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Original article

What percentage of AQP4-ab-negative NMOSD patients are MOG-ab positive? A study from the Argentinean multiple sclerosis registry (RelevarEM)

Edgar Carnero Contentti [1,*], Pablo A. Lopez [1], Juan Pablo Pettinicchi [1], Agustín Pappolla [2], Jimena Miguez [2], Liliana Patrucco [2], Edgardo Cristiano [3], Carlos Vrech [4], Verónica Tkachuk [5], Susana Liwacki [6,7], Jorge Correale [8], Mariano Marrodan [8], María I. Gaitán [8], Marcela Fiol [8], Laura Negrotto [8], María C. Ysrraelit [8], Marcos Burgos [9], Felisa Leguizamon [10], Dario Tavolini [11], Norma Deri [12], Maria E. Balbuena [5], Carolina Mainella [13], Geraldine Luetic [14], Patricio Blaya [15], Javier Hryb [16], María L. Menichini [17], Amelia Alvez Pinheiro [18], Pedro Nofal [19], Gisela Zanga [20], Andrés Barboza [21], Ivan Martos [22], Luciana Lazaro [23], Ricardo Alonso [23], Emanuel Silva [24], Santiago Bestoso [25], Maria E. Fracaro [26], Adriana Carrá [27,28], Orlando Garcea [29], Nora Fernandez Liguori [23,30], Marina Alonso Serena [31], Alejandro Caride [1], Juan I. Rojas [5,32]

[1] *Neuroimmunology Unit, Department of Neurosciences, Hospital Alemán, Buenos Aires*
[2] *Servicio de Neurología, Hospital Italiano de Buenos Aires, Buenos Aires*
[3] *Centro de esclerosis múltiple de Buenos Aires, CABA*
[4] *Departamento de Enfermedades desmielinizantes - Sanatorio Allende, Córdoba*
[5] *Sección de Neuroinmunología y Enfermedades Desmielinizantes, Servicio de Neurología - Hospital de Clínicas José de San Martín, CABA*
[6] *Clínica Universitaria Reina Fabiola, Córdoba*
[7] *Servicio de Neurología - Hospital Córdoba, Córdoba*
[8] *Departamento de Neurología - FLENI, CABA*
[9] *Servicio de Neurología - Hospital San Bernardo, Salta*
[10] *Hospital de Agudos, Dr. Teodoro Álvarez, CABA*
[11] *INECO Neurociencias Oroño - Fundación INECO, Rosario, Santa Fe*
[12] *Centro de Investigaciones Diabaid, CABA*
[13] *Hospital Español de Rosario, Santa Fe*
[14] *Instituto de Neurociencias de Rosario, Santa Fe*
[15] *Neurocomp, Trelew, Chubut*
[16] *Servicio de Neurología - Hospital Carlos G. Durand, CABA*
[17] *Sanatorio Británico, Rosario, Santa Fe*
[18] *Hospital San Martín, Paraná, Entre Ríos*
[19] *Hospital de Clínicas Nuestra Señora del Carmen, San Miguel de Tucumán, Tucumán*
[20] *Unidad asistencial César Milstein, CABA*
[21] *Hospital Central de Mendoza, Mendoza*
[22] *Clinica San Jorge. Ushuaia. Tierra del fuego*
[23] *Sanatorio Güemes, CABA*
[24] *Predigma - Centro de Medicina Preventiva, Posadas, Misiones*
[25] *Servicio Neurología - Hospital Escuela José F. de San Martín Corrientes, Corrientes*
[26] *Clinica el Castaño, San Juan*
[27] *Sección de Enfermedades Desmielinizantes - Hospital Británico, CABA*
[28] *Instituto de Neurociencias - Fundación Favaloro/INECO, CABA*
[29] *Centro Universitario de Esclerosis Múltiple - Hospital Dr. J. M. Ramos Mejía. Facultad de Medicina - UBA, CABA*
[30] *Hospital Enrique Tornú, CABA*
[31] *Servicio de clínica médica, Hospital Italiano de Buenos Aires, CABA*
[32] *Servicio de Neurología, Hospital Universitario de CEMIC, CABA*

* Corresponding author.
E-mail addresses: ecarnerocontentti@hospitalaleman.com, junior.carnero@hotmail.com (E. Carnero Contentti).

