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Review

Epidemiology of neuromyelitis optica in Latin America

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Abstract

A major development over the past two decades was the recognition of recurrent neuromyelitis optica (NMO) as a particular central nervous system disorder different from multiple sclerosis (MS). Here we reviewed the epidemiology of NMO in Latin America (LATAM). A predominance of a mixed population is found in this region. Recurrent NMO in black women was described in the Caribbean Islands and in Rio de Janeiro. The prevalence of NMO in LATAM varied from 0.37/100,000 (Volta Redonda city) to 4.2/100,000 inhabitants (Caribbean Islands). NMO differs significantly from MS with respect to gender, ethnicity, morbidity and genetic susceptibility. An association of the HLA DRB1*03 alleles with NMO was described in the French Antilles, Ribeirão Preto, Rio de Janeiro and Mexico. It is not common to find familial forms of NMO. NMO represents 11.8% of all inflammatory idiopathic diseases in South America (SA). In SA, the highest frequency of NMO occurs in African Brazilian young women. The overall relative frequency of NMO among MS cases in this region was 14%, decreasing following a north-south gradient, which parallels the percentage of nonwhite people.

***Keywords*:** Neuromyelitis optica, Latin America, epidemiology, prevalence, genetic susceptibility, HLA

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Introduction

In 1894, Eugène Devic, a French physician, while attending a medical meeting in Lyon, described a clinical pathological case of ''acute neuromyelitis optica'' (NMO) in a woman who developed paraplegia followed by a bilateral amaurosis with fatal course.[1] Since this report, NMO is also known as Devic's disease.[2]

For almost a century, NMO was classified as a monophasic variant of multiple sclerosis (MS).[3] A major development over the past two decades was the recognition of recurrent NMO as a particular disorder of the central nervous system (CNS) with clinical, imaging, laboratory and pathogenic mechanisms that distinguish it from MS.[4,5] Currently, NMO is defined as a severe form of inflammatory idiopathic demyelinating disease (IIDD) that affects mainly the optic nerve and the spinal cord. The majority of patients present with the NMO-immunoglobulin G (IgG) autoantibody, which was considered the first biomarker for this disease.[6] NMO-IgG binds selectively to the Aquaporin 4 (AQP4) water channel, a transmembrane protein located in astrocytic processes at the blood-brain barrier.[7] Brain magnetic resonance imaging (MRI) scans of NMO-IgG-positive individuals with NMO demonstrated lesions in the brainstem periaqueductal area, diencephalon, and periventricular areas, which are characterized by high AQP4 expression.[8] Thus, the presence of neurological signs outside the optic nerve and spinal cord, particularly in the brainstem, was verified. Since 2006, positivity to NMO-IgG has been included as a diagnostic criterion for NMO.[9] Considering these data, NMO was considered as an immune-mediated disease that mainly affects astrocytes and secondarily the myelin.[10] The term ''NMO spectrum disorders'' (NMOSDs) was coined to encompass NMO and other CNS syndromes in which the NMO-IgG antibody was identified.[11] The sero-negativity in NMO varies from 30% to 50%. Therefore, the diagnostic criteria for NMOSDs include patient sero-positivity and sero-negativity with spinal cord and brain MRI images typical for NMO.[12]

This article aimed to describe the epidemiology of NMO in Latin America (LATAM).

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Characteristics of the LATAM population

LATAM is a large region of the American continent that extends from the northern limit of Mexico to the southern of South America, including the Caribbean. Racial mix is the main feature of the population in LATAM. This is in part explained by intermarriage among native Indians, European colonizers from the Iberian peninsula, and more than five million black slaves brought from Africa to Americas between the 17th and 18th centuries. Luso-America includes only Brazil, a continental country with more than 200,000,000 inhabitants, of whom 54% are mulattos or blacks (Afro Brazilian). French America is represented by the Caribbean Islands, Martinique, Guadalupe and French Guiana. French Afro-Caribbeans are descendants of interracial mating that occurred between French Caucasians and black Africans in the 17th and the 18th centuries. Hispano America consists of more than 20 countries along the coast of the Pacific Ocean. The inhabitants include mainly white Hispanics and mestizos. It also includes Afro-descendants, particularly in Colombia and Venezuela.

