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Frequency of new asymptomatic MRI lesions during attacks and follow-up of patients with NMOSD in a real-world setting

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Abstract

Background: We aimed to assess the frequency of new asymptomatic lesions on brain and spinal imaging (magnetic resonance imaging (MRI)) and their association with subsequent relapses in a large cohort of neuromyelitis optica spectrum disorder (NMOSD) patients in Argentina.

Methods: We retrospectively reviewed 675 MRI (225 performed during an attack and 450 during the relapse-free period (performed at least 3 months from the last attack)) of NMOSD patients who had at least 2 years of clinical and MRI follow-up since disease onset. Kaplan–Meier (KM) curves were used for depicting time from remission MRI to subsequent relapse.

Results: We included 135 NMOSD patients (64.4% were aquaporin-4-immunoglobulin G (AQP4-IgG)-positive). We found that 26 (19.26%) and 66 (48.88%) of patients experienced at least one new asymptomatic MRI lesion during both the relapse-free period and attacks, respectively. The most frequent asymptomatic MRI lesions were optic nerves followed by short-segment myelitis during the relapse-free period and attacks. KM curves did not show differences in the time taken to develop a new relapse.

Conclusion: Our findings showed that new asymptomatic lesions are relatively frequent. However, the presence of new asymptomatic MRI lesions during the relapse-free period and at relapses was not associated with a shorter time to developing subsequent relapses.

Keywords: Neuromyelitis optica spectrum disorder, asymptomatic MRI lesions, relapses, MRI, Latin America

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Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare but often devastating central nervous system (CNS) inflammatory disease that is mainly characterized by severe attacks of transverse myelitis (TM), optic neuritis (ON), and/or brainstem syndrome (BSS).[1,2]

In patients with NMOSD, aquaporin-4 (AQP4), a water channel expressed on astrocytes, is targeted by autoantibodies (AQP4-IgG(immunoglobulin G)), which causes the selective destruction of astrocytes, resulting in secondary oligodendrocyte and neuronal damage.[1,3] In consequence, the disease requires long-term immunosuppression to reduce the high rate of relapse related disability.[1–5]

Brain abnormalities on magnetic resonance imaging (MRI) have been described in up to 80% of NMOSD patients at presentation, and around 50% are suggestive or typical of NMOSD.[1–3] Longitudinally extensive transverse myelitis (LETM) lesions on spinal cord MRI have been reported in up to 70% of NMOSD patients, while short-segment myelitis (STM) lesions in around 20% of them.[1]

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During the past years, typical asymptomatic acute brain lesions for NMOSD have been described in a small proportion of NMOSD patients; however, the frequency seems to be higher when a systematic and strict monitoring is performed.[6–9] These asymptomatic lesions have been described during the relapse period and the relapse-free period. Nevertheless, the exact role of new asymptomatic or silent lesions on MRI has not been fully elucidated with regard to prognosis, treatment failure, risk of subsequent relapses, or disease management.[6–10]

Considering that the frequency and the role of new silent brain and spinal cord MRI lesions during or outside a relapse period are still unclear in NMOSD patients, we aimed to assess the frequency of new asymptomatic lesions on brain and spinal cord MRI and their association with subsequent relapses in a large cohort of NMOSD patients in Argentina.

Methods

A retrospective study was conducted in a cohort of NMOSD patients followed up in multiple sclerosis (MS)/NMOSD centers from Argentina and enrolled in RelevarEM, a nationwide, longitudinal, observational, nonmandatory registry of MS and NMOSD patients (Clinical Trials' registry number: NCT03375177; www.latambase.com.ar). Details on RelevarEM procedures and methods have been previously published elsewhere.[11] 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 as follows: routine clinical practice (at baseline: disease onset, course, symptoms, recovery from attacks, serological test, and methodology used), patient demographics (at baseline: patient identification, center, informed consent, and administrative information), clinical findings (at baseline: date, Expanded Disability Status Scale (EDSS), attacks, and paraclinical tests; at follow-up: MRI date, MRI new lesions, and cerebrospinal fluid findings) as well as immunotherapy prescribed (treatment used for MS/NMOSD and safety: adverse events) and outcomes observed.[10] To reduce risk of selection bias, neurologists participating in this registry were required to register all patients followed in their clinical practice.[11]