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ABSTRACT

Background: Myelin oligodendrocyte glycoprotein antibodies (MOG-ab) have been described in aquaporin-4-antibodies(AQP4-ab)-negative neuromyelitis optica spectrum disorder (NMOSD) patients. We aimed to evaluate the percentage of AQP4-ab-negative NMOSD patients who are positive for MOG-ab in a cohort of Argentinean patients included in RelevarEM (Clinical Trials registry number NCT03375177).

Methods: RelevarEM is a longitudinal, strictly observational multiple sclerosis (MS) and NMOSD registry in Argentina. Of 3031 consecutive patients (until March 2020), 165 patients with phenotype of suspected NMOSD, whose relevant data for the purpose of this study were available, were included. Data on demographic, clinical, paraclinical and treatment in AQP4-ab (positive, negative and unknown) and MOG-ab (positive and negative) patients were evaluated.

Results: A total of 165 patients (79 AQP4-Ab positive, 67 AQP4-Ab negative and 19 unknown) were included. Of these, 155 patients fulfilled the 2015 NMOSD diagnostic criteria. Of 67 AQP4-Ab-negative patients, 36 (53.7%) were tested for MOG-Ab and 10 of them (27.7%) tested positive. Serum AQP4-ab levels were tested by means of cell-based assay (CBA) in 48 (35.2%), based on tissue-based indirect immunofluorescence assays in 58 (42.6%) and enzyme-linked immunosorbent assay in 4 (2.9%). All MOG-ab were tested by CBA. Optic neuritis (90%) was the most frequent symptom at presentation and optic nerve lesions the most frequent finding (80%) in neuroimaging of MOG-ab-associated disease. Of these, six (60%) patients were under immunosuppressant treatments at latest follow-up.

Conclusion: We observed that 27.7% (10/36) of the AQP4-ab-negative patients tested for MOG-ab were positive for this antibody, in line with results from other world regions.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare disease, characterized by the presence of inflammatory events within the central nervous system (CNS) that are associated with autoantibodies against aquaporin-4 (AQP4-ab) in the serum of approximately 70 % to 80% of cases (Wingerchuk et al., 2015; Carnero Contentti et al., 2020). The AQP4-ab are a specific biomarker that can differentiate patients with NMOSD from patients with multiple sclerosis (MS) (Lennon et al., 2004) or other demyelinating diseases of the CNS. In 2015, a panel of experts defined the diagnostic criteria for NMOSD, based on clinical manifestations, serological status and magnetic resonance imaging (MRI) (Wingerchuk et al., 2015). Currently, NMOSD is considered a different disease from MS, since different pathophysiological, clinical and MRI characteristics have been observed (Wingerchuk et al., 2015; Carnero Contentti et al., 2020; Lennon et al., 2004; Kawachi et al., 2017).

