monoclonal antibodies and advanced diagnostic tools, enabling a more precise and early diagnosis, and better outcomes. The issue of availability becomes crucial, alongside the need for evidence-based guidelines to facilitate the appropriate use of these interventions [7,105].

In this context, the diagnosis and treatment of NMOSD show a significant disparity worldwide, even within the LATAM region, which is characterized by an inequitable pattern. These issues may be observed especially in regions with a large number of lower-income populations, where no immunosuppressant treatments (ISTs) are accessible for NMOSD patients, even if approved. To address these inequities, nine goals were proposed for rectifying the situation [105,106]. These goals include: (1) improving access to diagnostic testing; (2) Advancing knowledge on NMOSD; (3) Developing best practices and guidelines for low-income settings; (4) Generating evidence on treatment choices and dosing of affordable medicines; (5) Ensuring that ISTs are consistently available in every country; (6) Negotiating rational drug pricing in low-income countries; (7) Establishing vertical programs for drug delivery; (8) Tracking disease incidence and outcomes to identify missed opportunities and (9) Ensuring continuity of NMOSD care over time.

Regarding availability and accessibility, a collaborative group of neurologists from 16 LATAM countries caring for NMOSD patients conducted a survey-based study to assess the availability of diagnosis testing and treatment [100]. Approximately half of the countries in the region had access to AQP4-IgG testing, similar to that of MOG-IgG. Essential diagnostic procedures such as lumbar puncture (LP) and cerebrospinal fluid (CSF) analysis, optic coherence tomography (OCT), MRI, and visual evoked potentials (VEP) tests are available in almost all countries in the region. However, the capability to calculate brain volume loss (BVL) was found to be available in only half of the countries examined. Notably, platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio (NLR) are less costly than the detection of other cytokines and have been assessed in NMOSD patients from LATAM as potential biomarkers of inflammation, underlying disease activity, and prognosis [107,108]. A recent meta-analysis conducted in Peru found NLR to be a useful biomarker of NMOSD as it was significantly increased in the patient group compared to the healthy control group with a high level of certainty [109]. Additionally, the NLR was applicable as an indicator of poor prognosis. Access to treatment for NMOSD relapse was widespread throughout the region. Intravenous methylprednisolone, oral steroids, plasmapheresis, and intravenous immunoglobulins were available in almost all countries. Regarding long-term NMOSD medica-

tions, nearly all countries had access to AZA, MMF (excluding Venezuela), and rituximab, except for Venezuela and El Salvador. New monoclonal antibodies were not widely available for NMOSD patients in the region at the time this paper was written. The most common challenges and obstacles reported in LATAM were the high cost of medications for the healthcare sector, followed by difficulties in reliably obtaining medicine supplies for affected patients, consistent with a previous study [110] which found that 70–100% of high-income countries' patients can afford treatment without incurring significant health expenses, while less than 10% of low-income country patients could. In terms of health coverage, half of the countries partially cover treatment. Although there have been discussions among physicians regarding the limited access to preferred medications, this barrier was not considered the most significant in clinical practice for NMOSD patients.

In this context, a study based in Argentina highlights barriers to access and utilization of NMOSD care, based on real-world patient experiences, in terms of access to care and NMOSD burden [9]. This cross-sectional study (N = 100) reported that 51% of patients were employed, 57.5% working full-time, while 11% were currently unemployed, and 13% had retired due to NMOSD. Before diagnosis, slightly more than half (55%) of patients visited between 2 and 3 specialists, either general neurologists or neuroimmunology specialists, for a second opinion, before the final NMOSD diagnosis was achieved. AQP4-IgG and MOG-IgG testing were requested for 91% of patients; health insurance covered this test partially in 15% of cases. Of note, one-third of these patients/families paid it in full, out of their funds. NMOSD patients receiving private medical care showed better access to MRI scans, more outpatient visits, and encountered fewer difficulties obtaining NMOSD medications, compared to those treated at public institutions. Furthermore, patients receiving care from public institutions experienced a longer mean waiting time for MRI scans and neurology visits compared to patients from the private sector. Additionally, 24% of patients underwent neurological rehabilitation, and one-third of them self-funded the treatment, which was significantly more common in the public sector than in the private sector. Private medical care (odds ratio [OR] = 3.84, $p = 0.01$) was the sole independent factor linked to appropriate access to IST in Argentina.

Guidelines and consensus recommendations play a crucial role in optimizing the care and treatment of NMOSD patients. Recognizing its importance, a panel of neurologists from LATAM, dedicated to the management of NMOSD patients, gathered virtually to establish consensus recommendations specifically tailored to the management and treatment of NMOSD patients within the LATAM region [7]. To ensure a comprehensive and evidence-based approach, the panel employed the Research and Development/University of California in Los Angeles (RAND/UCLA) methodology. The panel emphasized that the 2015 NMOSD and 2018 MOG-ab diagnostic criteria should be uniformly applied to patients in the region. Likewise, the utilization of CBA for testing AQP4-IgG and MOG-IgG was strongly recommended, ensuring accurate and reliable results. To facilitate consistent and effective diagnosis and follow-up, the panel also advocated for the implementation of a standardized MRI protocol. IVMP or PLEX in cases where a patient does not respond adequately to steroids are recommended to treat attacks. Rituximab or MMF were recommended as the first line of long-term treatment, providing clinicians with evidence-based options to support their treatment decisions. These consensus recommendations provide valuable and region-specific guidance for the management and treatment of NMOSD patients. By unifying practices and promoting standardized approaches, these recommendations aim to optimize patient care, improve outcomes, and enhance the overall management of NMOSD within the LATAM region. Although an increased number of publications on NMOSD have been generated and developed in LATAM, in comparison with previous years, more effort and better quality of data are needed to add results from LATAM to the international datasets. In this regard, an Argentinean MS/NMOSD registry (RelevarEM) was built to standardize the information shared among neurologists to better understand the diagnosis, treatment, and outcomes of NMOSD patients. Methodological aspects and directions have been published. Other registries are being developed in LATAM [111].