Recognition of recurrent NMO in America

Raul Mandler and colleagues (1993) described clinical, laboratorial and neuropathological features of eight women of different ethnicities (four whites, three Latinas and one African) with Devic's NMO in New Mexico (USA). These women presented with severe and selective involvement of the optic nerve and spinal cord with recurrent course and poor prognosis. The spinal cord MRI scans demonstrated long, cavitated, and enhanced lesions located in three or more segments. In contrast, no lesions were observed in the brain MRI scans. Characteristically thick blood vessels with perivascular necrosis were found in the CNS, with long necrotic lesions in the spinal cord. These findings led to the hypothesis that NMO is an autoimmune disease mediated by a soluble antibody.[4] These features were further confirmed. In 1999 they were included in the NMO diagnostic criteria to distinguish it from MS.[5]

Charles M Poser, from Harvard University, identified the first cases of recurrent NMO in LATAM. In the 1990s this researcher frequently visited the Caribbean Islands. With the aid of local neurologists, Poser was able to identify cases with acute and recurrent episodes of severe optic neuritis (ON) and paraplegia associated with endocrinopathies with high mortally. It was demonstrated that these cases were not due to MS or Devic's disease because they exhibited severe lesions in the spinal cord with cavitations and thickened blood vessels, normal brain MRI and a recurrent chronic course. In contrast to MS, this disease affected mainly black people. The new syndrome was named recurrent NMO with endocrinopathies. In 1997, Vernant and colleagues published, with Poser, the first eight cases in black women from Martinique and Guadalupe.[13]

The first series of Brazilian patients with optic spinal syndrome with recurrent clinical course was published by RM Papais-Alvarenga, Poser and other neurologists from Rio de Janeiro.[14] Several patients presented with endocrinological syndromes and other comorbidities such as pulmonary tuberculosis, neurocysticercosis, and immune-mediated diseases. MRIs showed large lesions in the spinal cord without brain lesions suggestive of MS. These findings gave further support to the notion that this was a new disease, different from MS.

Prevalence of NMO in LATAM

Unlike MS, NMO is considered a rare disease worldwide with a prevalence rate lower than 5/100,000 inhabitants.[15]

In Cuba, the prevalence of NMO was estimated to be 0.52/100,000 according to a 2009 nationwide, non-laboratory survey that analyzed 11.2 million people, featuring a mixture of African-Cubans and Spanish. It should be mentioned that two specialists performed the clinical testing at one center. In French Antilles (i.e. Martinique and Guadalupe), the prevalence of NMO was estimated to be 4.2/100,000 according to a 2009 population study that examined 645,000 people, of whom 73% had African ancestry.[16] The prevalence of NMO among Mestizos living in Mexico City and attending a single center was estimated to be 1/100,000.[17] In Volta Redonda city (Rio de Janeiro state, Brazil) only one case of recurrent NMO was found among 375,000 inhabitants; the estimated prevalence of NMO was 0.37/100.000.[18]

Descriptive epidemiology of NMO in LATAM

Recurrent NMO patients are found in the majority of LATAM countries.[17–19]

Demographic and clinical characteristics of patients diagnosed with the aid of criteria proposed by Wingerchuk et al. (1999, 2006) were described in the Caribbean Islands,[16,20] in the Southeast[21–23] and the Midwest regions of Brazil[24] and in Mexico City.[17] The patients were mainly females between 30 and 40 years old. However, children and elderly individuals were found among the patients. A Brazilian multicentric study described the main features

of pediatric NMO.[25] In the Caribbean Islands and in Rio de Janeiro, most of the patients were found to be Afro-descendants. Several studies confirm the increased morbidity and mortality of NMO as compared to MS.