Previous studies have reported up to 20%-30% of patients with NMOSD are persistently AQP4-ab negative, despite using the recommended assays such as transfected cell-based assay (CBA) (Prain et al., 2019). These percentages may be even higher in Latin America population (up to 30-40%), likely due to the methodology used in these reports (Carnero Contentti et al., 2018; Carnero Contentti et al., 2020). In patients with clinical features suggestive of NMOSD (Wingerchuk et al., 2015; Carnero Contentti et al., 2020) such as optic neuritis (ON), transverse myelitis (TM), area postrema syndrome, brainstem syndrome, symptomatic diencephalic syndrome and symptomatic cerebral syndrome, in addition to encephalopathy with acute disseminated encephalomyelitis (ADEM)-like symptoms, severe or bilateral ON, longitudinally extensive TM (LETM) or cortical signs, the myelin oligodendrocytes glycoprotein antibodies (MOG-ab) (Reindl et al., 2019; Jarius et al., 2018; Waters et al., 2015; Sato et al., 2014) testing is recommended, as its positivity was reported with a variable prevalence (Reindl et al., 2019). Thus, the clinical spectrum of MOG-ab-associated disease (MOGAD) has a widening range of phenotypes, including NMOSD and ADEM. An optimal test (e.g. CBA) is essential and recommended for the diagnosis of MOGAD (Waters et al., 2019). Currently, MOGAD is considered a disease different from AQP4-ab-positive NMOSD and MS with distinct clinical and therapeutic management at follow-up (Reindl et al., 2019). Thus, MOGAD is more common in children than adult compared with AQP4-ab-positive NMOSD (Reindl et al., 2019; Jarius et al., 2018; Waters et al., 2015; Sato et al., 2014). To date, there are no data on adult MOGAD patients in Argentina. In this regard, MS and NMOSD registries are important tools to provide relevant information on epidemiological aspects of the diseases, effectiveness and safety of real-life treatments as well as access to health care in affected patients (Jarius et al., 2018; Waters et al., 2015; Sato et al., 2014). We recently presented the methodology behind RelevarEM, the first nationwide MS and NMOSD registry in Argentina and Latin America (clinical trial registry number NCT03375177) (Rojas et al., 2019).

Given that frequency of adult MOGAD in real-life setting is still unknown in Argentina, we aimed to determine the percentage of adult AQP4-ab-negative NMOSD patients who are positive for MOG-ab and describe clinical and demographic aspects in a cohort of Argentinean patients included in RelevarEM.

2. Methods

RelevarEM is a longitudinal, strictly observational MS and NMOSD non-mandatory registry in Argentina. Detailed methodology of RelevarEM has been previously published elsewhere (Rojas et al., 2019; Rojas et al., 2020). The primary objective of the registry was to create an MS and NMOSD clinicians network involved in MS care in Argentina that collects information from routine clinical practice regarding clinical and demographic aspects (Rojas et al., 2019). To reduce the possibility of selection bias, all neurologists participating in the registry must include all their patients followed in clinical practice (Rojas et al., 2019).

Ethics committee approval was obtained for each participating center and a written informed consent (according to each committee, if necessary) was obtained from all participants before data collection.

Of 3031 consecutive patients (until March 2020), 165 patients with phenotype of suspected NMOSD, whose relevant data for the purpose of this study were available, were included. Thus, data on demographic, clinical, paraclinical, and treatment of AQP4-ab (positive, negative and unknown) and MOG-ab (positive and negative) patients were reviewed. Relevant variables were selected for this analysis considering their importance in clinical practice. Age and gender were included as demographic variables. Clinical and paraclinical variables included were: disease duration, comorbidities measured by the Charlson Comorbidity Index, disability measured by the Expanded Disability Status Scale (EDSS) score, clinical relapses, serological status and evaluation methods as well as neuroimaging (MRI) and treatments (acute and preventive) (Rojas et al., 2019; Rojas et al., 2020; Kurtzke, 1983). Some clinical data, such as the number and severity of relapses were not investigated, since this study focused on the seroprevalence of MOG-ab and AQP4-ab. Serum AQP4-ab levels were tested by means of CBA in 48 (35.2%), based on tissue-based indirect immunofluorescence (IIF)

assays in 58 (42.6%) and enzyme-linked immunosorbent assay (ELISA) in 4 (2.9%), as described previously (Lennon et al., 2004; Prain et al., 2019; Waters et al., 2015; Waters et al., 2019). MOG-ab were tested by means of CBA in all patients. Because MOGAD was previously considered a subset of NMOSD, especially in AQP4-ab-negative patients, the seroprevalence of MOG-ab was evaluated only in phenotypes with suspected NMOSD according to the 2015 criteria.

