






Assessing attacks and treatment response rates among adult patients with NMOSD and MOGAD: Data from a nationwide registry in Argentina

Edgar Carnero Contentti , Pablo A Lopez, Juan Pablo Pettinicchi, Juan Criniti, Agustín Pappolla, Jimena Miguez, Liliana Patrucco, Edgardo Cristiano, Susana Liwacki, Verónica Tkachuk, María E Balbuena, Carlos Vrech, Norma Deri, Jorge Correale, Mariano Marroddan , María C Ysraelit, Felisa Leguizamon, Geraldine Luetic , María L Menichini, Darío Tavolini, Carolina Mainella, Gisela Zanga, Marcos Burgos, Javier Hryb, Andrés Barboza, Luciana Lazaro, Ricardo Alonso  and, Nora Fernández Liguori, Débora Nadur, Aníbal Chercoff  Marina Alonso Serena, Alejandro Caride, Friedemann Paul and Juan I Rojas

Multiple Sclerosis Journal—
Experimental, Translational
and Clinical

July–September 2021, 1–14

DOI: 10.1177/
20552173211032334

© The Author(s), 2021.
Article reuse guidelines:
sagepub.com/journals-
permissions

Abstract

We aimed to examine treatment interventions implemented in patients experiencing neuromyelitis optica spectrum disorders (NMOSD) attacks (frequency, types, and response).

Methods: Retrospective study. Data on patient demographic, clinical and radiological findings, and administered treatments were collected. Remission status (complete [CR], partial [PR], no remission [NR]), based on changes in the EDSS score was evaluated before treatment, during attack, and at 6 months. CR was analyzed with a generalized estimating equations (GEEs) model.

Results: A total of 131 patients (120 NMOSD and 11 myelin oligodendrocyte glycoprotein-antibody-associated diseases [MOGAD]), experiencing 262 NMOSD-related attacks and receiving 270 treatments were included. High-dose steroids (81.4%) was the most frequent treatment followed by plasmapheresis (15.5%). CR from attacks was observed in 47% (105/223) of all treated patients. During the first attack, we observed CR:71.2%, PR:16.3% and NR:12.5% after the first course of treatment. For second, third, fourth, and fifth attacks, CR was observed in 31.1%, 10.7%, 27.3%, and 33.3%, respectively. Remission rates were higher for optic neuritis vs. myelitis ($p < 0.001$). Predictor of CR in multivariate GEE analysis was age in both NMOSD (OR = 2.27, $p = 0.002$) and MOGAD (OR = 1.53, $p = 0.03$).

Conclusions: This study suggests individualization of treatment according to age and attack manifestation. The outcome of attacks was generally poor.

Keywords: Neuromyelitis optica spectrum disorders, attacks, disability, treatment response, Latin America

Date received: 12 April 2021; accepted: 24 June 2021

Introduction

Neuromyelitis optica spectrum disorders (NMOSD) are rare but often devastating inflammatory diseases of the central nervous system (CNS) characterized mainly by severe attacks of transverse myelitis (TM), optic neuritis (ON) and/or brainstem syndrome (BSS).¹ A relevant proportion of patients

fulfilling the current diagnostic criteria harbors serum antibodies to the astrocyte water channel aquaporin-4 (AQP4). Disease presentation follows a relapsing course in up to 90% of NMOSD patients, while progressive forms are uncommon.^{1,2} Unlike multiple sclerosis (MS), neurologic disability typically accumulates with each clinical attack,

Correspondence to:
Edgar Carnero Contentti,
Neuroimmunology Unit,
Department of Neuroscience,
Hospital Alemán, Av
Pueyrredón 1640,
C1118AAT, Buenos Aires,
Argentina.
junior.carnero@hotmail.com
or



ecarnerocontentti@
hospitalaleman.com

Edgar Carnero Contentti
Pablo A Lopez,
Juan Pablo Pettinicchi,
Juan Criniti,
Neuroimmunology Unit,
Department of
Neurosciences, Hospital
Aleman, Buenos Aires,
Argentina

Agustín Pappolla,
Jimena Miguez,
Liliana Patrucco,
Servicio de Neurología,
Hospital Italiano de Buenos
Aires, Buenos Aires,
Argentina

Edgardo Cristiano,
Centro de Esclerosis
Múltiple de Buenos Aires,
CABA, Buenos Aires,
Argentina

Susana Liwacki,
Clínica Universitaria Reina
Fabiola, Córdoba, Argentina
Servicio de Neurología,
Hospital Córdoba, Córdoba,
Argentina

Verónica Tkachuk,
María E Balbuena,
Sección de
Neuroinmunología y
Enfermedades
Desmielinizantes, Servicio
de Neurología, Hospital de
Clínicas José de San Martín,
CABA, Buenos Aires,
Argentina

Carlos Vrech,
Departamento de
Enfermedades
desmielinizantes, Sanatorio
Allende, Córdoba, Argentina

Norma Deri,
Centro de Investigaciones
Diabaid, CABA, Buenos
Aires, Argentina

Jorge Correale,
Mariano Marrodan,
María CYSreilit,
Departamento de Neurología,
FLENI, CABA, Buenos
Aires, Argentina

Felisa Leguizamón,
Hospital de Agudos, Dr.
Teodoro Álvarez, CABA,
Buenos Aires, Argentina

Geraldine Luetic,
Instituto de Neurociencias de
Rosario, Santa Fe, Argentina

María L Menichini,
Sanatorio Británico, Rosario,
Santa Fe, Argentina

Darío Tavolini,
INECO Neurociencias
Oroño, Rosario, Santa Fe,
Argentina

Carolina Mainella,
Hospital Español de Rosario,
Santa Fe, Argentina

Gisela Zanga,
Unidad Asistencial César

resulting in long-term impairment of motor and/or visual function, as well as affecting other organ systems.^{1–3} attacks in patients with NMOSD also reduce life expectancy, when primary attacks involve the brainstem, or cervical lesions extend to reach the medulla, ultimately increasing the risk of respiratory failure.^{2–4} NMOSD attacks therefore require prompt evaluation and timely treatment, to restore function and mitigate disability. Moreover, once the diagnosis has been made, timely preventative immunotherapy, for example with B cell depleting agents or other immunosuppressants, is indicated to reduce the risk of subsequent attacks.^{1–3} Fortunately, several successfully completed clinical trials have paved the way for the official approval of immunotherapies to treat NMOSD.^{2,3}

On the other hand, myelin oligodendrocyte glycoprotein antibody (MOG-ab)-associated disease (MOG-AD) often present with similar NMOSD attacks in term of initial symptoms, is associated with a relapsing course in up to 83% of patients frequently involving the optic nerve.^{5–7} A number of clinical and neuroradiological similarities between NMOSD and MOG-AD have been described. MOG-AD was initially identified from cohorts of AQP4-ab-negative NMOSD patients.⁸ Between 33% and 42% of MOG-AD patients previously fulfilled NMOSD seronegative diagnostic criteria.^{9,10} However, MOG-AD is currently considered a separate nosologic entity pathogenetically distinct from both anti-Aquaporin4-antibodies (AQP4-ab)-positive NMOSD and from MS.⁸ Short- and long-term prognosis in patients presenting NMOSD or MOG-AD is uncertain, and will depend on individual case characteristics as well as several other variables including: place of residence and/or ethnicity of the patient, disease severity, type of debut symptom, treatment given or strategies proposed and time to treatment onset, among others.^{1–8} As a consequence, acute treatment response rates in both diseases should be evaluated separately.^{8–10}

Although there are no NMOSD and MOG-AD prevalence data in Argentina, epidemiologic information about MS/NMOSD ratio (21:1) and percentage of MOG-AD in AQP4-ab-negative NMOSD patients (27%) were recently published.^{10,11}

Consensus recommendations on therapeutic strategies to treat NMOSD and MOG-AD have been recently published for the Latin America (LATAM) region. In the case of treatment of NMOSD attacks²: high-dose IV methylprednisolone

(IVMP), therapeutic plasma exchange (PLEX) and/or intravenous immunoglobulins (IVIgG), were all reported, although with little evidence for the last of these. However, the combination of IVMP + PLEX (HR 5.1, 95% CI: 3.9–66.4) as first line treatment was an independent factor associated with complete improvement in a Colombian cohort.¹² Another study from Mexico showed that the response rate to PLEX was 39.3%, even when treatment initiation was delayed.¹³

Understanding attack activity, severity and response to treatment is important in order to optimize therapeutic decision-making, particularly in lower-income countries.² To the best of our knowledge, no evidence is available on how patients with NMOSD or MOG-AD from the LATAM region are managed and treated during an attack, or how they respond to different therapeutic strategies.

