Epidemiology of neuromyelitis optica spectrum. New and old challenges

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Introduction. This epidemiological review on neuromyelitis optica spectrum disorder (NMOSD) focuses on describing the methodologies employed in studies conducted under the 2015 NMOSD criteria and the studies conducted in Spain and Latin America, as well as examining factors related to the prognosis of the disease.

Development. The methodology used in the studies varies essentially in the application of different diagnostic criteria, sources of records, antibody detection techniques and standardisation methods. However, in general terms, NMOSD is distributed worldwide with an incidence/prevalence that is higher in women than in men, and in Asian and African-American countries than in Western countries. The frequency increases in parallel to age, with a peak incidence/prevalence in the 40-59 age range. The Latin American population has particular epidemiological characteristics linked to its racial and genetic mix. Finally, epidemiological variables, such as belonging to the black race, being of older age at onset and being female, are associated with a worse functional prognosis.

Conclusions. Epidemiological data on NMOSD vary from one study to another, largely due to discrepancies in the methodological designs. Although Latin American studies are scarce, the findings described are associated with their ethnic mix. The homogenisation of criteria and the use of similar diagnostic techniques and standardisation methods must be implemented for the correct study of the epidemiology of NMOSD.

Key words. Aquaporin-4 antibodies. Epidemiology. Latinoamerica. MOG antibodies. NMOSD. NMOSD criteria.

Introduction

Neuromyelitis optica (NMO) is an idiopathic autoimmune disease that is characterised by the presence of inflammatory lesions that affect different structures in the central nervous system, although predominantly the optic nerve and the spinal cord [1]. The characteristic symptoms in 95% of patients are attacks, with significant long-term sequelae: 36% will have permanent motor disability; 42%, visual impairment; and 23% will be confined to a wheelchair [2,3].

The discovery of a disease-specific antibody directed against the aquaporin-4 water channel (anti-AQP4) provided insight into the pathophysiology of the disease and expanded the clinical phenotype beyond the classic optic-spinal topography (e.g. incoercible hiccups or vomiting due to involvement of the bulbar area postrema, hypersomnia due to diencephalic involvement or encephalopathy) [4]. In addition, anti-AQP4 contributed to the development of the diagnostic criteria [5] and have gained notable relevance in the more recent criteria from 2015 [1]. In these criteria, the terms NMO and neuromyelitis optica spectrum (NMOSD) were merged into a single term, NMOSD, and the diagnostic criteria were divided according to the presence/absence of the anti-AQP4 antibody [1]. However, anti-AQP4 is not detected in the serum of 20-25% of NMOSD patients, despite using the most sensitive techniques [2,6]. Recently, a new antibody has been identified in the 40-50% of these patients who are seronegative for anti-AQP4: antibodies against myelin oligodendrocyte glycoprotein (anti-MOG) [7-9]. Anti-MOGs were initially described in paediatric patients with demyelinating inflammatory episodes of the central nervous system, mainly acute disseminated encephalomyelitis [10,11]. Subsequently, they were identified in patients with a clinical phenotype of NMOSD, albeit with some distinctive clinical features, as well as a course and prognosis that differ from those of anti-AQP4 patients [2,12,13]. Therefore, many authors have adopted the term 'anti-MOG-associated disease' to refer to patients with these antibodies [14,15].

NMOSD is a disease that occurs around the world. It is three to nine times more prevalent in women than in men; the mean age of presentation ranges from 33 to 45 years, although onset in the paediatric or in old age has also been reported [3,16,17]. Yet, the epidemiology of the disease is not well understood, as epidemiological studies carried out to date have been heterogeneous and cannot really be compared to one another. Many of them have applied old diagnostic criteria, have not always taken into account the biological marker of the disease (anti-AQP4), have used detection techniques with different degrees of sensitivity or have not examined the presence of anti-MOG. The studies also differ in terms of the source from which data were collected, ranging from population-based studies to hospital registries. Finally, many of them have not adjusted prevalence and incidence estimates according to age or sex standards of reference populations (e.g. World Health Organization standards).

The aim of this paper is to carry out an updated review of the NMOSD epidemiological data. To this end, firstly, the prevalence and incidence data from epidemiological studies carried out according to the 2015 NMOSD criteria will be detailed, and the methodological differences between them will be described. Secondly, the review will focus on the Latin American population, whose racial and genetic particularities deserve to be addressed together. Thirdly, the epidemiological situation of patients with anti-MOG will be described. Lastly, the epidemiological or demographic factors related to the prognosis of the disease will be explored in depth.

Epidemiological studies based on 2015 criteria

General methodology of the studies

To date, 13 studies have assessed the epidemiology of NMOSD according to the 2015 criteria. The studies were conducted on populations from 10 different countries: six studies in Europe/USA/Oceania [18-23], six in Asia [24-29] and one in Latin America [30]. A single source of information for data collection (hospital registry or national registry) was used in eight studies [18,20,24,26-28,30,31] and multiple sources (national registries, hospital registries and laboratories) were used in four studies [19,21,22,27]. Regarding the anti-AQP4 detection technique, in six studies, antibodies were analysed by cell-based assays with live or fixed cells [19,20,21,22,26,30,31]; in two studies, more than 90% of the samples were analysed by enzyme-linked immunosorbent assay (ELISA) or immunohistochemistry [18,24]; and one study in a European population combined several techniques (cell-based assays, ELISA and immunohistochemistry) [21]. In two of the studies, the technique used was not reported [27,28]. Finally, only four (30.8%) of the 13 studies using the 2015 criteria provide standardised rates based on reference populations: two European studies [19,22] and one Australian/New Zealand study [18] considered World Health Organization standards, while one Japanese study did so according to Japanese population standards [25] (Table I).