3. Statistical analysis

Categorical variables are expressed as frequency and percentage. Continuous variables are expressed as means and standard deviations (SD). Chi-square or Fisher exact test or Mann-Whitney test or t-test was used for unpaired bivariate comparisons among groups, as appropriate. The IBM SPSS v.20 software (IBM Corp., NY, USA) was used and statistical significance was established as $p < 0.05$.

4. Results

A total of 165 patients (79 AQP4-ab positive, 67 AQP4-ab negative and 19 unknown) were included. Demographic, clinical, and paraclinical characteristics of the studied Argentinean cohort are summarized in Table 1 and Figs. 1 and 2. Of these adults with suspected NMOSD, 155 patients fulfilled the 2015 NMOSD diagnostic criteria. Of 67 AQP4-ab-negative patients, only 36 (53.7%) were tested for MOG-ab and 10 of them (27.7%) tested positive and MOGAD was diagnosed (Table 2). Positivity for both antibodies was not found. Additionally, we determined that 6% of this cohort with a phenotype NMOSD are MOG-ab positive. No statistical differences between MOGAD and double seronegative patients regarding demographic, clinical and paraclinical characteristics were found, except for azathioprine use (0% vs. 34.6%, p=0.03, respectively). In addition, presence of relapses during the previous 6 months (40% vs 13.9%), shorter disease duration (3.9 vs 7.2 years), lower disability (2.3 vs 3.4) and lower use of azathioprine or lack of treatment, as well as treatment duration (1.5 vs 3.4 years), and lastly, both ON as presentation (90 vs 44.5) and optic nerve lesion on MRI (80% vs 22.7%) were significantly associated with MOGAD compared with AQP4-ab-positive NMOSD patients, respectively (Table 1).

5. Discussion

In recent years, the role of MOG-ab in inflammatory diseases of the CNS has been reviewed (Reindl et al., 2019; Jarius et al., 2018; Waters et al., 2015; Sato et al., 2014). Although these antibodies were associated to MS, their presence could not be reproduced in subsequent studies (Reindl et al., 2019; Waters et al., 2015). Likewise, clinical and radiological differences between diseases associated with AQP4-ab and MOG-ab have gained great interest, leading to revisions of the definitions of NMOSD and proposing an extended spectrum based on the detection of a specific antibody (Carnero Contentti et al., 2020). The presence of MOG-ab can discriminate AQP4-ab-negative NMOSD patients and MS patients (Carnero Contentti et al., 2020; Reindl et al., 2019; Juryńczyk et al., 2019). Positivity for both is extremely rare when performed using recommended techniques (Carnero Contentti et al., 2020; Reindl et al., 2019; Jarius et al., 2018; Waters et al., 2015; Sato et al., 2014; Waters et al., 2019; Juryńczyk et al., 2019). Although not all this cohort was tested for both antibodies, positivity for both was not observed. Recently, a Mayo Clinic study (Kunchok et al., 2020) reported that 15,598 adult and pediatric patients were tested for AQP4-ab and MOG-ab, and they strikingly showed a positivity of 8.3% (1291 patients) for MOG-ab and 2.3% for AQP4-ab (387 patients). Regarding the adult subgroup, 6.5% were positive for MOG-ab and 2.6% for AQP4-ab, while in the pediatric subgroup, positivity was significantly higher in MOG-ab than in AQP4-ab (21.1% vs. 1.9%). Only 10 patients (0.06%) had double positivity (high AQP4-ab titers and low MOG-ab titers) (Kunchok et al., 2020).

Table 1
Demographic, clinical, and paraclinical characteristics of the studied Argentinean cohort