Therefore, our aim was to analyze data from a nationwide MS/NMOSD registry in Argentina, *RelevarEM (MSregistry)* and examine treatment interventions implemented in patients experiencing NMOSD attacks (frequency, types, and response).

Methods

A retrospective study was conducted in a cohort of NMOSD patients followed in MS/NMOSD centers from Argentina and enrolled in *RelevarEM*, a nationwide, longitudinal, observational, non-mandatory registry of MS and NMOSD patients (Clinical Trials registry number NCT03375177; <https://www.latambase.com.ar/login>). Details on *RelevarEM* procedures and methods have been previously published elsewhere.¹⁴ One of the goals of the registry is to create a network of neurologists involved in caring for MS/NMOSD patients in Argentina and collect standardized relevant information from them on: routine clinical practice (at baseline: disease onset, course, symptoms, recovery, serological test and methodology used), patient demographics (at baseline: patient identification, center, informed consent, administrative information), clinical findings (date, Expanded Disability Status Scale [EDSS], bouts, paraclinical tests at follow-up: MRI date, MRI new lesions, CSF findings) as well as immunotherapy prescribed (treatment used for MS/NMOSD and safety: adverse events) and observed outcomes.¹⁴ To reduce risk of selection bias, neurologists participating in this registry were required to register all patients followed in their clinical practice.¹⁴

For the study, registry neurologists treating patients with phenotypes suggestive of NMOSD were invited to send information on any patient with confirmed NMOSD diagnosis according to 2015 NMOSD criteria,¹ or with MOG-AD, diagnosed based on core clinical characteristics and presence of serum MOG-ab.^{15,16} Attacks were assessed retrospectively and cases with insufficient or missing primary outcome data were excluded. To ensure homogeneous data collection, we designed a specific web-based platform to investigate NMOSD and MOG-AD attacks and review treatment choices and outcomes, and asked researchers to register and share relevant data from their patients for the purpose of this study.

Data on patient demographics, clinical and radiological findings, and treatments administered was collected (Figure 1). An attack was defined as an acute onset of neurologic symptoms lasting 24 hours or longer, occurring at least 30 days from the start of the last attack.¹ Symptoms must not be attributable to confounding clinical factors (e.g. fever, infection, injury, change in mood, adverse reactions to medications). NMOSD core clinical characteristics were classified as¹: 1) TM; 2) ON; 3) area postrema syndrome (APS); 4) BSS; 5) narcolepsy or diencephalic syndrome (DS); 6) cerebral syndrome (CS; including encephalitis/seizures) and/or 7) combined symptomatology (e.g. TM + ON). Physical disability levels during and post-attack were assigned a score,

graded using the EDSS and reviewed retrospectively.¹⁷

To further classify patients, AQP4-ab and MOG-ab status was also recorded at any time over the disease course. AQP4-ab status was determined by cell-based assay¹⁸ (CBA) in 72% of NMOSD patients, followed by tissue-based indirect immunofluorescence¹⁹ in 27%. MOG-ab levels were tested using CBA in all cases²⁰ (Table 1). Brain and spinal cord magnetic resonance images (MRI; using at least 1.5 Tesla scanners) were evaluated during attacks (<30 days), and lesions classified as suggestive of NMOSD according to Kim et al. (2015).²¹ Spinal cord lesions were categorized as longitudinally extensive TM (LETM) when involving over ≥3 vertebral segments or as short-segment transverse myelitis (STM) if <3 vertebral segments were affected.^{1,2,21}

Treatments given included: 1) Three to 5 consecutive days of IVMP, 1000 mg/day; 2) Five to 7 courses of PLEX, either at onset or as escalation treatment, with approximately 1.5 plasma volumes exchanged every other day, over a 2-week period; or 3) IVIgG, 0.4 mg/Kg/day for 5 days.^{1,2,22} Considering that this is a retrospective real-life study, there was no pre-defined therapy algorithm. Thus, treatment is generally based on the clinical judgement of an experienced clinician. Frequency and timing of treatment course and therapy used were reported for each attack. Additionally, adverse events (infections, hyperglycemia, sepsis, local complications at puncture site associated with PLEX or others) related to treatment of attacks were obtained from medical records and collected. Adverse events were defined as any symptomatic event which had any causal relationship with acute treatment.

When EDSS scores at 6 months returned to pre-attack values and lasting recovery from attack-related neurologic deficits was observed, patients were considered to have undergone a complete remission (CR). Remission was considered partial (PR) when EDSS scores at 6 months remained above pre-attack EDSS scores, but were less than those recorded during attacks. When EDSS scores at 6 months were equal to, or greater than intra-attack scores, no remission (NR) was registered.²² Remission status based on EDSS score was evaluated before treatment, during attack, and at 6 months, since sustained or confirmed change in EDSS after 6 months is the standard timeframe used to establish disability level in MS patients.²³

- Milstein, CABA, Buenos Aires, Argentina
- Marcos Burgos**, Servicio de Neurología, Hospital San Bernardo, Salta, Argentina
- Javier Hryb**, Servicio de Neurología, Hospital Carlos G. Durand, CABA, Buenos Aires, Argentina
- Andrés Barboza**, Hospital Central de Mendoza, Mendoza, Argentina
- Luciana Lazaro**, **Ricardo Alonso**, **Nora Fernández Liguori**, Sanatorio Güemes, CABA, Buenos Aires, Argentina
- Débora Nadur**, Sección de Neuroinmunología y Enfermedades Desmielinizantes, Servicio de Neurología, Hospital de Clínicas José de San Martín, CABA, Buenos Aires, Argentina
- Hospital Naval, CABA, Buenos Aires, Argentina
- Aníbal Chercoff**, Sección de Enfermedades Desmielinizantes, Hospital Británico, CABA, Buenos Aires, Argentina
- Marina Alonso Serena**, Servicio de Clínica Médica, Hospital Italiano de Buenos Aires, CABA, Buenos Aires, Argentina
- Alejandro Caride**, Neuroimmunology Unit, Department of Neurosciences, Hospital Alemán, Buenos Aires, Argentina
- Friedemann Paul**, NeuroCure Clinical Research Center, Charité, Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
- Experimental and Clinical Research Center, Max Delbrueck Center for Molecular Medicine and Charité, Universitätsmedizin Berlin, Berlin, Germany
- Juan I Rojas**, Centro de Esclerosis Múltiple de Buenos Aires, CABA, Buenos Aires, Argentina
- Servicio de Neurología, Hospital Universitario de CEMIC, CABA, Buenos Aires, Argentina

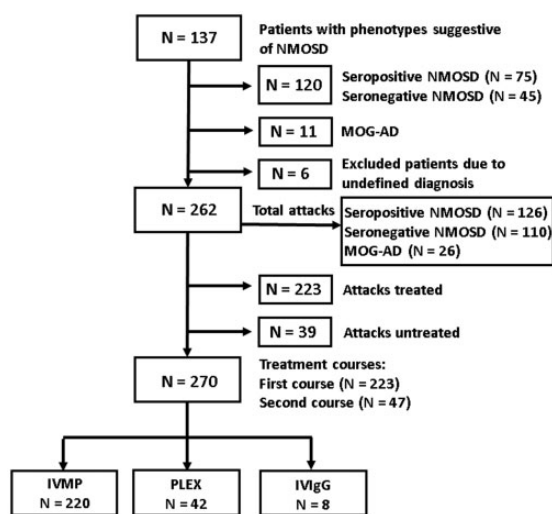


Figure 1. Consort flow diagram. NMOSD: neuromyelitis optica spectrum disorders; Seropositive NMOSD: AQP4-ab-positive NMOSD; Seronegative NMOSD: AQP4-ab-negative NMOSD; MOG-AD: MOG-associated diseases; IVMP: high-dose IV methylprednisolone; PLEX: therapeutic plasma exchange; IVIgG: intravenous immunoglobulins.

