



ORIGINAL ARTICLE

The prevalence, incidence, and clinical assessment of neuromyelitis optica spectrum disorder in patients with demyelinating diseases



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KEYWORDS

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Abstract

Background: Neuromyelitis optica spectrum disorder (NMOSD) is characterised by recurrent attacks of optic neuritis and transverse myelitis. The purpose of this work was to identify the incidence and prevalence of NMOSD and its clinical characteristics in the population treated for demyelinating diseases in Western Mexico.

Material and method: A descriptive, retrospective study was carried out in the Department of Neurology, at the Sub-specialty Medical Unit, Specialties Hospital (known by its Spanish abbreviation *UMAE-HE*), of the National Western Medical Center (*CMNO*), Mexican Institute of Social Security (*IMSS*). A review of the electronic files for all patients with a diagnosis of NMOSD in 2019, was carried out in the State of Jalisco, Mexico.

Results: Fifty-eight patients with NMOSD were included in the study. The incidence was 0.71/100 000 (CI 0.60-0.85) and the prevalence was 1.09/100 000 (CI 0.84-1.42). There were 79.3% women, and 20.6% were men ($P = .01$). All (100%) patients presented with anti-aquaporin-4 immunoglobulin G, and 89.6% showed seropositivity for anti-aquaporin-4 (CI 82.6-94.9). Magnetic resonance imaging was performed on 100% of patients, where 34.4% were normal, and 65.5% (38) abnormal, presenting with non-specific subcortical lesions ($P = 0.04$). The initial clinical presentation was optic neuritis (ON) in 58.6%; where 31.0% was bilateral ON, 20.7% was left ON, and 6.9% were right ON; transverse myelitis in 26.0%, area postrema syndrome (APS) in 10.3%, among others.

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PALABRAS CLAVE

Neuromielitis óptica;
Prevalencia;
Incidencia

Conclusions: The incidence of NMOSD exceeds 0.71/100 000, the prevalence is low at 1.09/100 000, and NMOSD is predominantly found in women.

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Prevalencia, incidencia y evaluación clínica del trastorno del espectro de la neuromielitis óptica en paciente con enfermedades desmielinizantes

Resumen

Antecedentes: El trastorno del espectro de la neuromielitis óptica (NMOSD por sus siglas en inglés) se caracteriza por ataques recurrentes de neuritis óptica y mielitis transversa. el propósito de este trabajo fue identificar la incidencia y prevalencia del NMOSD y sus características clínicas en la población tratada por enfermedades desmielinizantes en el occidente de México.

Material y método: Se realizó un estudio descriptivo retrospectivo en el departamento de neurología en la Unidad Médica de Alta Especialidad, Hospital de Especialidades (UMAE-HE), Del Centro Médico Nacional de Occidente (CMNO) México. Instituto Mexicano del Seguro Social (IMSS). Se realizó una revisión de los expedientes electrónicos de todos los pacientes con diagnóstico de NMOSD en 2019, en el estado de Jalisco, México.

Resultados: Cincuenta y ocho pacientes con NMOSD fueron incluidos en el estudio. La incidencia fue de 0,71/100,000 (IC 0,60–0,85) y la prevalencia fue de 1,09/100,000 (IC 0,84–1,42). El 79,3 eran mujeres y el 20,06 eran hombres ($P = 0,01$). Todos (100%) los pacientes presentaron inmunoglobulina G anti-acuaporina-4 y el 89,6% mostró seropositividad para anti-acuaporina-4 (IC 82,6–94,9%). Se realizó resonancia magnética al 100% de los pacientes siendo el 34,4% normales y el 65,5 % anormales, presentando lesiones subcorticales inespecíficas ($P = 0,04$). La presentación clínica inicial fue de neuritis óptica (NO) en el 58,6% donde el 31% eran bilaterales; el 20,7% eran izquierdos y el 6,9% eran derechos; mielitis transversa en el 26,0%; síndrome de área postrema (SAF) en el 10,3%.

Conclusiones: La incidencia de NMOSD supera el 0,71/100,000; la prevalencia es baja en un 1,09/100,000 y este se encuentra predominantemente en mujeres.