A multicentric cross-sectional study described the frequency and the clinical characteristics of patients with inflammatory idiopathic demyelinating diseases (IIDD) followed across 22 reference centers for MS treatment, distributed across 17 cities in four countries (Venezuela, Paraguay, Argentina and Brazil). In Brazil, the reference centers were located in five regions of the country: North, Northeast, Midwest, Southeast, and South.[26]

As indicated in Table 1, among a total of 1917 cases of IIDD, 226 (11.8%) cases of NMO were diagnosed according to the criteria described by Wingerchuk et al.[9]

In South America, NMO affects mostly young non-white women, causing moderate or severe disability. Except for ethnicity, these data are similar to the NMO series diagnosed among whites using the same criteria (2006).[9] Pediatric forms occurred in 15.0% of the cases and more than a quarter of these patients had their first acute event when they were younger than 10 years old. No differences in gender, ethnicity/skin color, or morbidity were found between patients younger and older than 18 years old.

As shown in Table 2, NMO differs significantly from MS with respect to gender, ethnicity and disability as previous studies in the southeastern region of Brazil have demonstrated.[23] Ethnicity did not affect NMO-related long-term disability.

Relative frequency of NMO

The relative frequency of NMO in relation to MS is calculated by the quotient involving the total cases of NMO divided by the sum of cases of NMO and MS.

In LATAM, the relative frequency of NMO was 27% in Martinique,[20] 8% in Mexico,[17] 6.8% in São Paulo, and as high as 20.5% in Rio de Janeiro.[23]

The relative frequency (RF) of NMO was calculated in the SA study[26] across the cities located between latitude 10 degrees north (N) (Caracas) and latitude 34 degrees south (S) (Buenos Aires). In addition, the

Table 1. The spectrum of idiopathic inflammatory demyelinating diseases in South America.

Major diagnostic category	Diagnostic subcategory	*N*	% (95% CI)
Acute IIDD with encephalopathy	Pseudotumor	4	0.21 (0.19–0.21)
N = 7 (0.37%; 95% CI = 0.34–0.39)	Balo's concentric sclerosis	3	0.16 (0.14–0.17)
Acute disseminated encephalomyelitis	ADEM monophasic	14	0.73 (0.71–0.75)
N = 19 (0.99%; 95% CI = 0.99–0.99)	ADEM polyphasic	5	0.26 (0.24–0.28)
CIS	CIS optic neuritis (ON)	33	1.7 (1.6–1.9)
N = 67 (3.5%; 95% CI = 3.3–3.7)	CIS brainstem (BS)	6	0.31 (0.29–0.33)
	CIS transverse myelitis	18	0.94 (0.93–0.95)
	CIS multifocal	10	0.52 (0.50–0.54)
Multiple sclerosis (MS)	RRMS	1384	72.2 (70.2–74.2)
N = 1474 (76.9%; 95% CI = 75.0–78.7)	PPMS	90	4.7 (4.5–4.9)
Neuromyelitis optica (NMO)	**NMO monophasic**	**38**	**2.0 (1.8–2.2)**
***N* = 226 (11.8%; 95% CI = 10.4–13.3)**	**NMO recurrent**	**188**	**9.8 (9.7–9.9)**
Other NMOSDs	LETM monophasic	25	1.3 (1.2–1.5)
	LETM recurrent	39	2.0 (1.9–2.2)
	LETM + BS	6	0.31 (2.9–3.3)
	Bilateral recurrent ON (BRON)	15	0.78 (0.76–0.80)
	ON + BS	1	0.05 (0.04–0.06)
	Optic spinal Asian type MS	38	2.0 (1.8–2.2)
Total		1917	100

IIDD: inflammatory idiopathic demyelinating disease; ADEM: acute disseminated encephalomyelitis; CI: confidence interval; CIS: clinical isolated syndrome; MS: multiple sclerosis; RRMS: relapsing–remitting at onset; PPMS: primary progressive; NMO: neuromyelitis optica; NMOSDs: NMO spectrum disorders; LETM: longitudinally extensive transverse myelitis.

Table 2. Neuromyelitis optica versus multiple sclerosis in South America.