	MOGAD (n=10)	P-NMOSD (n=79)	Double Negative (n=26)	p-value[a]	p-value[b]
Age at diagnosis mean (±SD), y	29.4 (±12.7)	38.2 (± 15.5)	36.6 (± 15.3)	0.06	0.16
Female N (%)	6 (60)	66 (83.5)	17 (65.3)	0.09	0.26
Disease duration mean (±SD)	3.9 (±3.9)	7.2 (±6.1)	4.1 (±3.9)	**0.03**	0.88
EDSS (±SD) at last FU*	2.3 (±1.2)	3.4 (±2.4)	3.0 (±2.3)	**0.03**	0.27
Relapses at last 6 months Yes	4 (40)	11 (13.9)	4 (15.3)	**0.06**	0.17
Charlson comorbidity index ≥ 1	1 (10)	13 (16.4)	3 (10.6)	1	1
First relapse					
Optic neuritis	9 (90)	39 (49.3)	14 (53.8)	**0.01**	0.059
Transverse myelitis	1 (10)	34 (43.1)	8 (30.7)	0.08	0.39
Area postrema syndrome	-	4 (5.1)	4 (15.3)	1	0.55
Brainstem syndrome	-	1 (1.2)	0	1	-
Simtomatic cerebral syndrome	-	1 (0.2)	0	1	-
MRI at presentation	8** (80)	18 (22.7)	10 (38.4)	**0.001**	0.059
Optic nerve lesions	1 (10)	11 (13.9)	2 (7.6)	0.35	1
STM	0	36 (45.5)	9***	0.04	1
LETM	0	4 (5.1)	(34.6)	1	0.55
Area postrema	0	2 (2.8)	4 (15.3)	-	-
Brainstem syndrome	0	2 (2.8)	0	1	-
Hemisferic white matter	0	6 (7.8)	0	1	-
No available			0		
Treatment time Mean (±SD)	1.5 (±0.5)	3.4 (±2.5)	1.5 (±1.5)	**0.001**	0.95
Preventive Treatment	3 (30)	38 (48.1)	10 (38.4)	0.33	0.71
Rituximab	0	30 (37.9)	9 (34.6)	**0.01**	**0.03**
Azathioprine	2 (20)	2 (2.5)	0	0.06	0.07
Micophenolate mofetil	4 (40)	6 (7.5)	5 (19.2)	**0.01**	0.22
No treatment	1 (10)	3 (3.8)	2 (7.6)	-	1
Others****					

MOGAD= MOG-ab-positive patients, P-NMOSD= AQP4-ab-positive NMOSD, CCI=Charlson Comorbidity Index, EDSS=Expanded Disability Status Scale, FU= follow-up, MRI= magnetic resonance imaging, y=years.

[a] MOG-ab-positive patient vs. AQP4-ab-positive NMOSD patient results were compared

[b] MOG-ab-positive patients vs. double negative (MOG-ab and AQP4-ab) patients results were compared

* Unpaired t test with Welch's correction. ** One patient had ON associated with brainstem syndrome

*** One patient had LETM extending to the brainstem

**** Others: tocilizumab (n=1) in the MOGAD group, eculizumab (n=2) and tocilizumab (n=1) in the P-NMOSD group and metrotexate (n=1) and plasmapheresis (n=1) in the double negative group.

In this study, we observed that 27.7% of AQP4-ab-negative NMOSD patients were positive for MOG-ab (in tested patients). In line with our results, unilateral or bilateral ON is the most frequent manifestation of MOGAD at disease onset in adult while an ADEM phenotype is more frequently found in children (less than 10 years-old), as reported in large series worldwide (Cobo-Calvo et al., 2018; Jurynczyk et al., 2017; Jarius et al., 2016; Cobo-Calvo et al., 2020). Additionally, after a follow-up of