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Introduction

Demyelinating diseases of the central nervous system (CNS) are a group of conditions of autoimmune etiology affecting the myelin of the central and peripheral nervous systems.¹ The cause of primary demyelination is unknown: demyelination is usually secondary to metabolic disorders, ischaemia, or inherited disorders; however, most of the time, it is attributed to an autoimmune origin, since in many cases the onset of the condition is preceded by a non-specific viral infection.²

Neuromyelitis optica spectrum disorders (NMOSD), otherwise known as Devic disease, are a group of predominantly autoimmune inflammatory diseases of the CNS, characterised clinically by recurrent attacks of optic neuritis and transverse (longitudinally extended) myelitis, which have a defined clinical and imaging picture.³ At first, it was believed that NMOSD was a variant of multiple sclerosis, but today it is known to be a different disease characterised by the presence of specific antibodies against aquaporin-4 (AQP4 IgG),⁴ which is the most abundant water channel of the CNS, expressed in astrocyte foot processes associated with the capillaries, ventricular ependyma, and interneuronal synapses. This channel regulates the flow of water between the blood and brain,

and between the brain and the cerebrospinal fluid (CSF).⁵ Optic neuritis is usually bilateral, with great compromise to visual acuity. Myelitis can be longitudinally extensive and is usually severe, with bilateral motor involvement and in other regions such as the diencephalic area, the post-mammary area, and the brainstem.^{6,7} To determine the diagnosis of NMOSD, the criteria given by Wingerchuk at the end of 2015 are taken into account.³

The Sub-specialty Medical Unit (known in Spanish as the UMAE), which is part of the Specialties Hospital (HE) of the National Western Medical Center (Centro Médico Nacional de Occidente [CMNO]) of the Mexican Institute of Social Security (Instituto Mexicano del Seguro Social [IMSS]), is a tertiary-care hospital in the western region of the country. In Jalisco (located on the west coast), most disease-modifying treatments for individuals with demyelinating diseases are only available at this aforementioned hospital; therefore, all patients diagnosed at other levels of care are, theoretically, referred to the Department of Neurology at the UMAE-HE CMNO IMSS.

The aim of the present work was to identify the incidence and prevalence of NMOSD, as well as their clinical characteristics, in the population treated for demyelinating diseases at the Neurology Department in the UMAE-HE CMNO IMSS.

Materials and methods

This was a retrospective, descriptive study carried out at the UMAE CMNO IMSS. In order to perform the study, a review of the database in the electronic file system of the UMAE CMNO IMSS was carried out, including all patients with NMOSD whose diagnosis was made from 1 January to 31 December of 2019. Patients were living in the State of Jalisco. We included a total of 58 patient records. Patients were ensured that the international diagnostic criteria of Wingerchuk³ were taken into account, and that they met at least 2 of 3 criteria, which included: brain magnetic resonance imaging (MRI) (normal presentation or lesions that did not meet diagnostic criteria for MS), spinal cord MRI (extensive longitudinal transverse myelitis occupying three or more vertebral segments), and the detection of immunoglobulins (IgG-NMOSD) selective against AQP4 channels. It was ensured that all the available anti-AQP4 antibody results were performed using the enzyme-linked immunosorbent assay (ELISA) method.³ The study was approved by the local Ethics Committee of the CMNO, with registration number: R-2017-1301-125.

Statistical analysis

For the categorical variables, the results are expressed in the form of proportions and frequencies. For the numerical variables, the difference between the groups was estimated with the *t*-test. In all cases, a 95% confidence interval and a value of $P < .05$ were considered statistically significant. As measures of NMOSD disease frequency, we obtained the cumulative incidence (as an indicator of the speed of occurrence of NMOSD in 2019) and the prevalence proportion (as an indicator of the magnitude of the presence of NMOSD in the Neurology Department without distinguishing whether or not they were new cases).⁸ The data were analysed using the statistical package SPSS v. 11.0 for Windows.