Table 1. Demographic and clinical features of NMOSD and MOG-AD.

	Seropositive NMOSD N = 75	Seronegative NMOSD N = 45	MOG-AD N = 11	P-value
Females, n (%)	63 (84)	31 (69)	4 (36)	0.004
Mean age at disease onset, SD (years)	38 ± 5	41 ± 6.5	36 ± 8	0.22
Median EDSS at disease onset, SD	3.3 ± 2.2	3.1 ± 1.9	2.8 ± 1.8	0.16
Disease duration at last follow-up, SD, (years)	6.1 ± 3	6.0 ± 3.1	3.1 ± 2.1	0.001
Mean time elapsed between first relapse and first immunotherapy treatment for NMOSD/MOG-AD, SD, (months) ^a	56 ± 17	63.2 ± 10	19.2 ± 12	<0.001
Mean time elapsed between first treated relapse (symptom/s onset) and start of relapse treatment, SD, (days)	13 ± 6	18 ± 4	21 ± 10	0.09
Serology test ^a				
IFI	21 (28)	11 (25)	0	
ELISA	1 (1.3)	0	0	
CBA	50 (66.6)	32 (70)	11 (100)	
Not reported	5 (6.6)	2 (5)	0	

Seropositive NMOSD: AQP4-ab-positive NMOSD; Seronegative NMOSD: AQP4-ab-negative NMOSD; MOG-AD: MOG-associated diseases; IIF: indirect immunofluorescence; ELISA: Enzyme-Linked ImmunoSorbent Assay; CBA: cell-based assay.

^aAll MOG-AD patients were tested for AQP4-ab by CBA and they were all negatives. However, we do not know how many seronegative NMOSD patients were tested for MOG-ab in this sample.

Significant p values are indicated in bold.

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.

Statistical analysis

Quantitative patient variables were analyzed descriptively. The Kruskal-Wallis test (nonparametric test) was used to estimate differences among the three groups. Given that treatment courses are dependent variables, and in order to maximize correlation between patients, we applied a generalized estimating equation (GEE)²⁴ model to assess attack treatment results and remission outcomes. To better compare remission rates for different clinical manifestations, as well after different attack and preventive therapies, GEE analyses were executed applying factors influencing therapies, together with known demographic and clinical variables (gender, age at attack, time from onset of disease to attack, diagnosis, clinical presentation and time from onset of attack to start of therapy). The dependent variables were the remission status as previously defined, and p values <0.05 were considered statistically significant. We used STATA (Data Analysis and

Statistical Software; StataCorp, College Station, TX) for the analysis and graphs were prepared on Prism 8 (Graph-Pad software, La Jolla, CA). Due to the retrospective and exploratory nature of the study no adjustment for multiple comparisons was made.

Results

Demographic, clinical and paraclinical features

Registry data was provided on a total of 137 patients, experiencing 262 NMOSD-related attacks and receiving 270 treatment interventions. Of these, 75 presented AQP4-ab-positive NMOSD, 45 AQP4-ab-negative NMOSD (but these met the 2015 NMOSD criteria) and 11 MOG-AD. Six patients with incomplete registry data were excluded. As shown in Table 1, 84% and 69% of positive and negative AQP4-ab NMOSD patients were women, respectively. Whereas in the MOG-AD group, only 36% were women. Median age at disease onset was 38 ± 5, 41 ± 6.5 and 36 ± 8 years for each of the three groups, and disease duration was 6.1 (±3), 6.0 (±3.1) and 3.1 (±2.1) years, respectively.

A total of 262 attacks (126 in AQP4-ab-positive NMOSD, 110 in AQP4-ab-negative NMOSD and 26 in MOG-AD) were analyzed. As shown in Table 2, the most frequent presentation during initial attack was ON in AQP4-ab-positive NMOSD and MOG-AD patients. In AQP4-ab-negative patients, TM was the most frequent. The most common finding on MRI during attacks was LETM in AQP4-ab-positive NMOSD (42.9%) and AQP4-ab-negative NMOSD patients (58.9%), followed by optic nerve lesions in 30.4% and 28.2%, respectively. In MOG-AD, we observed optic nerve lesions and LETM in 55.6% and 46% of patients, respectively. MRI results in all attacks analyzed are summarized in Supplementary Table 1.

Frequency of attacks and therapeutic interventions

One hundred and thirty-one initial, 81 second, 31 third, 12 fourth and 7 fifth attacks were evaluated in total in this patient cohort. As shown in Table 3, IVMP was the most frequent treatment, used in 81.4% of all interventions, followed by PLEX in

15.5%. No treatment was administered during the first, second, third, fourth and fifth attack, in 27 (20.6%), 7 (8.6%), 3 (10%), 1 (8%), and 1 patient (15%), respectively. No reason of attacks untreated was obtained.

Clinical outcome according to type of attack

After comparing all attacks, no significant differences in remission rates were observed between the three groups. However, after evaluating the first attack, and the response to treatment received (Figures 2 and 3), significant differences in remission rates were detected between ON vs. TM in the AQP4-ab-negative group (ON [CR:82%, PR:6% and NR:12%] vs. TM [CR:61%, PR:23% and NR:16%], p = 0.002). In the AQP4-ab-positive group, this was also the case, ON showed CR:88%, PR:3% and NR:9%, whereas for TM recovery rates were: CR:63%, PR:22% and NR:15% (p = 0.001) as occurred with the MOG-AD group, in which remission rates for ON were: CR:55%, PR:33% and NR:11%, vs. CR:100% for TM (p = 0.02).

Table 2. Frequency of relapse manifestations in NMOSD and MOG-AD.

Core clinical characteristics	First relapse			All relapses		
	Seropositive NMOSD	Seronegative NMOSD	MOG-AD	Seropositive NMOSD	Seronegative NMOSD	MOG-AD
Optic neuritis N, (%)	36 (48)	17 (37.8)	9 (81.8)	63 (50)	54 (48.8)	17 (65)
Transverse myelitis N, (%)	33 (44)	36 (57.8)	1 (9.1)	60 (48)	50 (45.8)	12 (48)
Optic neuritis + myelitis N, (%)	25 (34)	12 (26.6)		42 (34)	28 (25)	10 (38)
Area postrema syndrome N, (%)	4 (5.3)	2 (4.4)	–	3 (2.3)	4 (3.6)	–
Brainstem syndrome N, (%)	1 (1.3)	1 (2.2)	–	4 (3.4)	4 (3.6)	1 (3.8)
Diencephalic syndrome N, (%)	–	–	–	2 (1.5)	2 (1.8)	–
Cerebral syndrome N, (%)	1 (1.3)	–	1 (9.1)	2 (1.5)	2 (1.8)	–
Unknown N, (%)	–	–	–	4 (3.4)	7 (6)	2 (7.6)

Seropositive NMOSD: AQP4-ab-positive NMOSD; Seronegative NMOSD: AQP4-ab-negative NMOSD; MOG-AD: MOG-associated diseases.