Estimates of incidence and prevalence

Table I shows NMOSD prevalence and incidence data from the major studies conducted to date according to the 2015 criteria.

In addition to discrepancies in their methodology, the data differ fundamentally depending on the geographical distribution, with higher prevalence and incidence figures in Asian countries and in countries with African-American ethnicity. The estimated prevalence of NMOSD in Asian countries ranges from 0.34 per 100,000 inhabitants –95% confidence interval (95% CI) not reported– in the Arab Emirates to 4.1 (95% CI: 2.2-6.9) in the Japanese city of Tokachi [24-29]. In studies from Western countries with a majority Caucasian population (including Australia and New Zealand), the figures drop to between 0.7 (95% CI: 0.66-0.74) in Australia/New Zealand and 1.91 (95% CI: 1.52-2.28) in Hungary per 100,000 inhabitants [18-23]. The only Latin American study using the 2015 criteria was conducted in Venezuela and found a prevalence of 2.11 (95% CI: 1.85-2.37) per 100,000 inhabitants [30] (Figure).

Regarding incidence data, among Asian countries, only one study in Malaysia with a multi-ethnic population reported an incidence of 0.39 (95% CI: 0.35-0.47) per 100,000 inhabitants/year [27]. Most Western studies, however, showed incidences between 0.063 (95% CI: 0.045-0.081) in the Catalonia region of Spain and 0.37 (95% CI: 0.35- 0.39) per 100,000 persons/year in Australia and New Zealand [18-23].

When stratified by sex, the prevalence and incidence of the disease was at least three times higher in women than in men, both in the Asian studies from Tehran (Iran) and Penang Island (Malaysia)

Table I. Epidemiological data on the neuromyelitis optica spectrum from studies conducted according to the 2015 criteria.

	Population (million inhabitants)	Source of the register	Origin of patients with NMOSD	Antibody diagnostic technique (%)	Prevalence/105 inhab (95% CI) (total cohort/ AQP4+/AQP4–)	Prevalence/105 inhab (95% CI) by sex	Incidence/ 105 persons/year (95% CI) (total cohort/ AQP4+/AQP4–)	Incidence/ 105 persons/year (95% CI) by sex	Period of prevalence/ incidence
Australia and New Zealand, 2017	27,67	Paediatric/Adult Neurology Hospital Registry	25.8% Asian	IHC (100) ELISA (NR) Fixed-cell CBA (NR) Live-cell CBA (NR)	0.7 (0.66-0.74)/ NR/NR	NR	0.37 (0.35-0.39)/ NR/NR	NR	July 2013/2009-2012
Iran (Tehran), 2017	11.95	Reference hospital in Tehran	NR	ELISA (100%)	0.86 (0.76-0.91)/ NR/NR	W: 1.35 (NR) M: 0.26 (NR)	NR/NR/NR	NR	2016/NR
Japan (Tokachi), 2017	0.34	Hospital Registry	NR	Live-cell CBA (100%)	4.1 (2.2-6.9)/3.2 (NR)/0.9 (NR)	NR	NR/NR/NR	NR	March 2016/NR
Spain (Catalonia), 2018	7.52	Neurology hospital registry, laboratories	81% Caucasian, 11% LatAm, 3% African, 3% Asian, 3% Arab	Live-cell CBA (96%), IHC (3%), ELISA (1%)	0.89 (0.87-0.91)/0.64 (0.62-0.65)/0.25 (0.24-0.26)	W: 1.31 (1.27-0.34) M: 0.46 (0.44-0.48)	0.063 (0.045-0.081)/0.046 (0.03-0.061)/0.017 (0.008-0.027)	W: 0.09 (0.06-1.21) M: 0.035 (0.016-0.054)	January 2016/2006-2015
Central Denmark, 2018	1.27 (2012)	Neurology hospital registry	NR	ELISA (100)/ Fixed-cell CBA (100)	NR/NR/NR	NR	0.12 (NR)/NR/NR	NR	NR/January 2012 - December 2013
Denmark (whole country), 2018	4.59	National patient registry, National MS registry, laboratories, neurology hospital registry	89.3% Caucasian, 7.1% Asian, 1.8% Arab, 1.8% African.	Live/Fixed-cell CBA (79.5) IP (13.7) ELISA (6.8)/	1.09 (0.81-1.44)/0.76 (0.53-1.06)/0.32 (0.18-0.54)	W: 1.76 (1.26-2.39) M: 0.39 (0.18-0.76)	0.07 (0.05-0.1)/0.05 (0.03-0.07)/0.02 (0.01-0.04)	W: 0.1 (0.06-0.16) M: 0.04 (0.02-0.08)	January 2014/ January 2007-December 2013
Penang Island (Malaysia), 2018	0.702	Penang General Hospital Records	93% Chinese, 7% Malaysian	Fixed-cell CBA (100)	1.99 (1.09-3.35)/1.99 (1.09-3.35)/0	W: 1.99 (1.09-3.35) M: 0	NR/NR/NR	NR	July 2017/NR
United Arab Emirates (Abu Dhabi), 2018	2.9	Hospital Registry	NR	NR	0.34 (NR)/NR/NR	NR	0.05 (NR)/NR/NR	NR	2016/2010-2016
Malaysia (whole country), 2019	28.7	Hospital Registry/ Ministry of Health and MS societies	47.% Malaysian, 46.9% Chinese, 3.5% Indian, 2.3% others	NR	1.94 (1.77-2.1)/ NR/NR	NR	0.39 (0.35-0.47)/ NR/NR	NR	December 2017/January 2013-December 2017
Hungary, 2020	6.4 (> 16 years)	National patient registries, neurology hospital registries and laboratories	86.4% Caucasian 5.2% Romany, 8.4% unknown	Fixed-cell CBA (100)	1.91 (1.52-2.28)/1.61 (1.31-1.95)/0.31 (0.19-0.48)	W: 3.22 (2.65-3.89) H :0.47 (0.25-0.78)	0.13 (0.11-0.16)/1.15 (0.92-1.42)/0.17 (0.09-0.29)	W: 0.22 (0.18-0.27) M: 0.04 (0.02-0.06)	January 2016/ January 2006-December 2016

Table I. Epidemiological data on the neuromyelitis optica spectrum from studies conducted according to the 2015 criteria *(cont.)*.