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 myelin oligodendrocyte glycoprotein antibody (MOG-IgG)-associated disease (MOGAD), diagnosed based on core clinical characteristics and the presence of serum MOG-IgG.[12,13] Although AQP4-IgG-positive and AQP4-IgG-negative are recognized to be distinct diseases with potential different pathogenesis and distinct treatment strategies, we included all patients with confirmed NMOSD diagnosis according to 2015 NMOSD criteria (AQP4-IgG-positive and AQP4-IgG-negative NMOSD patients). All AQP4-IgG-negative NMOSD patients were MOG-IgG-negative. Thus, these data are more relevant to real-world clinical practice with the observations having been performed in a realistic clinical context with patients coming from different centers in Argentina.

To be included, patients must have had at least 2 years of clinical and MRI follow-up since disease onset (first attack) and brain and spinal cord MRI performed must have been done at 1.5 T or a 3.0 T machines. Relapses and MRI (during relapse and remission phases) data were assessed retrospectively, and MOGAD patients and cases with insufficient or missing primary outcome data were excluded (Figure 1). Data on patient demographics, clinical, MRI findings, and administered treatments were collected and evaluated. A relapse 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 (i.e. fever, infection, injury, change in mood, and adverse reactions to medications). NMOSD core clinical characteristics were classified as (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 plus ON).[1] To further classify patients, AQP4-IgG and MOG-IgG status were also recorded. AQP4-IgG status was determined by cell-based assay (CBA) and tissue-based indirect immunofluorescence (IIF).[13–15] Serum samples were determined in different laboratories according to each participating patient/center, and noncentralized determinations were obtained. The presence of MOG-IgG was tested using CBA in all cases, and positive patients were excluded.[15] The demographic variables evaluated were gender, city of residence, and working status. Clinical variables included age at disease onset (first relapse of the disease), age at diagnosis, EDSS at study entry, current treatment, and first treatment received. Although there was no standardized MRI protocol between centers, follow-up brain scans included T2-weighted imaging, fluid-attenuated inversion recovery (FLAIR), gadolinium-enhanced T1-weighted imaging, and/or diffusion-weighted

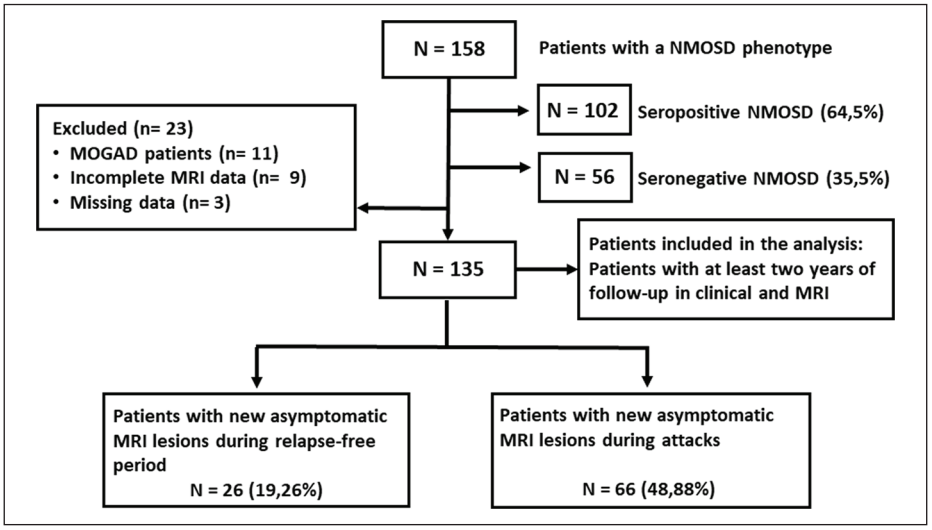

Figure 1. Flow diagram of the studied population.
MOGAD = myelin oligodendrocyte glycoprotein antibody (MOG-Ab)-associated disease; NMOSD = neuromyelitis optica spectrum disorders.