Results

Fifty-eight (58) patients with NMOSD were studied, of whom 79.3% (46) were women, and 20.6% were men ($P = .01$). The mean age at onset of symptoms was 36 years (standard deviation [SD] 19.9), with no significant differences noted between sexes ($P = .12$). The mean age at diagnosis was 41 years (SD 14.1), with no significant differences noted between sexes ($P = .10$). All (100%) patients were residents of the State of Jalisco (Table 1).

The cumulative incidence in 2019 was 0.71/100 000 (CI 0.60–0.85) and the NMOSD prevalence ratio in our population was 1.09/100 000 (CI 0.84–1.42).

Initially, 31.03% of the patients had been diagnosed with multiple sclerosis (MS), and 25.8% of them received disease-modifying treatment for MS prior to the definitive diagnosis of NMOSD. In the present study population, 100% of patients had AQP4 IgG (using the ELISA method). Findings showed that 89.6% presented seropositivity for AQP4 (CI 82.6–94.9%). An MRI of the brain was performed in 100% of the study population: 34.4% were normal, and 65.5% were abnormal and presented with non-specific subcortical lesions ($P = .04$). In the spinal cord MRI, 38% showed no symptoms of myelitis or lesions; and 62.0% had transverse myelitis ($P = .04$), of which 44.8% had a cervical location, 8.6% thoracic location, and 8.6% cervical and thoracic locations, with significant differences in presentation of symptoms ($P = .03$) (Table 2).

The onset of symptoms began in 2019 in 24.1% (14) patients; and, even earlier in 39.6% of patients who were diagnosed in 2019. The initial clinical presentation was optic neuritis (ON) in 58.6%, with significant differences noted between sexes (0.04); where in 31.0% ON was bilateral, 20.7% left, and 6.9% right. To a lesser extent, patients had transverse myelitis (26.0%), APS (10.3%), ataxia (1.7%), and other symptoms (3.4%); with significant differences between symptoms ($P = .02$).

The clinical course of the disease was recurrent in 94.8% of the patients, while only 5.2% presented a monophasic course ($P = .01$) with less than 6 months of clinical follow-up.

The treatment of choice at the latest revision of the patients, was rituximab in 82.7%, mycophenolate mofetil in 10.4%, and azathioprine in 6.9% ($P = .00$), while 100% of patients diagnosed with NMOSD were on disease-modifying treatment (Table 3).

Discussion

The main objective of this study was to identify the incidence and prevalence of NMOSDs, as well as their clinical characteristics, in the population treated for demyelinating diseases at the Department of Neurology, UMAE CMNO IMSS. In relation to sex, we clearly see how NMOSD is a disease predominantly found in women.

Although we only have the cumulative incidence calculated for the year 2019, it is striking that our population had a higher incidence than that reported in other studies, except reports of studies in black populations, such as the Flanagan study,⁹ and another from southern Denmark¹⁰; while our incidence is almost three times that of the rest of the reports in mostly Caucasian populations.^{11,12} Interestingly, we could consider that our population had a low prevalence of the disease, while non-Caucasian populations like the Japan cohort report 4.1/100 000,¹³ Malaysia- 1.99/100 000,¹⁴ Iran- 1.9/100 000,¹⁵ and India- 2.6/100 000¹⁶ have a medium prevalence; and cohorts with black patients, such as the Martinique cohort, have a high prevalence of 10/100 000.¹⁷ Although this rule does not appear to be fulfilled in some Caucasian cohorts with a medium prevalence,^{18,19} these data suggest differences in the risk of NMOSD between populations with different genetic backgrounds. Nevertheless, to date, few studies, like the one by Flanagan et al., which describe Caucasian and black cohorts (3.9/100 000 vs. 10/100 000, respectively) and the study by Buhkari comparing Asian and non-Asian races (1.23/100 000 vs 0.44/100 000), have made this distinction notorious. In the Cuban cohort study,²⁰ although prevalences by race were analysed, no statistically significant difference was found between groups, possibly due to the smaller sample size of black subjects. In our study, all patients are Mexican mestizo, which could explain why the prevalence is higher than in most Caucasian populations, but lower than in black or Asian populations.