	Population (million inhabitants)	Source of the register	Origin of patients with NMOSD	Antibody diagnostic technique (%)	Prevalence/105 inhab (95% CI) (total cohort/ AQP4+/AQP4–)	Prevalence/105 inhab (95% CI) by sex	Incidence/ 105 persons/year (95% CI) (total cohort/ AQP4+/AQP4–)	Incidence/ 105 persons/year (95% CI) by sex	Period of prevalence/ incidence
Venezuela (central and western regions), 2020	11.77 (2015)	National registry	86.7% mixed race, 7.2% Caucasian, 4.8% Native American, 4.8% Afro-Venezuelan	Live-cell CBA (100)	2.11 (1.85- 2.37), NR/NR	NR	NR/NR/NR	NR	2006-2015/NR
Oxfordshire, 2020	0.65 (2011)	Neurology hospital registry	81.8% Caucasian, 18.2% Afro-Caribbean	Live-cell CBA	1.6 (0.8-2.9)/1.2 (0.5-2.3)/0	W: 2.3 (1.0-4.6) M: 0.9 (0.2-2.6)	0.25 (0.08-0.58)/ NR/NR	NR	July 2018/2015-2018

AQP4⁺: aquaporin-4 serostatus positive; AQP4⁻: aquaporin-4 serostatus negative; CBA; cell-based assay; CI: confidence interval; ELISA: enzyme-linked immunosorbent assay; IHC: immunohistochemistry; inhab: inhabitants; IP: immunoprecipitation; LatAm: Latin American; M: men; MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum; NR: not reported; persons/year: incident cases reported in persons/year; W: women.

[24-26], and in the European studies from Spain, Denmark and Hungary [19,21,22]. Regarding the epidemiological data according to age range, the peak prevalence and incidence was found in patients aged 40-59 years for both sexes in the two studies that reported it [19,22] (Table II).

Finally, the few studies that provide data stratified by serostatus report higher prevalence figures in Asia than in Europe for anti-AQP4 patients. The prevalences of NMOSD patients with anti-AQP4 were 1.99 (95% CI: 1.09-3.35) and 3.2 (95% CI: not reported) in the studies from Japan and Penang Island, Malaysia [25,26], respectively, compared with prevalences of 0.76 (95% CI: 0.53-1.06), 1.2 (95% CI: 0.5-2.3) and 1.61 (95% CI: 1.31-1.95) per 100,000 inhabitants in the Danish, Hungarian and Oxfordshire studies, respectively [21-23]. The study conducted in Catalonia reported a progressive increase in the prevalence figures of patients with NMOSD with anti-AQP4 parallel to age, with a peak of 0.89 (95% CI: 0.85-0.92) per 100,000 inhabitants aged 40-59 years [19] (Table II). This same study showed that anti-AQP4 is more prevalent in women than in men in all age ranges, especially in the 40-59 age range – women, 1.43 (95% CI: 1.36-1.5) versus men, 0.35 (95% CI: 0.32-0.39) [19]. In contrast, if we focus on seronegative patients with NMOSD, the prevalence in men and women was similar for most age ranges [19].

Regarding the incidence according to serostatus, only European studies are available. The incidences of NMOSD patients with anti-AQP4 were 0.05 (95% CI: 0.03-0.07) in Denmark [21] and 1.15 (95% CI: 0.92-1.42) in Hungary [22]. The study in Catalonia showed a progressive increase in the incidence of patients with NMOSD with anti-AQP4 parallel to age, which was 0.062 (95% CI: 0.028-0.096) per 100,000 persons/year in the range of 40-59 years [19]. Again, the incidence was higher in women than in men in all the age groups [19].

Epidemiology of neuromyelitis optica spectrum in Latin America

Main studies

Several studies have estimated prevalence or incidence figures for NMOSD in Latin America; however, as previously mentioned, there is currently only one that has used the 2015 diagnostic criteria to estimate prevalence [30]. It is a multicentre retrospective study conducted in the central and western regions of Venezuela (Table II). A total of 249 cases were identified using information from the medical records of the hospitals in the areas studied, which was then contrasted with that included in the registry of the National Multiple Sclerosis Programme to avoid duplicates. Regarding demographic characteristics, a higher proportion of women was observed (n = 206; 82.7%). The population was young, with a mean age of 34 years,

Figure. Prevalence of NMOSD according to the 2015 NMOSD criteria. Islands belonging to the Lesser Antilles are shown enlarged and framed in red. The island highlighted in red is Martinique, where a NMOSD prevalence of 10.0 (CI: 95%; 6.8-13.2) per 100,000 inhabitants has been reported.