Table 3. Frequency of relapses and therapeutic interventions in NMOSD and MOG-AD.

	First relapse N = 131	Second relapse N = 81	Third relapse N = 31	Fourth relapse N = 12	Fifth relapses N = 7	Total N = 262
IVMP N, (%)	102 (77.9)	74 (91)	27 (87)	11 (92)	6 (84)	220 (81.4)
PLEX N, (%)	19 (14.5)	14 (17.3)	7 (22.6)	1 (8.3)	1 (14.3)	42 (15.5)
IVIgG N, (%)	3 (7.6)	2 (3%)	1 (3.3)	2 (16.6)	–	8 (3.1)
Relapses treated N (%)	104 (79.4)	74 (91.4)	28 (90)	11 (92)	6 (85)	223 (85.1)
Relapses untreated N (%)	27 (20.6)	7 (8.6)	3 (10)	1 (8)	1 (15)	39 (14.9)

IVMP: IV methylprednisolone; PLEX: therapeutic plasma exchange, IVIgG: intravenous immunoglobulin.

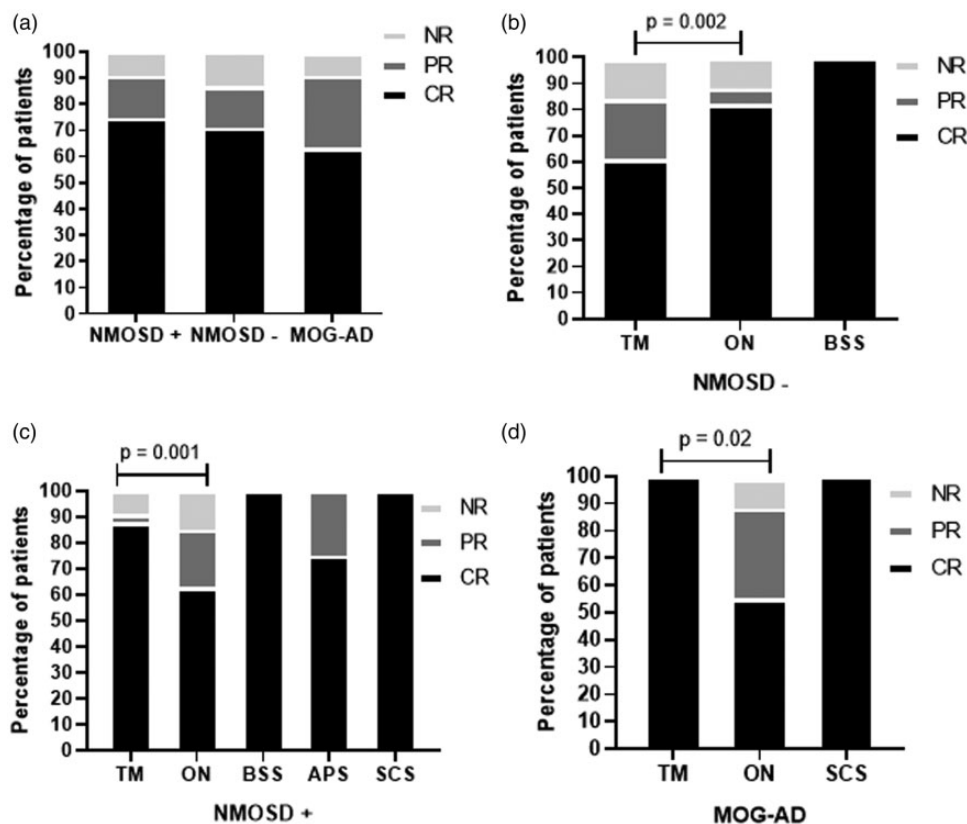


Figure 2. Clinical outcomes after first attack. Evaluation of 131 attacks. Panel A: Distribution between groups of all initial attacks; Panel B: first attack in the AQP4-ab-negative NMOSD group according to initial neurologic manifestation; Panel C: first attack in the AQP4-ab-positive NMOSD group according to initial manifestation; Panel D: first attack in the MOG-AD group according to initial manifestation.

CR: complete remission; NR: no remission; PR: partial remission; NMOSD+: AQP4-ab-positive NMOSD; NMOSD-: AQP4-ab-negative NMOSD; MOG-AD: MOG-associated diseases; TM: transverse myelitis; ON: optic neuritis; APS: area postrema syndrome; BSS: brainstem syndrome; SCS: symptomatic cerebral syndrome.

Thus, remission rates in NMOSD patients were significantly higher for ON than TM ($p < 0.01$), especially in the CR category. Comparisons between remission rates after third, fourth and fifth attacks were not performed as the number of attacks registered was small.

Clinical outcome according to treatment

As shown in Table 4, 98% ($n = 102$) of treated patients received IVMP; 14.5% ($n = 19$) were treated with PLEX and 7.6% ($n = 3$) were treated with IVIgG as initial or escalation treatment during first attack. PLEX was used in 85% as escalation therapy followed by IVIgG 15% for first attack. Interestingly, PLEX was also used as first treatment option in 2%, 3%, 7%, 9% and 16% during first, second, third, fourth and fifth attacks, respectively. IVIgG was only used as escalation therapy. Second treatment courses were indicated in 28.8%, 21.6%, 25%, 27.2% and

16.6% of first, second, third, fourth, and fifth attacks, respectively.

As shown in Table 5, CR after the first course of treatment was observed in 71.2%, PR in 16.3% and NR in 12.5%. After first course of treatment for second, third, fourth, and fifth attacks, CR was observed in 31.1%, 10.7%, 27.3%, and 33.3%, respectively. In patients presenting ON, CR after the first course of treatment was observed in 83.7%, PR in 9.3% and NR in 7%. During second ON attacks, CR was observed in 60% and in 50% with the first and second course of treatment, respectively. No response was observed with the third course. Remission rates were significantly lower in patients with TM during the first (CR: 60%) and second (50%) course of treatment. Response was more robust however after a second attack of TM, in which CR rates were 22.7% after first course of treatment. Remission rates for all attacks and