Variables		MS, $n = 1384$	NMO, $n = 226$	p value
Gender, *N* (%)	Female (F)	1011 (73.0%)	**191 (84.5%)**	<0.001
	Male (M)	373 (27.0%)	**35 (15.5%)**	
Skin color, *N* (%)	White (W)	922 (66.6%)	**103 (45.6%)**	<0.001
	Afro	362 (26.2%)	**89 (39.4%)**	<0.001
	Mestizo	82 (5.9%)	**30 (13.3%)**	<0.001
	Asian	2 (0.1%)	**1 (0.4%)**	
	Missing	16 (1.2%)	**3 (1.3%)**	
Age at onset, *N* (%)	First decade	11 (0.8%)	**10 (4.4%)**	<0.001
	Second decade	152 (11.0%)	**36 (15.9%)**	0.038
	Third decade	430 (31.1%)	**69 (30.5%)**	0.33
	Fourth decade	410 (29.6%)	**48 (21.2%)**	0.010
	Fifth decade	258 (18.6%)	**38 (16.8%)**	0.26
	Sixth decade	99 (7.2%)	**22 (9.7%)**	0.10
	Seventh decade	11 (0.8%)	**3 (1.3%)**	0.25
	Eighth decade	0	**0**	
	Missing	13 (0.9%)	**0**	
Age at onset (years)	Mean ± SD	32 ± 11 (4.0–66.0)	**31.2 ± 13.5 (2.0–68.0)**	0.14
Disease time (years)	Mean ± SD	9.6 ± 7.7 (1–47)	**8.9 ± 6.89 (1–38)**	0.19
Disability	Median (minimum–maximum)	1.0 (1.0–4.0)	**4.0 (0–9.5)**	<0.001
	EDSS mild	807 (58.3%)	**58 (25.7%)**	<0.001
	EDSS moderate	345 (24.9%)	**93 (41.2%)**	<0.001
	EDSS severe	225 (16.3%)	**73 (32.3%)**	<0.001
	Missing	7 (0.5%)	**2 (0.9%)**	

EDSS: Expanded Disability Status Scale; MS: relapsing–remitting multiple sclerosis; + MS secondary progressive; NMO: neuromyelitis optica.

frequency of nonwhite patients (Afro-descendants) was also calculated.

Table 3 shows that the RF of NMO decreases following an N-S gradient (Venezuela 43.2%, Brazil 14.0%, Paraguay 8.7%, and Argentina 2.1%). The highest RF of NMO was found in Venezuelan cities (Caracas and Maracaibo), where the percentage of nonwhite people is 79.15%. The lowest RF of NMO was found in Argentina (Buenos Aires), where the percentage of nonwhite people is only 1.0%. These data support the fact that ethnic origin influences the NMO frequency in LATAM. Figure 1 compares the relative frequency of NMO in LATAM with those from Italy27, Australia28, Wales29 and Japan[30].

Positivity of NMO-IgG antibody in NMO

The identification of the NMO-IgG autoantibody in the serum of NMO patients has been considered an important finding in elucidation of the immune mechanism that underlay this disease. In the original study, the antibody was found in 73% of NMO patients.[6]

Table 4 describes the data from five studies in LATAM that analyzed the presence of NMO-IgG antibody in NMO patients.[21,22,24,26,31] The presence of the antibody varied from 33% to 73.5%.

NMO genetic epidemiology in LATAM

The first study on genetic susceptibility to NMO in the occidental population was performed by Zephir and collaborators in 2009.[32] They studied class I and class II human leukocyte antigen (HLA) alleles in 45 French-Caucasian patients with NMO complex syndrome with definite NMO and six with limited NMO syndrome. The authors found an association between NMO and HLA DRB1*03 alleles. In LATAM, four studies reported genetic susceptibility to NMO. They analyzed Latin American patients from the Caribbean Islands,[33] Ribeirão Preto (Brazil),[34] Mexico City[35] and Rio de Janeiro (Brazil).[36] The data support an association between NMO and the

Table 3. The relative frequencies of NMO among patients with NMO + MS by latitude in South America.