It is important to emphasise the difference between monophasic and recurrent forms of the disease. In 1999, Wingerchuck et al., described 67.6% of patients with recurrent disease, having at least 3 years of follow-up. Although other studies show marked heterogeneity in follow-up, and some describe neuromyelitis optica, and other NMOSDs, most studies have described recurrent forms in between 60% and 89% of patients, whereas in the present study it was 94.8%. In Mexico, the Rivera study¹² describes a monophasic course in 67% of the described cohort, while in the present study only 5.2% patients presented a monophasic course and all of them had a follow-up of less than 6 months. While it is very likely that in the study by Rivera et al. in 2008 the short follow-up time was an important reason for this higher percentage of monophasic forms of the disease, we hypothesise that monophasic forms are rare in our cohort because they are quite possibly underdiagnosed and so less referred to our medical unit. It should also be noted that the prevalence of NMOSD has increased markedly over time, and although prior to 2015 there were no NMOSD criteria, the retrospective evaluation of patients who fulfilled these criteria was also much lower with 1 to 2 patients per year, up to the year 2010. Since then, we have seen a noticeable increase, to the extent that 14 patients (corresponding to 24.1% of the present cohort), began having symptoms in 2019, and even more (23 patients, corresponding to 39.6% of the present study patients) were diagnosed in 2019, which shows a great increase in both detection and awareness of the disease. Nevertheless, this raises doubts as to whether in the past, many patients may not have been diagnosed, or were not referred to our medi-

Table 1 Sociodemographic data of NMOSD patients.

	Median	Women	Men	P-value
Sex (%)	—	79.3% (46)	20.6% (12)	*.01
Age at onset (years) mean (SD)	36 (19.9)	36 (16.8)	37 (19.7)	.12
Age at diagnosis (years) mean (SD)	41 (14.1)	40 (15.3)	41 (14.1)	.10

SD: standard deviation.

* statistically significant.

Table 2 Clinical status of NMOSD patients.

	Total n = 58 % (F)	Women n = 46 % (F)	Men n = 12 % (F)	P-value
IgG-AQP4				
Positive	100% (58)	100% (46)	100 % (12)	
Brain MRI				
No lesions or symptoms	34.5% (20)	30.4% (14)	50.0% (6)	*.04
Abnormal (non-specific brain lesions)*	65.5% (38)	69.5% (32)	50.0% (6)	
Spinal cord MRI				
No spinal symptoms or MRI lesions	38% (22)	32.6% (15)	58.3% (7)	*.04
Transverse myelitis	62.0% (36)	67.3% (31)	41.6% (5)	
- Cervical	44.8% (26)	52.1% (24)	16.6% (2)	*.03
- Thoracic	8.6% (5)	6.5% (3)	8.4% (1)	
- Cervical and thoracic	8.6% (5)	8.7% (4)	16.6% (2)	

MRI: magnetic resonance imaging; TM: transverse myelitis.

* White matter lesions not compatible with multiple sclerosis.

Table 3 Initial clinical presentation in NMOSD patients.

	Total n = 58 % (F)	Women n = 46 % (F)	Men n = 12 % (F)	P-value
First symptoms				
Optic neuritis	58.6% (34)	60.8% (28)	50.0% (6)	*.04
- bilateral	31.0% (18)	30.4% (14)	33.4% (4)	
Clinical presentation				
- left	20.7% (12)	23.9% (11)	8.3% (1)	*.02
- right	6.9% (4)	6.5% (3)	8.3% (1)	
Acute myelitis	26.0% (15)	23.9% (11)	33.4% (4)	
Area postrema syndrome	10.3% (6)	8.7% (4)	8.3% (1)	
Ataxia	1.7% (1)	2.2% (1)	8.3% (1)	
Other symptoms (hemiparesis, acute brain)	3.4% (2)	4.4% (2)	—	
Clinical course				
Relapsing	94.8% (55)	93.5% (43)	100% (12)	*.01
Monophasic	5.2% (3)	6.5% (3)	—	
Treatment				
Rituximab	82.7% (48)	80.4% (37)	91.7% (11)	*.00
Azathioprine	6.9% (4)	8.7% (4)	—	
Mycophenolate mofetil	10.4% (6)	10.9% (5)	8.3% (1)	

* statistically significant.

cal unit. If the rest of the population of Mexico behaved similarly to the state of Jalisco, according to our standardised prevalence, for a State population of 125 930 000 Mexicans in 2019, a total of 894 individuals with NMOSD would be estimated at the nationwide level.