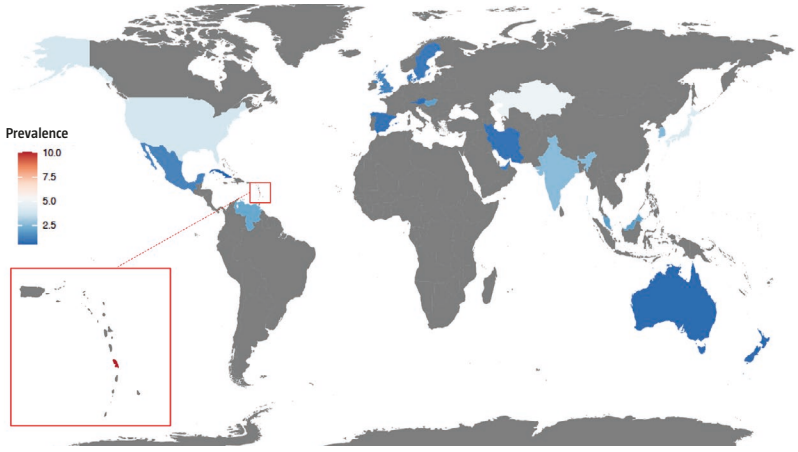

Table II. Prevalences and incidences of neuromyelitis optica spectrum stratified by age and sex in studies conducted according to the 2015 diagnostic criteria.

	Population (million inhab) (age groups and sex)		Prevalence/10^5 inhab (95% CI)	Incidence/ 10^5 persons/year (95% CI)
Catalonia (Spain), 2018	18-39	Women	1.36 (1.29-1.43)	0.131 (0.065-0.197)
		Men	0.28 (0.2 -0.32)	0.016 (−0.006-0.039)
	40-59	Women	1.79 (1.71-1.87)	0.126 (0.057-0.194)
		Men	0.7 (0.65-0.5)	0.057 (0.011-0.103)
	> 60 years	Women	1.39 (1.32- 1.47)	0.032 (−0.004-0.068)
		Men	0.64 (0.58-0.69)	0.041 (−0.005-0.088)
Hungary, 2020	18-39	Women	2.95 (2.04-4.12)	2.35 (1.6-3.34)
		Men	0.5 (0.18-1.08)	0.22 (0.045-0.64)
	40-59	Women	4.77 (3.55-6.27)	3.5 (2.47-4.8)
		Men	0.58 (0.21-1.26)	0.59 (0.22-1.28)
	> 60 years	Women	2.07 (1.33-3.08)	1.64 (0.95-2.62)
		Men	0.26 (0.03-0.94)	0.3 (0.036-1.08)

CI: confidence interval; inhab: inhabitants.

and the mixed race population was the most affected (n = 206; 86.7%). On interpreting the results it should be noted that in Venezuela it is difficult to determine the presence of anti-AQP4 in all the patients studied, while it is currently not possible to determine anti-MOG. The estimated prevalence was 2.11 (95% CI: 1.85-2.37) cases of NMOSD per 100,000 inhabitants.

The pre-2015 study that may be most similar to the Venezuelan study is the one comparing incidence and prevalence in Martinique with that of Olmsted County, Minnesota, United States [32]. In this study, the authors used 2006 criteria or selected patients with positive anti-AQP4 determination and one or more of the following syndromes that did not meet the 2006 criteria: simple or recurrent transverse myelitis, monophasic or recurrent optic neuritis, brainstem attack or cerebral (hemispheric) attack. Incidence was calculated using the periods 1st January 2003 to 31st December 2011, while prevalence was calculated as of 31 December 2011. It should be noted that these estimates were obtained by standardising by sex and age based on the total US population in 2010 and that four age groups were used (0-18, 19-39, 40-64 and 65 years and older). The demographic characteristics of the Martinique cases are very similar to those of the Venezuela study in terms of the proportion of women affected and age of onset, taking into account the different way of measuring age as the mean or median (Tables I and II). In the case of Martinique, however, the large proportion of Afro-Caribbean patients (n = 38/39; 97%) stands out, which most likely explains the results. The incidence per 100,000 persons/year was 0.73 (95% CI: 0.45-1.01), while the prevalence per 100,000 inhabitants was 10 (95% CI: 6.8-13.2). These results contrast with those of the Olmsted County cases, with a predominantly Caucasian population (n = 5/6; 83%), which demonstrated an incidence of 0.07 (95% CI: 0-0.21) per 100,000 persons/year and a prevalence of 3.9 (95% CI: 0.8-7.1) per 100,000 inhabitants.

Other studies in chronological order

In the following, in-depth details are given about the main studies carried out on the prevalence or incidence of NMOSD in Latin America. First, the demographics of Mexico will be discussed. Second, we will focus on the Caribbean basin, which includes the French islands of Martinique and Guadeloupe, and their comparison with the demographic data in Cuba. Subsequently, the Central American studies conducted in Panama and Costa Rica will be mentioned. Finally, we will detail the prevalence data in Brazil (Table III).

In Mexico, a retrospective study was conducted at a single tertiary care centre in Mexico City [33].

After reviewing the medical records of patients diagnosed with inflammatory demyelinating diseases of the central nervous system, 34 patients were identified with NMO according to the 1999 criteria [34]. As in previous studies, the proportion of affected women was higher (n = 24; 70.6%) and the mean age of onset was 34 years. All patients were of mixed race. Based on the total population of Mexico City in 2005, the prevalence of NMOSD was estimated at 1.3 (95% CI: 0.9-1.8) per 100,000 inhabitants. Unfortunately, at the time of the study it was not possible to determine anti-AQP4 antibodies. Another important consideration when interpreting these results is that the study was based on information included in the medical records of a reference centre and not in a population registry, so the characteristics of the patients studied in that centre may not be representative of the population with NMOSD in Mexico.