imaging in all patients. In addition, spinal cord (at least cervical) MRI were acquired and included T2-weighted imaging, T1-weighted imaging, and short tau inversion recovery (STIR) sequences. Follow-up brain and spinal cord MRI were obtained using nonuniform protocols from different MRI scanners (but all the included patients had standard clinical sequences used in clinical practice) and magnetic field strengths (1.5 or 3.0 T). Optic nerve lesions were assessed via the conventional brain scans. All abnormalities within the brain or spinal cord identified by the MRI specialist were confirmed and reported by the MS/NMOSD specialist in the standardized data collection developed for the study. To ensure homogeneous data collection, we designed a specific web-based platform to investigate NMOSD and MOGAD information, and asked researchers to register and make available relevant data from their patients for the purpose of this study.

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 and definitions

The MRI scans were classified as relapse MRI if performed during the clinical demyelinating events (<30 days apart) and as remission MRI if performed at least 3 months from the last attack and the patient was completely free of new symptoms.[8] During the first attack, asymptomatic lesions were defined as follows: increased diffusion-weighed signals or gadolinium-enhancement lesions and during subsequent relapses as newly developed T2-hyperintense lesions associated with one of the following: (1) increased diffusion-weighed signals, (2) gadolinium enhancement, or (3) resolution or decrease in size on a follow-up MRI, as previously reported.[7] On an attack, asymptomatic lesions on MRI were defined as those unrelated to the clinical symptoms and signs. In this context, it is important to highlight that asymptomatic lesions on MRI were defined by the presence or absence of clinical manifestations (symptoms and signs detected by neurologists), and no other examinations were performed at the time of the follow-up MRI to confirm for example that the optic nerve (e.g. optical coherence tomography or visual evoked potential) or spinal cord (e.g. motor potential evoked) involvements were really asymptomatic, as performed in clinical practice. No data about other examinations performed at the time of the remission were available to detect subtle clinical involvements, being this an important limitation. Patients were excluded if MRI was performed between 30 days and 3 months. On remission, new asymptomatic lesions were defined as a new or newly enlarging T2/FLAIR hyperintense lesion or T1 gadolinium-enhancing lesion in the absence of clinical overt symptoms on follow-up MRI during the relapse-free period (3 months).[6,8] We compared lesions on the MRI to the last reference MRI. On the attack MRI, we identified new (T2-weighted imaging/FLAIR) attack silent lesions as those unrelated to the clinical symptoms and signs (patient must be completely free of new

symptoms and signs). In consequence, we stratify the periods in MRI during relapse-free period and MRI during relapse.[6,7] Spinal cord MRI lesions were categorized as LETM when involving ⩾3 vertebral segments and as STM if <3 vertebral segments were affected. Baseline characteristics of the studied cohort were reported in percentages for categorical data and in median interquartile range for continuous data. The Kruskal–Wallis test (nonparametric test) was used to estimate differences among patients with and without asymptomatic lesions. Kaplan–Meier (KM) curves were used for depicting time from remission MRI to subsequent relapse. Group comparison (patients with and without asymptomatic lesions) was evaluated by log-rank test.[8] Multivariable regression models were created to assess the independent predictive value of demographic and clinical characteristics to relapses and time to relapses in patients with and without asymptomatic lesions. We used STATA Data Analysis and Statistical Software (StataCorp, College Station, TX) to examine data patterns, and the p values < 0.05 were statistically significant.

Table 1. Baseline characteristics of included patients.