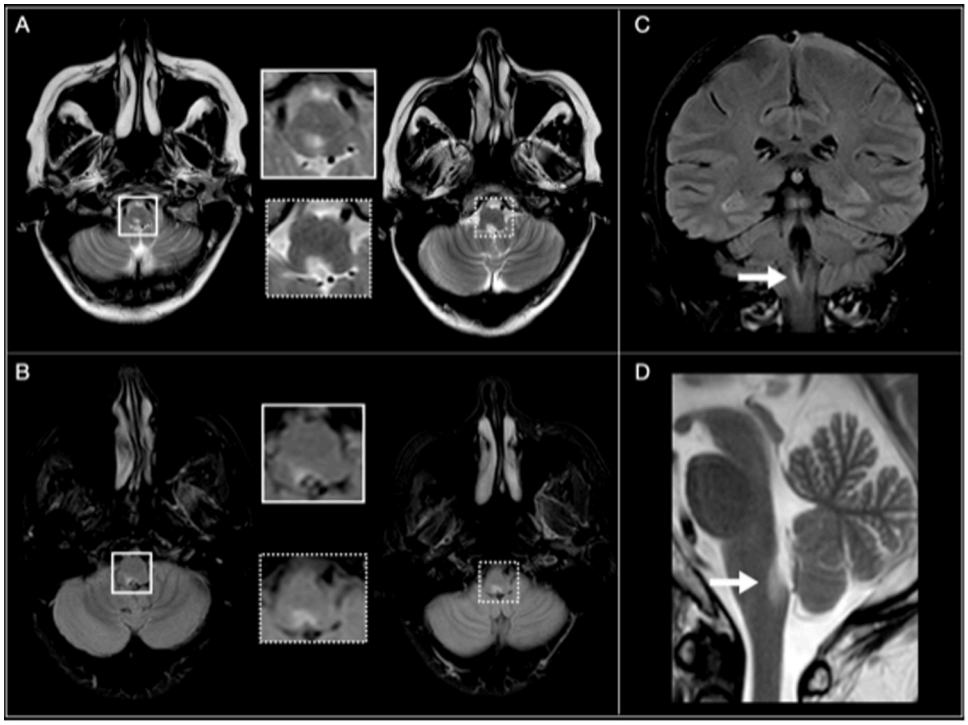

Fig. 1. Lesion in the area postrema in a MOGAD patient. Brain images from patient number 8. A-Axial T2-weighted MRI and B-Axial T2-FLAIR, squares magnify hyperintense lesion in dorsal medulla. C-coronal T2-FLAIR, and D Sagittal T2-weighted Arrows point to the same lesion.

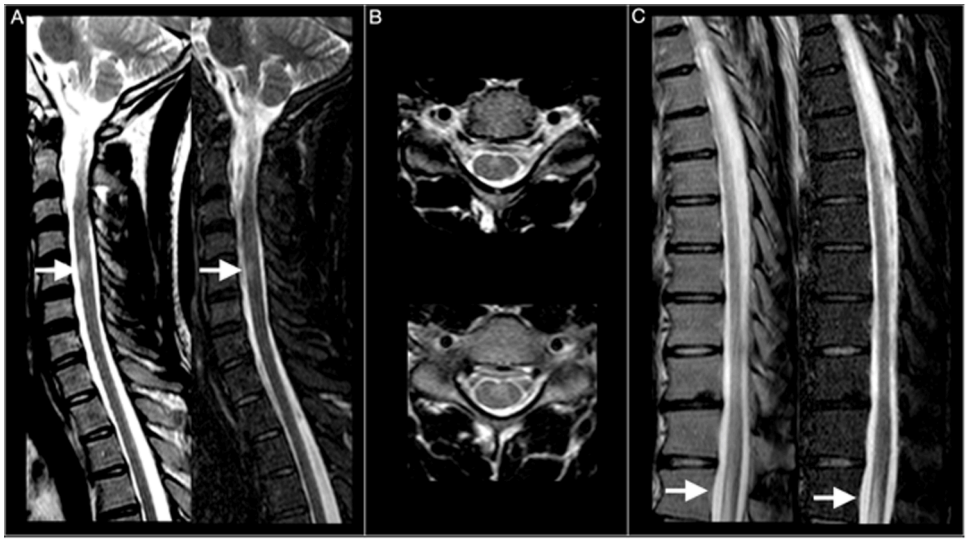

Fig. 2. Spinal cord lesions in a MOGAD patient. Brain images from patient number 10. A- Sagittal T2-weighted and STIR, arrows point to an anterior cervical lesion, B-axial T2 weighted showing the pointed lesion in A. C-Sagittal T2-weighted and STIR, arrows point to a lesion in the conus