It is important to mention that 31.03% of patients were initially diagnosed with MS, and 25.8% patients received disease-modifying treatment, a phenomenon that is increasingly rare; we attribute

this to an increased knowledge and awareness of the disease from the beginning, and the description of the NMOSD diagnostic criteria made in 2015.

Regarding the prevalence of MS and NMOSD, studies in the United States of America (USA) report a ratio of MS:NMO of 54:1,¹⁷ and in Sweden, a ratio MS:NMO of 175:1²¹; while in Mexico the ratio of MS:NMO is approximately 15:1, similar to the Martinique cohort with 13:1¹⁷; Argentina with 21:1,²² and Ecuador.²³ Most NMOSD

cohort studies have described the AQP4 positivity of approximately 70% to 90%,^{22,24} while in the present cohort the positivity was 89.6%; however, other authors have also described a positivity lower than 70%.^{25–28}

There is marked heterogeneity in the clinical events of the disease. In the present cohort, 58.6% of patients started with optic neuritis, although most previous studies report ON in 23% to 45%.^{20,29} Almost a quarter of patients (26%) started with transverse myelitis, compared to higher percentages in other cohorts where this type of onset has been reported in up to 80% of patients.³⁰

Few prevalence studies describe the treatment of included patients, while the present study has the highest percentage of patients treated with rituximab (82.7%) compared to other studies that used it in less than half of their patients.^{13,15} We perceive that this strong tendency to use rituximab derives from the high recurrence and severity of the disease in our patients who have recurred when using previous treatments (most frequently azathioprine and mycophenolate mofetil), and because we consider rituximab to be the most effective of them. However, this hypothesis was not systematically explored in the present study.

Among the most important limitations of this study are: (1) the retrospective design, which is why we rely on information collected from electronic files that do not have a homogeneous structure in all cases; (2) despite the fact that the referral system to our subspecialty medical unit allows us to reduce biases, in any case our prevalence and incidence estimates should be considered as minimum estimates^{31,32}; since, on the one hand, although there is a referral system to us for diagnosis of NMOSD, on the other hand there are no regulations that monitor its obligation. Medical doctors from other levels of care might not send patients to this catchment center, and, on the other hand, many patients entitled to healthcare at the IMSS and other institutions, like the public health workers in Mexico, typically seek private medical services, so the target population used in our prevalence calculation could include patients who prefer to use private health systems, for which there is also no central registry. Therefore, it is not possible to carry out population-based studies like those conducted in countries with universal public health systems, such as Sweden.²¹

We consider that this is the first study in Mexico to define, with greater precision, the prevalence and incidence of NMOSD in one state (Jalisco) of the country, which permits obtaining a general panorama of the region (western Mexico) for patients with NMOSD. However, it also raises questions about the response we have obtained when using rituximab more frequently than in other populations, or whether the response to azathioprine, or mycophenolate mofetil, is similar to that of other populations reported.

Likewise, in the only other previous study of NMOSD in Mexico,¹² there is greater disability than that reported in other studies, and we consider it relevant to explore if the clinical behavior in this cohort is similar to that which was referred to in the aforementioned study; therefore, we aim to explore these questions in future studies.

Conclusion

Compared with other regions, the present study population has a cumulative incidence of NMOSD which is higher than 0.71/100 000 (CI 0.60–0.85), and the prevalence ratio is low at 1.09/100 000 (CI 0.84–1.42). We reveal how NMOSD is a disease found predominantly in women, with symptoms appearing in the third decade (mean age of 36 years), with the diagnosis made in the fourth decade (mean age of 41 years). All patient were 1AQP4-IgG seropositive, 65.5% presented MRI abnormalities. Transverse myelitis was the most frequent symptom (62.0%), whereas the most frequent initial symptom was neuromyelitis optica in 58.6%. In 94.8% of the cases, the disease was recurrent; the most-used treatment was rituximab 82.7%.

Disclosure of conflict of interest

None.

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