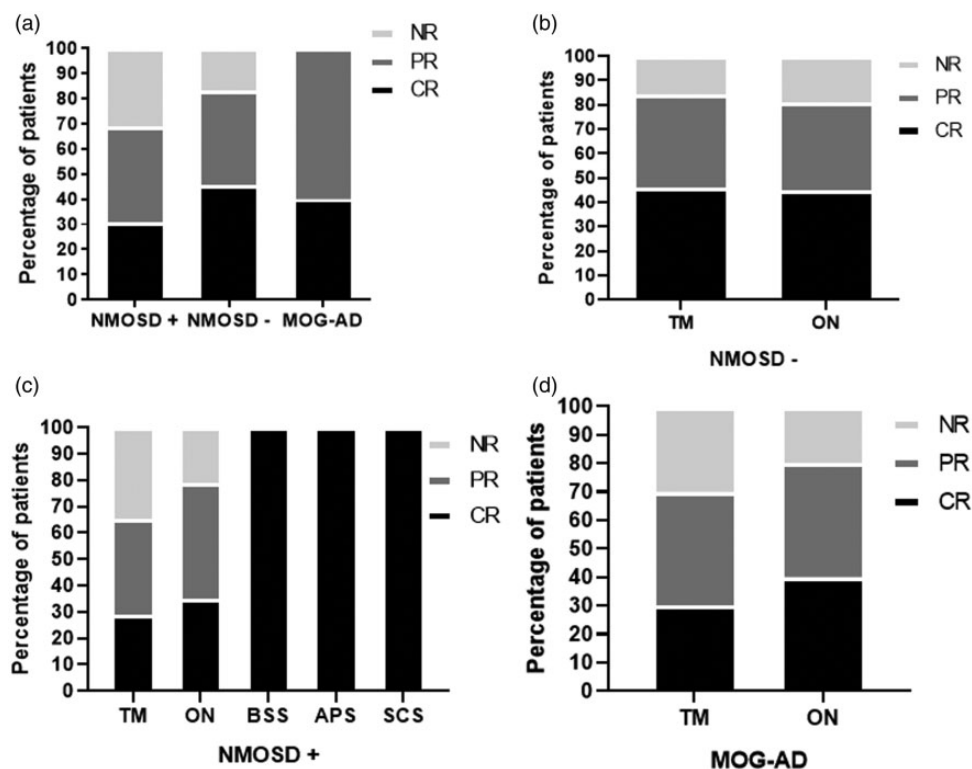


Figure 3. Clinical outcome after second attack. Evaluation of 81 second attacks. Panel A: Distribution of second attacks between groups; Panel B: second attack in the AQP4-ab-negative NMOSD group according to manifestation; Panel C: second attack in the AQP4-ab-positive NMOSD group according to manifestation; Panel D: second attack in the MOG-AD group according to manifestation. CR: complete remission; NR: no remission; PR: partial remission. NMOSD+: AQP4-ab-positive NMOSD; NMOSD-: AQP4-ab-negative NMOSD; MOG-AD: MOG-associated diseases.

treatments in ON and TM cases in relation to first and second attack and after first, second or third courses of treatment are shown in Figure 4.

Safety evaluation

A total of 45 adverse events related to treatment of attack were reported. Of these, 26 were associated with PLEX and 19 with IVMP, including: infections (n = 10), hyperglycemia (n = 5), sepsis (n = 4), local complications at puncture site associated with PLEX (n = 16) or others (n = 10). Because the total number of events was relatively low, statistical analysis was not performed.

Long-term treatment

During the first attack, 84.4% of AQP4-ab-negative, 92% of AQP4-ab-positive NMOSD and 67.7% of MOG-AD patients received preventive treatment. The most frequently administered immunosuppressive therapy in each of the mentioned groups was azathioprine in 60%, 61.3% and 27.3%, respectively. Interestingly, initial treatment was switched in 44.7% of AQP4-ab-negative and in 40.6% of AQP4-ab-positive patients due to a new attack in

50% of cases. Currently, rituximab is the most frequently used treatment in AQP4-positive (50.6%) and MOG-AD (54.5%) patients. Results from long-term treatment are summarized in Supplementary Table 2.

Predictors of complete remission

Given that treatment courses are dependent events, we applied a GEE model as mentioned in the statistical analysis section to determine independent predictors, avoid potential confounders and maximize correlation between patients. As shown in Table 6, age at disease onset (OR= 2.32, CI95% 1.27-3.45, p = 0.01) was identified as an independent predictor of CR in multivariate GEE analysis, when all attacks in the three groups were evaluated. In addition, age at disease onset was also identified as an independent predictor of CR in NMOSD patients (OR= 2.27, CI95% 2.11-4.12, p = 0.002) and in MOG-AD patients (OR = 1.56, CI95% 1.22-2.01, p = 0.03). There was no influence in the use of PLEX determined by the type of relapse or serological status, as shown in Supplementary Table 3.

Table 4. Frequency and timing of treatment course and therapies used for NMOSD or MOG-AD.

	First relapse n = 131/ treated n = 104		Second relapse n = 81/ treated n = 74		Third relapse n = 31 / treated n = 28		Fourth relapse n = 12/ treated n = 11		Fifth relapse n = 7 / treated n = 6	
	First course	Second course	First course	Second course	First course	Second course	First course	Second course	First course	Second course
IVMP N, (%)	102 (98)	0	72 (97)	2 (12.5)	26 (93)	1 (14)	10 (91)	1 (33)	5 (84)	1 (100)
PLEX N, (%)	2 (2)	17 (85)	2 (3)	12 (75)	2 (7)	5 (72)	1 (9)	0	1 (16)	0
IVIgG N, (%)	0	3 (15)	0	2 (12.5)	0	1 (14)	0	2 (67)	0	0

IVMP: IV methylprednisolone; PLEX: therapeutic plasma exchange.
Significant p value is indicated in bold.

Results from GEE multivariate analysis are shown in Supplementary Tables 3 and 4.

Significant p value is indicated in bold.

Discussion

In this study based on data from the RelevaEM registry,^{10,11,14} we evaluated 262 attacks and 270 therapeutic interventions in 131 NMOSD and MOG-AD patients followed and treated in Argentina. Neurologists registering patients in RelevaEM, were from every part of the country, ensuring a representative national sample of patients. In this cohort, we observed: i) a high prevalence of first line management with IVMP, ii) CR rates were higher after first attack compared to overall attack (lower CR rates in the subsequent attacks) and iii) age at disease onset was identified as an independent predictor of CR in the three groups (NMOSD positive and negative, and MOG-AD) in our prediction model.

Although class I evidence on best acute treatment for NMOSD/MOG-AD patients is not available, neurologists in Argentina indicated IVMP alone as initial therapy most often followed by PLEX, which is in line with standard practice worldwide.^{2,3} IVMP treatment rates for NMOSD attacks were higher (81.5%) than in previous studies (58%-72.1%).^{22,25,26} IVMP inhibits the inflammatory cascade through suppression of inflammatory cytokines, inhibition of T cell activation, and modulation of different B cell subsets, promoting remission in a vast proportion of attacks.^{27,28} In this study, IVMP and PLEX led to CR in 72% and 50% of all attacks (Figure 4). Of note, time from onset of attack symptoms to initiation of both acute and long-term immunosuppressant therapy may play a relevant role in term of remission. Thus, patients from Argentina needed about 2-3 weeks from symptoms onset (patient-reported symptoms and/or objective findings) until the institution of acute therapy. This may be due to diagnostic/therapeutic barriers such as limited access to specialized NMOSD care, delay in admission, patient evaluation, attack diagnosis or MRI confirmation, among others. In addition, intervals between treatment courses were distinct in this study, so it could have impacted on therapeutic responses. Moreover, other concomitant long-term immunosuppressive therapies could have influenced the frequency and severity of attacks. Pre-existing disability could have been another confounding cofactor in terms of treatment responses. In this cohort, time from onset of attack to start of treatment and duration of long-term immunosuppressant

Table 5. Frequency of remission rates according to therapeutic interventions used during first course of treatment.

	First relapse n = 131		Second relapse n = 81		Third relapse n = 31		Fourth relapse n = 12		Fifth relapse n = 7	
	IVMP	PLEX	IVMP	PLEX	IVMP	PLEX	IVMP	PLEX	IVMP	PLEX
CR N, (%)	73 (72)	1 (50)	22 (30.6)	1 (50)	2 (7.7)	1 (14)	2 (20)	1 (100)	1 (20)	1 (100)
PR N, (%)	17 (17)	0	30 (41.6)	0	7 (26.9)	5 (72)	4 (40)	0	2 (40)	0
NR N, (%)	12 (11)	1 (50)	20 (27.8)	1 (50)	17 (65.4)	1 (14)	4 (40)	0	2 (40)	0

CR: complete remission; PR: partial remission; NR: no remission; IVMP: IV methylprednisolone; PLEX: therapeutic plasma exchange.