3.9 (± 3.9) years, we observed that 20% of patients with MOGAD experienced a moderate to severe disability (EDSS ≥4). This finding is similar to that of the UK cohort (n = 252), where approximately 25% had moderate to severe disability (EDSS ≥4) (Jurynczyk et al., 2017). As described in other series (Reindl et al., 2019; Jarius et al., 2018; Waters et al., 2015; Sato et al., 2014; Waters et al., 2019; Juryńczyk et al., 2019; Kunchok et al., 2020; Cobo-Calvo et al., 2018; Jurynczyk et al., 2017; Jarius et al., 2016; Cobo-Calvo et al., 2020; Kitley et al., 2012; Siritho et al., 2016), in this cohort we observed that patients with MOGAD have significantly less disability than patients with AQP4-ab-positive NMOSD patients. In a study carried out in Oxford, it was observed that 4 of 27 adult AQP4-seronegative NMO/NMOSD patients, who were tested for MOG-ab, were positive for this antibody (Kitley et al., 2012). Patients with MOGAD (3 out of 4 men) experienced severe ON and/or LETM with good recovery after steroids or plasmapheresis treatments. In our cohort, none of our patients received plasmapheresis and only 30% received acute treatment with intravenous corticosteroids, a fact that differs significantly from the European series (83.8%) (Cobo-Calvo et al., 2018). Furthermore, in this series (Cobo-Calvo et al., 2018), at latest follow-up only 58.4% of the patients had started preventive therapy. Of them, 43.3% received rituximab, 34.6% azathioprine, and 33.7% mycophenolate mofetil, in line with what was observed in our studied cohort (Table 2). In a study from Thailand (Siritho et al., 2016), it was observed that MOG-ab were positive in six patients with a history of ON

Table 2
Demographic, clinical, and paraclinical characteristics of the 10 MOG-ab positive patients

Patient	Age	Gender	Symptoms at presentation	Comorbilities	EDSS at last FU	Relapses at last 6 mo	MRI at presentation	Acute treatment	Preventive treatment	FU at last visit (y)
1	33	F	ON	None	0	No	ON lesion	No	AZA	3
2	27	F	ON	None	4	No	ON lesion	No	RTX	13
3	19	F	ON	None	4	No	ON lesion	No	RTX	2
4	36	F	ON	CCI = 1	3.5	Yes	Normal	IVMP	None	1
5	16	M	ON	None	3	No	ON lesion	No	TCZ	5
6	43	M	ON	None	2	Yes	ON lesion	No	AZA	2
7	37	F	ON	None	2	No	ON lesion	No	None	8
8	11	F	ON/Brainstem	None	2	No	ON lesion/ Brainstem	No	RTX	4
9	51	M	ON	None	2	Yes	ON lesion	IVMP	None	0
10	21	M	ATM	None	1	Yes	Myelitis	IVMP	None	1

CCI=Charlson Comorbidity Index, EDSS=Expanded Disability Status Scale, FU= follow-up, mo=months, MRI= magnetic resonance imaging, y=years, F=female, M=male, ON=optic neuritis, ATM=acute transverse myelitis, IVMP= intravenous methylprednisolone, AZA=azathioprine, RTX=rituximab, TCZ=tocilizumab

(bilateral ON in three patients), associated or not with brain lesions and/or TM, representing 20.7% (6/29) of AQP4-seronegative patients. None of these patients presented positivity for both antibodies and the majority experienced relapses with good recovery after treatment. AQP4-ab were positive in 64.3% (9/14) of NMO patients defined by the 2006 revised criteria (ON associated with TM) (Wingerchuk et al., 2006) and five patients had a limited phenotype, in line with our findings. In another study published from a referral center in Liverpool (Hamid et al., 2017), it was reported that 42% (15/36) of its cohort, that was seronegative for AQP4-ab, tested positive for MOG-ab, reaching 11% of the total of cases studied with suspected inflammatory disease of the CNS. Additionally, the 2018 annual Oxford NMO service (Oxford University Hospitals NHS Foundation, (NMO) Annual Report 2018; Hor et al., 2020) reported that 145 patients with NMOSD were seropositive for AQP4-ab, 111 MOGAD and 28 double seronegative. This proportion of MOGAD within the NMOSD study represented a rate that appears to be high. In the NMOSD epidemiological study from Catalonia, based on the 2015 NMOSD criteria, 12% of the studied cohort were positive for anti-MOG-ab (Sepúlveda et al., 2018) antibodies. Recognizing MOGAD patients is now crucial, particularly in AQP4-ab-negative NMOSD, since specific management and therapeutic requirements are different from MS and AQP4-ab-positive NMOSD.