Special mention should be made of the Caribbean Basin. Incidence and prevalence studies have been conducted in Martinique in conjunction with populations on other Caribbean islands or, as described above, with Olmsted County in the United States. The first estimate of the prevalence of NMO in Martinique was conducted as part of a study focused primarily on the epidemiology of multiple sclerosis in an Afro-Caribbean population [35]. Initially, 11 patients diagnosed with NMO were identified; the prevalence of NMO was estimated to be 3.1 per 100,000 inhabitants (95% CI: 1.5-5.5). Another study estimated the incidence and prevalence of NMO in the French West Indies (Martinique and Guadeloupe), as well as the prevalence in Cuba [36]. The 1999 criteria were used because of difficulties in performing antibody and MRI studies in the populations under study at that time and a total of 98 patients were identified. The general characteristics were described by aggregating the data from the French West Indies and Cuba, although it is noted that, despite not being statistically significant, the mean age at onset was lower in Hispanic patients (28.7 years) than in Afro-Caribbean patients (31.8 years). The higher proportion of affected females was most apparent in their 30s and 40s. Incidence was reported only in the French West Indies by dividing the time of the study into three periods, and was found to be virtually unchanged between 1992-1997 (0.22), 1997-2002 (0.18) and 2002-2007 (0.2), with an incidence of 0.19 per 100,000 inhabitants (95% CI: 0.19-0.23) between 1992 and 2007 [36,37]. Conversely, between the periods 1992-1997 and 2002-2007 there was an increase in the prevalence of NMO from 1.88 (95% CI: 0.82-2.94) to 4.2 (95% CI: 2.7-5.7) per 100,000 inhabitants, most likely due to a decrease in mortality in Martinique and Guadeloupe over the years. This contrasts with the estimated prevalence of NMO in Cuba in 2004, which was 0.52 (95% CI: 0.39-0.67) per 100,000 inhabitants [36]. One of the causes of this difference could be the origin of the population, which in the French Antilles is predominantly of African descent with a weak interbreeding with a population of European origin, whereas in the Cuban study the proportion of Afro-Caribbeans is much lower [38]. In both populations there is a higher prevalence of NMO in women. In the French West Indies the prevalence in women increased from 3.35 (95% CI: 1.37-5.28) in July 1992 to 7.14 (95% CI: 4.45- 9.83) in June 2007. When stratified by age group, prevalence ranged from 3.1 in the 55-65 age group to 16.7 in the 45-65 age group, while in men prevalence ranged from 0 in several age groups to 4.8 in the 25-35 age group. In Cuba, the prevalence in women was estimated at 0.91 (95% CI: 0.68-1.2), while in men it was 0.12 (95% CI: 0.05-0.25) [36].

The results of the Cuban study are described in more detail in another publication focusing exclusively on that country [38]. As in the other studies, women accounted for the majority of cases and the median age was 30.5 years. Just over half of the cases were of Caucasian origin, one third were of mixed race and just over 15% were Black. In addition to the above-mentioned study of the prevalence in the total population according to the 1999 NMO diagnostic criteria, it was also evaluated according to ethnicity, without finding any significant differences, a result that the authors attribute to the small sample size. The annual incidence per 100,000 inhabitants was also presented and was estimated at 0.053 (95% CI: 0.04-0.068). As in the case of prevalence, no differences in incidence were observed when stratifying by ethnicity.

Several studies have been conducted in Central America and published in Spanish. One of them was carried out in Panama using the 2006 diagnostic criteria to estimate incidence and prevalence [39]. Based on a sample of 13 patients, the annualised incidence per 100,000 inhabitants was estimated to be between 0.03 and 0.11, and the prevalence was 0.29 per 100,000 inhabitants. The other study was conducted in Costa Rica, also using the 2006 criteria, and found an annualised incidence between 0.08 (95% CI: 0.01-0.43) and 0.3 (95% CI: 0.14-0.66) per 100,000 inhabitants [40]. One thing these two studies have in common is that roughly two thirds of the cases were women,

Table III. Latin American epidemiological studies on the prevalence and/or incidence of the neuromyelitis optica spectrum.

	Period of study	Sources of the register	Cases of NMOSD, *n* (criteria)	Women, *n* (%)	Age at onset	Origin of patients with NMOSD, *n* (%)	Proportion of anti-AQP4 antibodies, *n* (%)	Antibody diagnostic technique	Incidence/105 persons/year (95% CI)	Prevalence/105 inhab (95% CI)
Martinique (versus Olmsted County, United States), 2016	2003-2011	Insurance records, neurology hospital registries and MS patients associations	39 (2006, other definitions)	36 (90)	35 (14-82)[b]	Negro: 38 (97) Caucasian: 1 (3)	31 (79%)	Flow cytometry	0.73 (0.45-0.1)	10 (6.8-13.2)
Mexico City, Mexico 2008	1993-2005	Hospital Registry	34 (1999)	24 (70.6)	34[c]	Mixed race: 34 (100)	NR[d]	NR	NR	1.3 (0.9-1.8)
French Antilles and Cuba, 2009	1992-2007 and 2003-2004	Hospital registries, primary care, social security departments, patients associations	98 (1999)	9.8[f]	30.9 (11-74)[f]	Afro-Caribbean: 68 (69.4) Spain: 30 (30.6)	NR	NR	French Antilles: 1992-1997: 0.22 (0.06-0.38) 1997-2002: 0.18 (0.04-0.32) 2002-2007: 0.2 (0.05-0.35)	French Antilles: 4.2 (2.7-5.7) Cuba: 0.52 (0.39-0.67)
Cuba, 2009	2003-2004	Hospital registries, primary care, national MS registry, patients associations, clinical trials registries	58 (1999)	51 (87.9)	30.5 (11-62)[b]	Caucasian: 31 (53.4) Mixed race: 18 (31) Black: 9 (15.5)	NR	NR	0.053 (0.04-0.068)	0.52 (0.39-0.67)
Panama, 2014	2005-2012	National registry	13 (2006)	9 (69.2)	35.5 (12.2)[a]	Mixed race: 5 (38.5) Of African descent: 4 (30.8) Caucasian: 3 (23.1) Oriental: 1 (7.6)	4/4 (100.0)	ELISA	0.03 to 0.11 (95% CI not reported)	0.29
Costa Rica, 2018	2011-2015	Hospital Registry	40 (2006)	25 (62.5)	35.5 (16-66)[b]	NR	15/23 (65.2)	ELISA	From 0.08 (0.01-0.43) to 0.3 (0.14-0.66)	NR