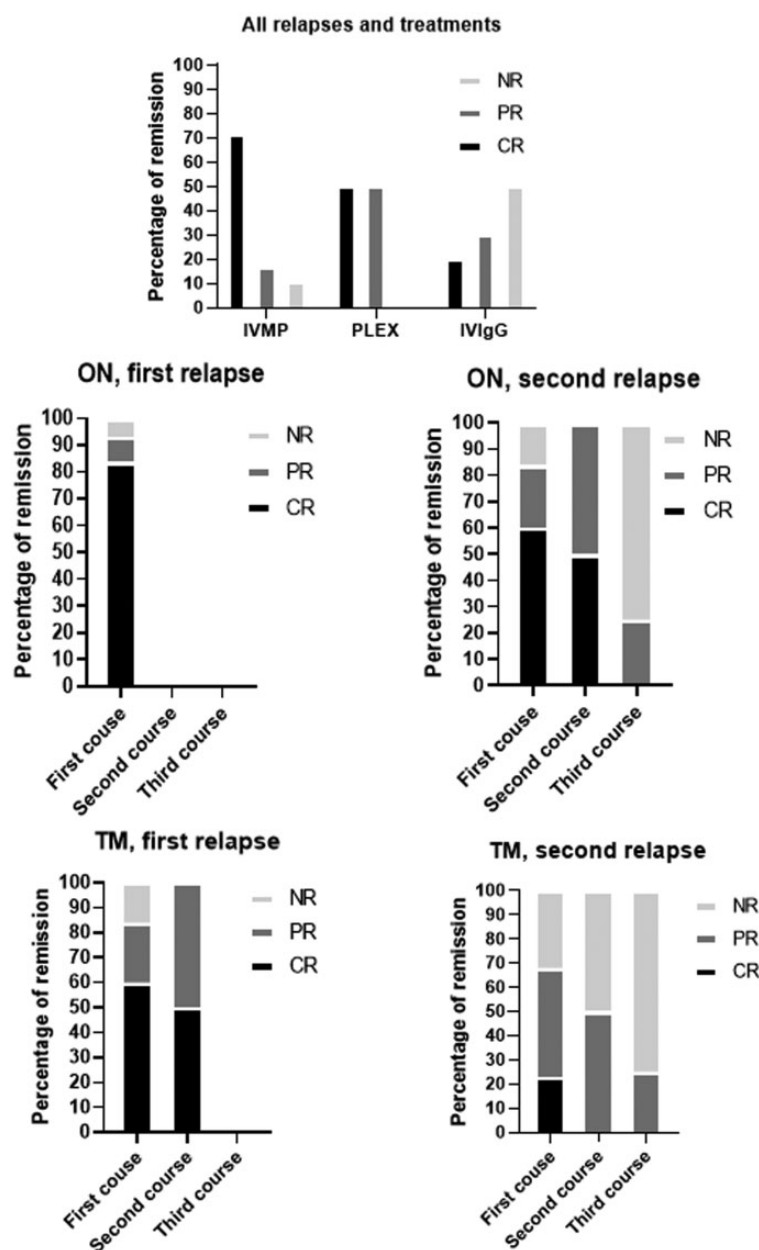


Figure 4. Clinical outcome in all attacks and according to treatments for ON and TM. CR: complete remission; NR: no remission; PR: partial remission. NMOSD+: AQP4-ab-positive NMOSD, NMOSD-: AQP4-ab-negative NMOSD, MOG-AD: MOG-associated diseases.

Table 6. Predictors of complete remission from relapses in all patients included (NMOSD and MOG-AG).

	OR	95%CI	P
Age at disease onset	2.32	1.27–3.45	0.01
Female	0.35	0.10–1.24	0.106
Symptom at onset	0.67	0.45–3.24	0.765
Time from onset of relapse to start of treatment	1.12	0.85–1.89	0.972
Duration of long-term immunosuppressive treatment	0.99	0.87–1.78	0.493
First line treatment for relapse	1.11	0.65–1.97	0.176

Significant p values are indicated in bold.

therapy were not identified as independent predictors of CR. Probably, due to the limitations of this study (retrospective design and small numbers of patients included). In a Chinese cohort of NMOSD patients previously treated with immunosuppressants, higher levels of cerebrospinal fluid protein, and more active MRI brainstem lesions were found to be predictors of poor response to IVMP treatment during attack.²⁶ Another study from Britain reported immunosuppressive treatments reduced severity but did not abolish attacks.^{29,30} In yet another European study,³¹ adult MOG-AD patients started on immunosuppressants experienced lower risk of new attacks compared to untreated patients.

PLEX was used in 14.5% of attacks and in 85% of those cases as an escalation strategy. Although PLEX is frequently used in clinical practice to improve clinical outcomes, particularly when the response to IVMP is insufficient, less use of PLEX was observed in this cohort when compared to other cohorts,^{25,32} probably due to a lack of availability in all centers. The rationale behind indicating this treatment is to eliminate autoantibodies and complement components (pathogenic plasma factors).^{25,30} Benefit of adding PLEX to IVMP for NMOSD attack treatment has been reported in large cohorts from Germany²⁵ and Martinique.³²

CR from attacks was observed in 47% (105/223) of all treated patients, although this result decreased slightly when all attacks were analyzed together (40.1%, 105/262). Surprising and somewhat in contradiction to the literature that CR was lower in MOG-AD than AQP4-ab-positive patients (retrospective design and small numbers of patients included can be some reasons of these differences). CR rates in our cohort were higher than those reported by the German registry (NEMOS)²² or by an Australia/New Zealand study,³³ 21.6% and 29%, respectively. Yet another study from the US reported 35% of IVMP-treated patients returned to baseline EDSS scores during follow-up.³⁴

We observed that CR rates after first NMOSD attack ranged between 63.3% and 74.6% in this cohort. The German registry study reported 19.1%.²² However, authors speculated lower remission rates may have been due to inadequate patient follow-up. CR was more common in patients with ON compared to TM in the three groups. Time to initiating treatment is also important. In a study on patients with ON and AQP4-ab or MOG-ab, IVMP treatment started within 5 days of ON onset increased likelihood of CR (visual acuity recovery), compared to results observed in patients starting treatment 6 or more days after ON onset.³⁵ Other European multicenter studies reported PR or NR in NMOSD patients in 66% of ON attacks followed, and in over 80% of TM attacks.³⁶ In MOG-AD, PR/NR was observed in 48% and 65% of ON and TM attacks, respectively.³⁷ Interestingly, second attacks led to switching of long-term treatment in 50% of patients in this cohort.

In line with results from a study based on outcome prediction models in AQP4-ab-positive NMOSD patients from the UK, US, Japan and Martinique,²⁹ we observed that after a second attack, only 30.9% to 45.8% of patients achieved CR, highlighting the risk of increased disability with recurrent NMOSD attacks. In addition, in another two European studies,^{36,37} CR was most frequent after the first attack, with lower remission rates observed after subsequent attacks. Interestingly, we found use of PLEX increased from 14.5% during the first attack to 22.6% during the second, although PLEX was indicated in less than 30% of second attack treatments in general, and repeating PLEX did not increase CR rates in subsequent attacks. The reasons behind the better response to treatment in the first attack compared to subsequent attacks remain unclear and could have been a threshold effect. Poor recovery from attacks results in the accrual of physical disability over time, when measured by the EDSS score.^{1–3} However, NMOSD patients may experience a good

outcome for many years without treatment before suffering a disabling attack, as previously reported.³⁸ Attack recovery may be influenced by many factors, including age at disease onset, ethnicity, disease duration, acute or long-term immunosuppressive treatments, among others.^{29,30} Further controlled studies evaluating the impact of these factors on attack recovery are needed.