MS location center	Latitude	Ethnicity Frequency of nonwhites	Frequency of NMO among NMO + RRMS	Brazilian regions	Country
Caracas	10 degrees N	79.1%	43.3%	–	Venezuela (43.3%)
Belém (1)	1 degrees S	41.6%	12.5%	North (15.2%)	Brazil (14.0%)
Belém (2)	1 degrees S	66.7%	16.6%		
Recife	8 degrees S	96.8%	3.2%	Northeast (3.2%)	
Brasília	15 degrees S	37.1.%	18.8%		
Cuiabá (1)	15 degrees S	50.0%	37.5%	Midwest (11.6%)	
Cuiabá (2)	15 degrees S	30.4%	8.9%		
Goiânia	16 degrees S	39.0%	1.3%		
Belo Horizonte	19 degrees S	56.0%	20.5%	Southeast (17.9%)	
Rio Janeiro (1)	22 degrees S	38.3%	10.4%		
Rio Janeiro (2)	22 degrees S	11.9%	4.4%		
Rio Janeiro (3)	22 degrees S	27.9%	16.3%		
Rio de Janeiro-Sul Fluminense	22 degrees S	30.6%	18.3%		
Santos	23 degrees S	16.1%	8.9%		
São Paulo	23 degrees S	41.7%	38.1%		
Curitiba	25 degrees S	4.2%	4.1%	South (5.1%)	
Joinville	26 degrees S	1.3%	7.7%		
Florianópolis	27 degrees S	17.9%	3.1%		
Asunción (1)	25 degrees S	12.5%	25.0%		Paraguay (8.7%)
Asunción (2)	25 degrees S	32.8%	6.5%		
Buenos Aires	34 degrees S	1.0%	2.1%		Argentina (2.1%)

MS: relapsing–remitting multiple sclerosis; NMO: neuromyelitis optica; N: north; S: south.

Table 4. Positivity of the NMO-IgG in LATAM NMO series.

Authors LATAM regions	Year	Number	Method	NMO-IgG positivity
Cabrera-Gómez et al.[31] Cuba and French West Indies (Caribbean)	2009	NMO = 48	IFI	33%
Bichuetti et al.[21] São Paulo (Brazil)	2009	NMO = 17	IFI	41%
Adoni et al.[22] São Paulo (Brazil)	2010	NMO = 28	IFI	64.3%
Papais-Alvarenga et al.[26] Venezuela, Paraguay, Argentina and Brazil	2015	NMO = 162	IFI	58.64%
Del Negro et al.[24] Brasília (Brazil)	2017	NMO = 34	ELISA with human AQP4	73.5%

NMO: neuromyelitis optica; IgG: immunoglobulin G; LATAM: Latin America; IFI: indirect immunofluorescence; ELISA: enzyme-linked immunosorbent assay; AQP4: Aquaporin 4.

allele HLA DRB1*03 in Afro-Caribbeans, Afro- and white Brazilians, and mestizos.

Familial NMO is not usual, even in the Asian population. Cabrera-Gómez et al. described two sisters in Cuba, one with NMO and the other with MS.[37]

One study analyzed the frequency of familial NOMSD in LATAM. Among 220 patients with