AQP4: aquaporin 4; CI: confidence interval; ELISA: enzyme-linked immunosorbent assay; inhab: inhabitants; MOG: myelin oligodendrocyte glycoprotein; MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum; NR: not reported. [a] Mean (standard deviation); [b] Median (range); [c] Mean (standard deviation not reported); [d] Antibody determination was not possible locally at the time of the study; [e] women:men ratio; [f] Mean and range are reported.
This table does not include the epidemiological study of Venezuela, since the 2015 criteria were used (Table I).

that the mean or median age was 35.5 years, that there were difficulties in testing for anti-AQP4 in all patients and that when this was achieved it was by ELISA, as well as having similar incidence estimates. As regards ethnicity, the Panama study had a small sample size, but patients of African descent and mixed race predominated. The Costa Rican study does not present the distribution by ethnicity. However, the author does mention the fact that the Costa Rican population is mixed. According to a genetic study conducted in this country in 2013, which included 160 men, 45.6% were of European descent, 33.5% were Native American, 11.7% were of African origin and 9.2% were Chinese [41]. These proportions could vary in some of the provinces of Costa Rica, so it is striking that Limón, the province with the highest prevalence of people of African descent, did not

have the highest incidence (0.2, 95% CI: 0.07-0.58) [40]. Possible explanations for this finding include the difficult access to health systems in rural areas, farther away from the centre of the country (although the population studied represents 85.5% of the Costa Rican population), the possibility that NMO goes underdiagnosed due to the difficulty of accessing the determination of AQP4-IgG or possible diagnostic errors.

Finally, we should mention a prevalence study with few available data conducted in a city in the state of Rio de Janeiro in Brazil. One Caucasian woman with anti-AQP4 was identified and a crude prevalence of 0.39 per 100,000 inhabitants was estimated [42].

Relative frequency of the neuromyelitis optica spectrum compared to multiple sclerosis

Partly due to the difficulties related to the methodology and access to diagnostic tests mentioned earlier, in Latin America the relative frequency of NMOSD is commonly assessed with respect to multiple sclerosis in epidemiological studies. This is calculated by dividing the total number of cases of NMOSD by the sum of the cases of NMOSD and multiple sclerosis [43]. Relative frequencies have been reported ranging from 6.8% in Sao Paulo, Brazil, 8% in Mexico and 20.5% in Rio de Janeiro to 27% in Martinique [43]. In a study involving South American populations from Caracas, Venezuela, to Buenos Aires, Argentina, the relative frequency of NMOSD to multiple sclerosis was calculated. The results revealed a descending north-south gradient, with a relative frequency of NMOSD of 43.2% in Venezuela, 14% in Brazil, 8.7% in Paraguay and 2.1% in Argentina, which tallied with a higher proportion of non-Caucasian patients in Venezuelan cities (79.3%) in the north and a lower proportion of non-Caucasians in Buenos Aires (1%) in the south [44].

Epidemiological studies in disease associated with myelin oligodendrocyte glycoprotein

Approximately 20% of adult patients with anti-MOG-associated disease meet the 2015 NMOSD criteria [12]. The remaining patients have an opticospinal clinical phenotype without fulfilling NMOSD criteria [9,45] or varied clinical phenotypes: cortical encephalitis with or without epileptic seizures [46-49], monophasic or recurrent acute disseminated encephalomyelitis [50] or cranial nerve involvement [51]. The course of patients with anti-MOG-associated disease is relapsing in 70-93% of cases, although it depends on the age of onset, and generally has a good prognosis compared to that of patients with anti-AQP4 [12,13].

Five population studies (Catalonia, the Netherlands, Oxfordshire, Martinique and Brazil) have analysed the epidemiology of anti-MOG-associated disease [19,23,52-54]. In the epidemiological study conducted in Catalonia, which evaluated both children and adults, 12% of patients meeting the 2015 NMOSD criteria were anti-MOG positive in serum. Focusing on adults, both prevalence and incidence increased progressively in parallel with age: prevalence/incidence from 0.1 (95% CI: 0.08-0.11)/0.008 (95% CI: –0.003-0.002) in the 18-39 years range to 0.22 (95% CI: 0.2-0.24)/0.014 (95% CI: –0.002-0.031) in the 40-59 years range per 100,000 inhabitants and 100,000 person-years, respectively [19]. Compared to this last study, which only included patients who met the 2015 criteria, other population-based studies have reported higher incidences. The mean incidences in the Dutch and English (Oxfordshire) studies were 0.016 (95% CI: 0.011-0.023) and 0.034 (95% CI: 0.014-0.069) per 100,000 persons/year, respectively [23,52]. For the calculation of estimates in children, and unlike the Spanish and the English studies, where the reference was the whole population, the Dutch study took only the child population as a reference. In this case, the incidence of patients with anti-MOG was higher in this group in children (0.31; 95% CI: 0.17-0.51) than in adults (0.13; 95% CI: 0.08-0.19) per 100,000 persons/year [23].