Two aspects should be mentioned in relation to NMOSD/MOG-AD attacks: 1) how attack recovery is measured and 2) how attack is defined. Remission rates (outcome) was evaluated based on EDSS score¹⁷ (retrospectively applied), and although this is familiar and well validated in MS, cerebellar and cerebral functional system might be not really applicable for NMOSD patients. Thus, functional system scores of the EDSS can be affected by this type of attack. In this regard, EDSS may be limited in sensitivity to detect visual acuity changes and improvements in neurological function in patients who cannot walk. However, it is the most widely used disability scale in both NMOSD and MOG-AD worldwide and other functional systems are assessable. Most recently, clinical attack criteria (a panel of NMOSD experts defined up to 18 NMOSD attack criteria) were defined specifically for each new clinical trial.³⁹ Symptoms, clinical examination, exclusion of pseudorelapses and perhaps MRI attack confirmation were needed, particularly in milder cases of ON or TM or when clinical findings were equivocal or nonspecific.^{39,40}

Prediction of NMOSD or MOG-AD attacks based on findings into soluble activity marker such as serum GFAP or serum neurofilament light chain (sNfL) have been recently published.^{41–43} Subclinical astrocyte damage represented by increased GFAP serum concentration could serve as a biomarker of NMOSD activity, attack risk, and treatment effects.^{41–43} Additionally, sNfL levels increased during attacks in MOG-AD patients and both sNfL and sGFAP concentrations correlated positively with EDSS scores in NMOSD and MOG-AD patients.⁴²

On the other hand, it is important to note that 14.9% of patients were not treated during an attack in this cohort. Getting to the infusion center or hospital could have been a barrier to treatment. In the current epidemiological scenario, neurologists may consider the new evidence on the similar efficacy of both oral and IV steroids for attacks.⁴⁴ Using oral steroids during the pandemic would be an useful and safe option for these patients.

Studies from Europe, Asia and LATAM have previously shown that older NMOSD patients accrue greater levels of disability compared to younger ones.^{30,45–48} In this cohort, age at onset was the only independent predictor of CR, both in AQP4-ab-positive and negative NMOSD patients and in MOG-AD patients, a finding is similar to that of the German cohort, in which CR rates decreased by 3% per year, and by 24% with each decade.²² These results suggest treatment responses and repair mechanisms are reduced in elderly NMOSD patients, and adult MOG-AD patients have demonstrated to present worse functional recovery⁷ compared to children.⁴⁹ There is robust evidence that the use of PLEX as an add-on therapy to IVMP treatment during an acute attack in NMOSD patients is associated with returning to baseline EDSS at discharge and last follow-up. It should be especially considered in older patients with TM.^{22,25,32,50}

The retrospective design of this study is a limitation, and findings should be interpreted with caution. Also, unintentional selection bias may have occurred given the relatively small numbers of patients included in the different subgroups, thus reducing statistical power. CBA for testing AQP4-ab and/or MOG-ab is not currently available in Argentina through the public healthcare system, and therefore was not carried out in all participating centers. More patients in this cohort may have been AQP4-ab-positive or MOG-AD, ultimately affecting epidemiological analysis by selecting or excluding certain centers based on access to the test. Of note, 37.5% of attacks analyzed in the NMOSD group were AQP4-ab-negative patients, which is a higher proportion of seronegative patients than in most NMOSD studies, but it is in line with previous studies from LATAM.^{11,47} Seronegative patients are often a heterogeneous group of patients that could impact on the results. Although MOG-ab status in AQP4-ab-negative patients was published recently (performed in 53.7% [36/67] of seronegative NMOSD cohort) for this registry,¹⁰ it is worth mentioning that we do not know how many seronegative patients were tested for MOG-ab in this sample. All MOG-AD patients were tested for AQP4-ab and they were all negatives. These results reflect real-world evidence of clinical practice. Finally, the role of preceding treatment was not studied and it may have impacted on the results, it being another limitation.

To the best of our knowledge, this is the first large cohort study from a LATAM region. In the

Argentine population analyzed, and despite the limitations described above, our findings showed different remission rates depending on both the type of clinical event and the therapeutic intervention indicated, compared to data on patients from other parts of the world including Europe, USA and Asia. Thus, our study provides relevant data for clinical practice.

Conflict of Interests

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


Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was supported by Roche Argentina.


ORCID iDs

Edgar Carnero Contentti  <https://orcid.org/0000-0001-7435-5726>

Mariano Marrodan  <https://orcid.org/0000-0002-4142-8375>

Geraldine Luetic  <https://orcid.org/0000-0002-5716-6082>

Ricardo Alonso  <https://orcid.org/0000-0001-9955-8343>

Anibal Chercoff  <https://orcid.org/0000-0002-8645-6134>

Supplemental material

Supplementary material for this article is available online.

References

1. Wingerchuk DM, Banwell B, Bennett JL, et al.; International Panel for NMO Diagnosis. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* 2015; 85: 177–189.
2. Carnero Contentti E, Rojas JI, Cristiano E, et al. Latin American consensus recommendations for management and treatment of neuromyelitis optica spectrum disorders in clinical practice. *Mult Scler Relat Disord* 2020; 45: 102428.
3. Jarius S, Paul F, Weinshenker BG, et al. Neuromyelitis optica. *Nat Rev Dis Primers* 2020; 6: 85.
4. Mealy MA, Kessler RA, Rimler Z, et al. Mortality in neuromyelitis optica is strongly associated with African ancestry. *Neurol Neuroimmunol Neuroinflamm* 2018; 5: e468.
5. Cobo-Calvo A, Ruiz A, Maillart E, et al.; OFSEP and NOMADMUS Study Group. Clinical spectrum and prognostic value of CNS MOG autoimmunity in adults: the MOGADOR study. *Neurology* 2018; 90: e1858–e1869.
6. Ramanathan S, Mohammad S, Tantsis E, et al.; Australasian and New Zealand MOG Study Group. Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination. *J Neurol Neurosurg Psychiatry* 2018; 89: 127–137.
7. Jurynczyk M, Messina S, Woodhall MR, et al. Clinical presentation and prognosis in MOG-antibody disease: a UK study. *Brain* 2017; 140: 3128–3138.
8. Reindl M and Waters P. Myelin oligodendrocyte glycoprotein antibodies in neurological disease. *Nat Rev Neurol* 2019; 15: 89–102.
9. Hamid SHM, Whittam D, Mutch K, et al. What proportion of AQP4-IgG-negative NMO spectrum disorder patients are MOG-IgG positive? A cross sectional study of 132 patients. *J Neurol* 2017; 264: 2088–2094.
10. Carnero Contentti E, Lopez PA, Pettinicchi JP, et al. What percentage of AQP4-ab-negative NMO spectrum disorder patients are MOG-ab positive? A study from the Argentinean multiple sclerosis registry (RelevarEM). *Mult Scler Relat Disord* 2021; 49: 102742.
11. Rojas JI, Alonso Serena M, Garcea O, et al.; on behalf RelevarEM investigators. Multiple sclerosis and neuromyelitis optica spectrum disorders in Argentina: comparing baseline data from the Argentinean MS registry (RelevarEM). *Neurol Sci* 2020; 41: 1513–1519.
12. Restrepo-Aristizábal C, Giraldo LM, Giraldo YM, et al. PLEX: the best first-line treatment in nmosd attacks experience at a single center in Colombia. *Heliyon* 2021; 7: e06811.
13. Gómez-Figueroa E, Alvarado-Bolaños A, García-Estrada C, et al. Clinical experience of plasmapheresis for neuromyelitis optica patients in Mexico. *Mult Scler Relat Disord* 2021; 52: 103022.
14. Rojas JI, Carrá A, Correale J, et al. The Argentinean multiple sclerosis registry (RelevarEM): methodological aspects and directions. *Mult Scler Relat Disord* 2019; 32: 133–137.
15. Jurynczyk M, Jacob A, Fujihara K, et al. Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease: practical considerations. *Pract Neurol* 2019; 19: 187–195.
16. Jarius S, Paul F, Aktas O, et al. MOG encephalomyelitis: international recommendations on diagnosis and antibody testing. *J Neuroinflammation* 2018; 15: 134134.
17. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33: 1444–1452.
18. Waters PJ, McKeon A, Leite MI, et al. Serologic diagnosis of NMO: a multicenter comparison of aquaporin-4-IgG assays. *Neurology* 2012; 78: 665–671; discussion 669.
19. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet* 2004; 364: 2106–2112.
20. Waters P, Woodhall M, O'Connor KC, et al. MOG cell-based assay detects non-MS patients with