Although hospital-based studies largely did not find any significant racial preponderance for MOG-antibody-associated disease (Kunchok et al., 2020; Cobo-Calvo et al., 2018), different prevalence were recently reported in Brazil and Korea (Papais-Alvarenga et al.; Hyun et al., 2020). In Brazil, particularly in a non-Caucasian (52% Afro-Brazilian) population from Rio de Janeiro, these results were significantly lower (7%; 5/68) (Papais-Alvarenga et al.) than in Europe, suggesting a racial/ancestral influence. In this regard, a Korean study (Hyun et al., 2020) reported that 36 (6.1%) of 586 adults with suspected inflammatory diseases of the CNS tested positive for MOG-ab and 185 (31.6%) adults tested positive for AQP4-ab. These results suggest that Asian population have a lower seroprevalence of MOG-ab compared to Western countries, but similar to Brazilian population (Hyun et al., 2020).

Interestingly, we did not observe differences between MOGAD and double negative patients. So far, there is no robust evidence on clinical, paraclinical and treatment in double negative patients (AQP4-ab and MOG-ab), using the most sensitive method. Currently, patients who have had at least two attacks (one should be ON, TM or area postrema syndrome) associated with typical MRI lesions, in absence of a "better explanation", are considered to have seronegative NMOSD, according to the 2015 NMOSD criteria (Wingerchuk et al., 2015). Additionally, previous data have come principally from North America, Europe and Asia, but there are few data on cohort of Latin American patients, who would be expected to present differences in comparison with patients in these other regions.

We are aware that this study has several limitations and they should be mentioned. This study had a retrospective design with inherent design biases. Another important limitation was the number MOGAD patients included in this non-mandatory registry. Thus, there is probably an underestimation of the total number of patients. Furthermore, the identification of patients with MOGAD is often complex and recently described, so this may also contribute to underreporting. Only 21.8% (36/165) of all NMOSD cohort in this registry were tested for MOG-ab, therefore, these results should be confirmed with future studies. However, our results do not differ significantly from those of the rest of the published series (Kitley et al., 2012; Siritho et al., 2016; Wingerchuk et al., 2006; Hamid et al., 2017). The lack to access to MOG-ab and AQP4-ab testing by the recommended methods (CBA) (Carnero Contentti et al., 2020; Waters et al., 2019), what is even more restricted in some regions than others within Argentina, is likely the more important limitation (Chiong-Rivero et al., 2019). These restrictions could also influence the epidemiological analysis by selecting or excluding certain centers based on access to these tests. However, it is a study base on real-life setting.

Despite these limitations, our study provides relevant data for clinical practice since it responds, at the moment, on the seroprevalence of MOGAD in the real-life context: patients with NMOSD phenotype who are negative for AQP4-ab and are positive for MOG-ab (27.7%). Considering that the course and prognosis can be distinct in MS, NMOSD and MOGAD (Wingerchuk et al., 2015; Reindl et al., 2019), it is probably that treatment strategies are different during follow-up (Reindl et al., 2019). Likewise, the findings found in this study have important practical implications, since they offer the patient a definitive diagnosis of MOGAD, thus trying to avoid errors in both diagnosis and treatment.

Declaration of Conmpeting Interest

None of the authors have any potential financial conflict of interest relating to this manuscript.

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Contributors

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