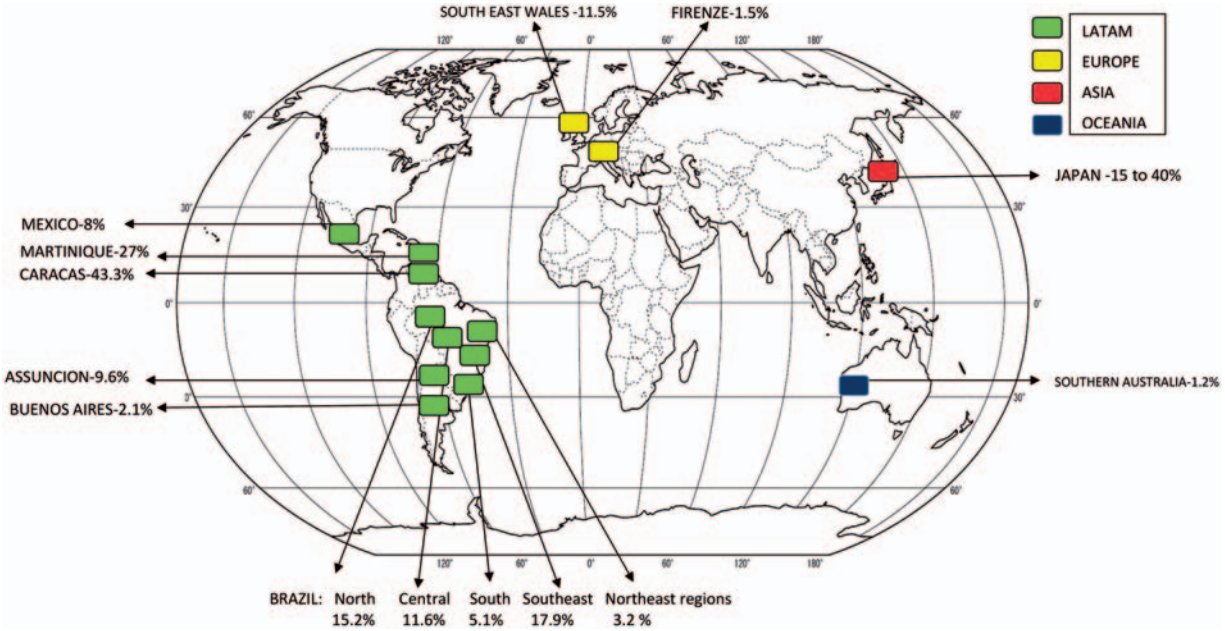

Figure 1. compares the relative frequency of NMO in LATAM with those from Italy,[27] Australia,[28] Wales[29] and Japan.[30] LATAM: Latin America.

NMOSD treated in one single center in Rio de Janeiro, only six patients had relatives with the syndromes: two sisters; one uncle/one nephew; and two cousins. The first family consisted of two sisters: one NMO and the other, bilateral recurrent optic neuritis (BRON). The second family included an uncle with NMO and a nephew with monophasic longitudinal extensive transverse myelitis (LETM). The third family consisted of two cousins: one optic spinal MS (OS-MS), and the other, monophasic LETM. The frequency of familial forms of the NMO spectrum syndromes was 2.8%. No patients with NMO had relatives with the same disease.[38]

Discussion

For almost a century, Devic's disease was considered as a variant of MS. MS is a worldwide disease that is related to genetic and environmental factors. Since 1980, MS has been found to be highly prevalent among Caucasians in the northern hemisphere. In contrast, lower prevalence has been described in Japan, China, and in LATAM.

In contrast, NMO is considered a rare disease. However, in the regions where MS is low, the prevalence of NMO is high. Caucasians show a low RF of NMO. In Japan, the OS-MS Asian type affects 40% of all MS patients. In addition, the RF of NMO is increased in mestizos and in Afro-descendants. As a comparison, among 80 Italian MS patients[27] there is only one case of NMO, whereas among six MS Brazilian patients in Rio de Janeiro, one suffers from NMO.[23]

A multicentric study was conducted across different regions of SA with the purpose to analyze the relative frequency of NMO versus latitude and the ethnicity of the patients. The overall RF of NMO in SA was 14.0%, rising in an S-N gradient. Buenos Aires, which had strong European colonization and no African slaves, showed the lowest NMO frequency (2.1%), very similar to Caucasians in Italy[27] and Australia.[28] In Paraguay, where 30% of the patients were mestizos, the RF of NMO was 8.7%, which is similar to Mexico City. Caracas and Maracaibo (Venezuela) exhibited the highest frequency of NMO cases (43.3%) and the highest frequency of nonwhite patients (79.1%). Similar results were found in Brazil. A low relative frequency of NMO was found in the S region (5.1%), which has a strong history of German and Italian colonization, increasing in frequency toward the N. The authors emphasized the implications of the high frequency of NMO in the health care services in these regions. The severity of the acute events demands expensive treatments and requires intensive care units. Finally, there is no approved medication for this condition, and, as a consequence, treatment of the disease is performed with off-label drugs that are not available in the health care systems.

Conclusions

NMO in LATAM affects mainly young women and causes moderate/severe disability. Antibody positivity varied from 33% to 74%. An association of NMO with HLA DRB1*03 alleles was confirmed in Martinique, Brazil, and Mexico. A relative frequency of 14% of NMO cases was identified with an S-N gradient, showing a higher frequency of NMO among nonwhite populations living in areas with low prevalence of MS.

Conflicts of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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