Pregnancy holds particular significance when considering its implications in NMOSD patients as it commonly affects women of childbearing age. Despite its relevance, there remains a notable scarcity of data and research on pregnancy and NMOSD, especially in LATAM.

In a Mexican obstetric population with NMOSD [112], 29 out of the 40 eligible patients were included. Among them, 19 patients had experienced at least one previous pregnancy. A total of 50 pregnancies were analyzed, with 44 of them occurring three or more years before the first clinical manifestation of NMOSD. Among the reported pregnancies, 12 resulted in pregnancy losses, including five miscarriages and three stillbirths. Ten of these pregnancy losses occurred three or more years before the NMOSD diagnosis, while one occurred after the first manifestation. It is noteworthy that all pregnancy losses were observed in eight patients. Almost half of patients with previous pregnancies experienced at least one pregnancy loss, with most occurring three or more years before the NMO diagnosis. This percentage surpasses the expected rates for their respective age group in the country, highlighting the potential impact of NMOSD on pregnancy outcomes in the Mexican population.

The LATAM consensus recommendations offer relevant guidance for minimizing potential risks associated with NMOSD during pregnancy, addressing issues such as

the use of methylprednisolone and plasmapheresis for acute relapse treatment, as well as IST in this specific population. New LATAM NMOSD guidelines addressing this topic are currently being developed for publication. These forthcoming guidelines will contribute to advancing the knowledge and management strategies surrounding NMOSD and pregnancy by incorporating the latest research and insights.

## 10. Conclusions and Future Perspectives

In recent years, different characteristics of NMOSD have been reported in LATAM. Data from this region are of particular interest worldwide, considering that LATAM is a large geographical area with probably greater ethnic and socioeconomic diversity, compared with previously studied cohorts involving Caucasian and Asian populations [6]. Therefore, new evidence focused on LATAM countries is relevant to the international dataset, as shown and summarized in this narrative review.

Global inequities in NMOSD diagnosis and treatment have been published [105], especially in lower-income countries, and LATAM is no exception. NMOSD is associated with a significant economic burden in terms of healthcare resource utilization and costs of NMOSD treatment. In this context, the standard of care for NMOSD patients has become highly unequal globally, and differences in management and access to NMOSD care were reported in the region [9]. Recently, nine collective goals were proposed to be considered for the global NMOSD community to rectify global inequities in NMOSD diagnosis and treatment, especially for resource-limited populations [105]. These aims can be pursued in parallel as multiple actions will be needed by multiple parties.

In recent years, many courses, meetings, and NMOSD/MS mentoring programs, in person or virtually, have been designed and developed for physicians, patients, family members, and caregivers to improve the visibility and awareness of NMOSD in the region. Different regional or global MS/NMOSD associations, foundations, Latin American Committee for Treatment and Research in Multiple Sclerosis (LACTRIMS), and pharmaceutical companies are supporting these types of activities. However, more options for medical training, especially hands-on experiences in LATAM, there should be an emphasis on gaining more experience in caring for NMOSD patients. Furthermore, there have been significant efforts in clinical research in the region. Collaborative multicenter studies have notably increased, and referral centers in LATAM are now participating in global research led by main centers worldwide, likely due to the need to include data from this large and multiethnic region [113,114]. Colleagues from Brazil and Argentina have contributed to the development of the 2015 NMOSD criteria. Additionally, a consensus recommendation for LATAM has been published to ensure NMOSD patients receive a common standard of care, and other regional consensus recommendations on relevant NMOSD topics will be published soon. In this line, some LATAM groups are working on creating regional NMOSD registries to standardize data and share it in a central dataset. This will lead to more insights into the behavior of this condition and improve the quality of information.

Despite encountering various financial, social, and economic limitations in the region, the medical community in LATAM has made extensive efforts in medical education and research, leading to a better understanding of the characteristics of patients in our region and enabling early and timely diagnosis and treatment to improve QoL. Improving access to diagnostic tests and NMOSD treatments is crucial.

## Author Contributions

Concept and design: ECC and RA. Acquisition, analysis, or interpretation of data: ECC, RA, BE, PAL, BS, VAT and ST. Drafting of the manuscript: ECC, RA, BE, PAL, BS, VAT and ST. Critical revision of the manuscript for important intellectual content: ECC, RA, BE, PAL, BS, VAT and ST. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.


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## Conflict of Interest

The authors declare no conflict of interest.

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