It is important to note that, in contrast to what was observed in NMOSD and anti-AQP4 patients, a recent study has shown a higher prevalence (3.42; 95% CI: 0.42-6.4) and incidence (0.24; 95% CI: 0-0.51) of anti-MOG-associated disease in the Caucasian population (Olmsted County, USA) compared to that observed in the Afro-Caribbean population (Martinique, France) –prevalence, 1.6 (95% CI: 0.3-2.9) per 100,000 inhabitants; incidence, 0.11 (95% CI: 0.002-0.22) per 100,000 persons/year [54]–. Along the same lines, a recent study conducted in the population of Rio de Janeiro, Brazil, confirmed the low prevalence of anti-MOG-associated disease in non-Caucasian populations and found a lower proportion of patients with anti-MOG among those with idiopathic demyelinating diseases (3%) or those with NMOSD according to 2015 criteria (7.4%) [53].

Epidemiological factors involved in the prognosis of the disease

Several epidemiological factors have been related to the prognosis of the disease, both in terms of disability (visual or motor) and in relation to the risk of relapses (Table IV).

In patients with anti-AQP4-positive NMOSD, being Black has been associated with younger age at symptom onset, optic neuritis as the initial manifestation and a higher likelihood of developing visual impairment compared to White and Asian patients [3,55]. In a study of two North American hospital cohorts of patients with NMOSD, Black patients also had a higher mortality rate than White patients, despite their similarity in age, sex, serostatus, time to diagnosis or acute treatment [56]. Another study involving anti-AQP4 seronegative and seropositive NMOSD patients in Brazil found an association between being Black and higher levels of disability, both at diagnosis and at the end of follow-up [57]. Being of Asian origin has also been associated with younger age at disease onset and lower risk of relapse (except for attacks affecting the trunk) [55,58]. Studies that included White and mixed-race Latin American patients found no differences in disability between races [59,60]. Genetic factors (in addition to environmental factors), especially variations in genomic regions involved in the major histocompatibility complex, have been suggested to explain these differences between races, although no conclusions have been reached. The DRB1*03 allele seems to be associated with anti-AQP4 patients in the White European population [61], while a recent study in a Mexican population showed an increased susceptibility for NMOSD in Native American patients carrying DQB1*03:01, DRB1*08:02 or DRB1*16:02 alleles [62].

Being female appears to confer an increased risk of attack and disability in patients with anti-AQP4-positive NMOSD [55].

In relation to age, numerous studies including patients of different races have shown an association between older age at disease onset and worse functional prognosis, both visual and motor [2,55,58,60]. Late disease onset, above the age of 50 years, has also been associated with a worse prognosis compared to patients who start below that age [16,59].

On the other hand, the underlying antibody in NMOSD is a prognostic marker of the disease showing that anti-MOG patients constitute a specific subgroup with a better functional prognosis compared to anti-AQP4 or double seronegative patients [2,12]. Interestingly, in patients with NMOSD diagnosed according to the 2006 diagnostic criteria, no prognostic differences were found between anti-AQP4 positive and negative patients [2,63].

Finally, it should be noted that, in NMOSD, the occurrence of attacks was identified as an independent factor with a poor prognosis [55,58,64], as was residual disability remaining from the first event [2,65]. In this regard, in anti-AQP4-positive patients, initiating immunosuppressive treatment after the first event and before the first relapse was associated with a longer time to the first relapse [55], while delaying the initiation of immunosuppressive treatment was an independent risk factor for increased disability [58].

Conclusions

Current data on the epidemiology of NMOSD vary substantially from one study to another. The use of different methodological designs seems to be the fundamental cause of the discrepancies observed, despite the fact that racial factors influence the prevalence/incidence of the disease. In this sense, epidemiological data available from Latin American or African countries are scarce in comparison to other parts of the world. The homogenisation of criteria, the use of high-precision diagnostic techniques and stratification by sex and race are essential in order to have comparable epidemiological studies.

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Tabla IV. Main studies in patients with neuromyelitis optica spectrum that have included analyses of prognostic factors.