- inflammatory neurologic disease. *Neurol Neuroimmunol Neuroinflamm* 2015 ; 2: e89.
21. Kim HJ, Paul F, Lana-Peixoto MA, et al.; Guthy-Jackson Charitable Foundation NMO International Clinical Consortium & Biorepository. MRI characteristics of neuromyelitis optica spectrum disorder: an international update. *Neurology* 2015; 84: 1165–1173.
 22. Kleiter I, Gahlen A, Borisow N, et al.; Neuromyelitis Optica Study Group. Neuromyelitis optica: evaluation of 871 attacks and 1,153 treatment courses. *Ann Neurol* 2016 ; 79: 206–216.
 23. Giovannoni G, Turner B, Gnanapavan S, et al. Is it time to target no evident disease activity (NEDA) in multiple sclerosis? *Mult Scler Relat Disord* 2015; 4: 329–333.
 24. Dahmen G, Rochon J, König IR, et al. Sample size calculations for controlled clinical trials using generalized estimating equations (GEE). *Methods Inf Med* 2004; 43: 451–456.
 25. Kleiter I, Gahlen A, Borisow N, NEMOS (Neuromyelitis Optica Study Group), et al. Apheresis therapies for NMOSD attacks: a retrospective study of 207 therapeutic interventions. *Neurol Neuroimmunol Neuroinflamm* 2018 ; 5: e504.
 26. Zeng Q, Dong X, Ruan C, et al. CD14+CD16++ monocytes are increased in patients with NMO and are selectively suppressed by glucocorticoids therapy. *J Neuroimmunol* 2016; 300: 1–8.
 27. Quan C, Zhang Bao J, Lu J, et al. The immune balance between memory and regulatory B cells in NMO and the changes of the balance after methylprednisolone or rituximab therapy. *J Neuroimmunol* 2015; 282: 45–53.
 28. Qin C, Tao R, Zhang SQ, et al. Predictive factors of resistance to high-dose steroids therapy in acute attacks of neuromyelitis optica spectrum disorder. *Front Neurol* 2020; 11: 585471.
 29. Palace J, Lin DY, Zeng D, et al. Outcome prediction models in AQP4-IgG positive neuromyelitis optica spectrum disorders. *Brain* 2019; 142: 1310–1323.
 30. Tackley G, O'Brien F, Rocha J, et al. Neuromyelitis optica relapses: race and rate, immunosuppression and impairment. *Mult Scler Relat Disord* 2016; 7: 21–25.
 31. Cobo-Calvo A, Sepúlveda M, Rollet F, et al. Evaluation of treatment response in adults with relapsing MOG-Ab-associated disease. *J Neuroinflammation* 2019; 16: 134.
 32. Bonnan M, Valentino R, Debeugny S, et al. Short delay to initiate plasma exchange is the strongest predictor of outcome in severe attacks of NMO spectrum disorders. *J Neurol Neurosurg Psychiatry* 2018; 89: 346–351.
 33. Khalilidehkordi E, Clarke L, Arnett S, et al. Relapse patterns in NMOSD: evidence for earlier occurrence of optic neuritis and possible seasonal variation. *Front Neurol* 2020; 11: 537–516.
 34. Abboud H, Petrak A, Mealy M, et al. Treatment of acute relapses in neuromyelitis optica: steroids alone versus steroids plus plasma exchange. *Mult Scler* 2016; 22: 185–192.
 35. Stiebel-Kalish H, Hellmann MA, Mimouni M, et al. Does time equal vision in the acute treatment of a cohort of AQP4 and MOG optic neuritis? *Neurol Neuroimmunol Neuroinflamm* 2019; 6: e572.
 36. Jarius S, Ruprecht K, Wildemann B, et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: a multicentre study of 175 patients. *J Neuroinflammation* 2012; 9: 14.
 37. Jarius S, Ruprecht K, Kleiter I, et al.; in cooperation with the Neuromyelitis Optica Study Group (NEMOS). MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. *J Neuroinflammation* 2016; 13: 280.
 38. Collongues N, Cabre P, Marignier R, et al. A benign form of neuromyelitis optica: does it exist? *Arch Neurol* 2011; 68: 918–924.
 39. Levy M, Fujihara K and Palace J. New therapies for neuromyelitis optica spectrum disorder. *Lancet Neurol* 2021; 20: 60–67.
 40. Cree BA, Bennett JL, Sheehan M, et al. Placebo-controlled study in neuromyelitis optica – ethical and design considerations. *Mult Scler* 2016; 22: 862–872.
 41. Hyun JW, Kim Y, Kim SY, et al. Investigating the presence of interattack astrocyte damage in neuromyelitis optica spectrum disorder: Longitudinal analysis of serum glial fibrillary acidic protein. *Neurol Neuroimmunol Neuroinflamm* 2021; 8: e965e965.
 42. Chang X, Huang W, Wang L, et al. Serum neurofilament light and GFAP are associated with disease severity in inflammatory disorders with aquaporin-4 or myelin oligodendrocyte glycoprotein antibodies. *Front Immunol* 2021; 12: 647618.
 43. Aktas O, Smith MA, Rees WA, et al.; N-MOmentum scientific group and the N-MOmentum study investigators. Serum glial fibrillary acidic protein: a neuromyelitis optica spectrum disorder biomarker. *Ann Neurol* 2021; 89: 895–910.
 44. Segamarchi C, Silva B, Saidon P, et al. Would it be recommended treating multiple sclerosis relapses with high dose oral instead intravenous steroids during the COVID-19 pandemic? Yes. *Mult Scler Relat Disord* 2020; 46: 102449.
 45. Sepulveda M, Delgado-García G, Blanco Y, et al. Late-onset neuromyelitis optica spectrum disorder: the importance of autoantibody serostatus. *Neurol Neuroimmunol Neuroinflamm* 2019 ; 6: e607.
 46. Seok JM, Cho HJ, Ahn SW, et al. Clinical characteristics of late-onset neuromyelitis optica spectrum disorder: a multicenter retrospective study in Korea. *Mult Scler* 2017; 23: 1748–1756.
 47. Carnero Contentti E, Daccach Marques V, Soto de Castillo I, et al. Clinical features and prognosis of late-onset neuromyelitis optica spectrum disorders in a Latin American cohort. *J Neurol* 2020; 267: 1260–1268.
 48. Carnero Contentti E, Daccach Marques V, Soto de Castillo I, et al. Age at onset correlate with disability

- in Latin American aquaporin-4-IgG-positive NMOSD patients. *Mult Scler Relat Disord* 2020; 44: 102258.
49. Cobo-Calvo A, Ruiz A, Rollet F, et al.; NOMADMUS, KidBioSEP, and OFSEP study groups. Clinical features and risk of relapse in children and adults with myelin oligodendrocyte glycoprotein Antibody-Associated disease. *Ann Neurol* 2021; 89: 30–41.
50. Siritho S, Nopsopon T and Pongpirul K. Therapeutic plasma exchange vs conventional treatment with intravenous high dose steroid for neuromyelitis optica spectrum disorders (NMOSD): a systematic review and meta-analysis. *J Neurol* 2020; 10. Oct doi: 10.1007/s00415-020-10257-z. Epub ahead of print. PMID: 33037886. <https://pubmed.ncbi.nlm.nih.gov/33037886/>