	Population	No. of patients Ethnicity	Age at onset % of women	Inclusion criteria/ anti-AQP4 determination	Factors associated to the EDSS 6.0	Factors associated with blindness	Factors associated with mortality
Carnero et al, 2020	Argentina Brazil Venezuela	140 82 White 17 Black 39 mixed race 1 Asian 1 Native American	38.2 (13.8)[a] 86%	dc 2015/CBA, IFI	Older age at onset (positive correlation between age at onset and final EDSS, r = 0.34, $p < 0.0001$)	–	–
Palace et al, 2019	United States United Kingdom Martinique Japan	441 210 White 115 Black 100 Asian 11 Latin American 5 mixed race	41.2 (15.4)[a] 89%	Only patients anti-AQP4+/CBA	Female, HR 1.52, $p = 0.027$ Age < 35 years at onset, HR 0.33, $p < 0.001$	Black, HR 1.72, $p < 0.001$ Female HR 1.63, $p = 0.002$ Age < 35 years at onset, HR1.48, $p = 0.009$ Optic neuritis at onset, HR 3.81, $p < 0.001$	Asian, HR 0.29, $p = 0.02$ Age < 35 years at onset, HR 0.33, $p = 0.002$
Sepúlveda et al, 2019	Spain	238 204 Caucasian 24 Latin American 2 Black 4 Asian 4 Arab	41 (10-84)[b] 89%	dc 2015/CBA	Older at onset, HR 1.63, $p < 0.001$ Residual disability after first attack, HR 1.57, $p = 0.001$ Annualised relapse rate, HR1, 58, $p = 0.009$ Seronegative (only in patients with onset > 50 years), HR 3.74, $p = 0.045$	–	–
Fragoso et al, 2019	Brazil	153 71 Caucasian 81 Black 1 Asian	28 (6-63)[b] 80%	dc 2015/IFI	Black ($p < 0.001$, Fisher Test)	–	–
Kim et al, 2018	Denmark Germany Korea United Kingdom United States Thailand	603 304 Asian 207 White 92 Black	38.2 (16)[a] 89%	dc 2015/CBA, ELISA	Older age at onset, OR 1.05 (CI 95%:1.034-1.067) Greater number of attacks, OR 1.133, (CI 95%: 1.075-1.193)	Longer disease duration, OR 1.05, (CI 95%: 1.011-1.09) Greater number of attacks before treatment, OR 1.125 (CI 95%: 1.059-1.194) Optic neuritis at onset, OR 5.61, (CI 95%: 3.746-8.394)	
Uribe-San Martín et al, 2017	Chile	36 White Mixed race	44 (16.2)[a] 81%	dc 2015/CBA	Age at onset > 50 years, OR 45.8, $p = 0.006$ Receive rituximab, OR 7.6, $p = 0.02$	–	–
Sepúlveda et al, 2016	Spain	181 155 White 19 Latin American 2 Black 3 Asian 2 Arab	39 (10-77)[b] 87%	dc 2006/CBA	Non-Caucasian race, HR 4.3, $p < 0.012$ Older at onset, HR 1.7, $p < 0.0001$ Greater residual disability after first attack, HR 1.3, $p = 0.017$	Older at onset, OR 1.9, $p = 0.005$ Greater residual disability after first attack, OR 1.7, $p = 0.015$	–
Jiao et al, 2013	United States	159 102 White 57 non-White	39 (5-71)[b] 86%	dc 2006/IFI, CBA	Older at onset, HR 1.32, $p = 0.006$	Optic neuritis at onset, HR 1.92, $p = 0.004$ Non-Caucasian race, HR 1.67, $p = 0.02$	–
Kim et al, 2012	Korea	106 106 Asian	32 (7-59)[b] 91%	Dc 2006/ELISA, CBA	Delay > 4 years at start of immunosuppressants, OR 5.1, $p = 0.003$	–	–

Tabla IV. Main studies in patients with neuromyelitis optica spectrum that have included analyses of prognostic factors *(cont.)*.

	Population	No. of patients Ethnicity	Age at onset % of women	Inclusion criteria/ anti-AQP4 determination	Factors associated to the EDSS 6.0	Factors associated with blindness	Factors associated with mortality
Kitley et al, 2012	United Kingdom Japan	106 45 White 12 Black 47 Asian	40.5 (3-77)[b] 87%	Only anti-AQP4+/ CBA	White (only versus Asian), HR 3.85, $p = 0.001$ Greater age at onset, HR 1.82, $p < 0.001$ Onset as myelitis, HR 3, $p = 0.004$ (only in the United Kingdom cohort)	Male sex, HR 4.9, $p = 0.003$ Black, HR 1.83, $p = 0.046$ Onset with optic neuritis, HR 4.31, $p = 0.023$	Greater age at onset HR 2.12, $p = 0.003$ Asian with lower risk than White, HR 0.177, $p = 0.032$

CBA: cell-based assay; dc: diagnostic criteria; EDSS: Kurtzke expanded disability status scale; ELISA: enzyme-linked immunosorbent assay; HR: hazard ratio; IFI: indirect immunofluorescence; OR: odds ratio. a Means (standard deviation); b Median (range).

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Epidemiología del espectro de neuromielitis óptica. Nuevos y viejos desafíos

Introducción. La presente revisión epidemiológica sobre el espectro de neuromielitis óptica (NMOSD) se focaliza en la descripción metodológica de los estudios realizados bajo los criterios del NMOSD de 2015, en la descripción de estudios realizados en España y Latinoamérica, así como en los factores relacionados con el pronóstico de la enfermedad.

Desarrollo. La metodología utilizada en los estudios varía fundamentalmente en la aplicación de diferentes criterios diagnósticos, fuentes de registros, técnicas de detección de anticuerpos y métodos de estandarización. Sin embargo, en términos generales, el NMOSD tiene una distribución mundial con una mayor incidencia/prevalencia en las mujeres que en los hombres, y en los países asiáticos y afroamericanos que en los países occidentales. La frecuencia aumenta de manera paralela a la edad, con un pico de incidencia/prevalencia en el rango entre 40 y 59 años. La población latinoamericana presenta unas características epidemiológicas particulares ligadas a su mezcla racial y genética. Finalmente, variables epidemiológicas, como la raza negra, una mayor edad en el inicio y el sexo femenino, se asocian a un peor pronóstico funcional.

Conclusiones. Los datos epidemiológicos del NMOSD varían entre los diferentes estudios, debido, en gran parte, a discrepancias en los diseños metodológicos. Aunque son escasos los estudios latinoamericanos, los hallazgos descritos se asocian a su mezcla étnica. La homogeneización de criterios, utilización de técnicas diagnósticas y métodos de estandarización similares es de fundamental aplicación para el correcto estudio de la epidemiología del NMOSD.

Palabras clave. Anticuerpos acuaporina-4. Anticuerpos anti-MOG. Criterios de NMOSD. Epidemiología. Latinoamérica. NMOSD.