	Total $N = 135$
Female gender, *n* (%)	103 (76.3)
Median EDSS at study enter, IQR (years)	4.0 (0–7)
Mean disease duration ± SD, IQR (years)	8.1 ± 4 (0–21)
Mean age at disease onset ± SD, IQR (years)	35.2 ± 11 (11–49)
Current mean age ± SD, IQR (years)	46.5 ± 14 (18–72)
AQP4-IgG-positive	87 (64.44)
AQP4-IgG-negative	48 (35.56)
Serological test	
IIF	50 (37)
CBA	84 (62.2)
ELISA	1 (0.8)
First treatment for disease	
Azathioprine	87 (64.4)
MMF	3 (2.2)
Rituximab	32 (23.8)
Other	1 (0.8)
None	12 (8.8)

MMF = mycophenolate mofetil; CBA = cell-based assay; IIF = indirect immunofluorescence; IQR = interquartile range; EDSS = Expanded Disability Status Scale; SD = standard deviation; AQP4-IgG = aquaporin-4-immunoglobulin G.

Results

Demographic, clinical, and MRI features

We included 135 patients with confirmed diagnosis of NMOSD, 87 (64.4%) were AQP4-IgG-positive and all AQP4-IgG-negative NMOSD patients fulfilled the 2015 NMOSD diagnostic criteria.[1] All AQP4-IgG-negative NMOSD patients were MOG-IgG-negative. As shown in Table 1, 76.3% of patients were women with a mean age at disease onset of 35.2 ± 12 years, a mean disease duration was 8.3 ± 4.2 years and a median EDSS of 4 (0–7).

A total of 675 MRI were available for the analysis, 225 performed during an attack (262 relapses, 86% of patients had an MRI during relapse) and 450 during the relapse-free period (Supplemental Table 1). Data on brain and spinal cord MRI only were included (MRI orbits were not included).

Asymptomatic MRI lesions during the relapse-free period

In NMOSD patients with at least 2 years of follow-up (clinical and MRI), we found that 26 (19.26%) of patients experienced at least one new asymptomatic MRI lesion during the relapse-free period, as shown in Table 2. The most frequent asymptomatic MRI lesions were optic nerves (38.46%) followed by STM (23.07%), and no differences between AQP4-IgG-positive and AQP4-IgG-negative patients were observed (Supplemental Table 2). Brain and spinal MRI asymptomatic lesions are illustrated in Figure 2. No differences between patients who had asymptomatic MRI lesions versus those without asymptomatic MRI lesions were found after evaluating demographic, AQP4-IgG serostatus, and pharmacological treatments (Table 3). In addition, no independent factors were found after applying multivariate linear and logistic regression models (Supplemental Tables 3 and 4). KM curves did not show differences in the time taken to develop a new relapse (log-rank test: $p = 0.30$), and no differences were found either when comparing the cumulative hazard risk of subsequent relapses (HR = 1.22, 95% CI = 0.67–2.34, $p = 0.23$) between NMOSD patients with and without asymptomatic MRI lesions (Supplemental Figures).

Asymptomatic MRI lesions during relapses

We identified a total of 262 attacks over a median disease duration of 9 ± 5.25 (range: 0–25 years) years. We detected that 66 (48.88%) NMOSD patients had at least one new asymptomatic MRI lesion during attacks (outside of symptomatic attacks) (Table 4). The most frequent asymptomatic MRI lesions during

Table 2. Frequency and location of new asymptomatic MRI lesions.

	At the relapse-free period	Preceding relapse	At relapses	Preceding relapse
Frequency of new asymptomatic MRI lesions, No (%)	26 (19.26)	Location (n*)/time** (median time ± SD months)	66 (48.88)	Location (*n*)
Location of new asymptomatic MRI lesions, No (%)				
STM	6 (23.07)	ON (16) 15 ± 3.5	9 (13.63)	ON (22)/APS (1)
LETM	0	—	3 (4.54)	ON (12); CS (1)
Optic nerve(s)	10 (38.46)	TM (24) 10 ± 3.5	17 (25.75)	TM (56); CS (1); BS (1)
Optic chiasm	2 (7.66)	TM (11) 11 ± 4.2	4 (6.06)	TM (10)
Area postrema	2 (7.66)	ON (10) 16 ± 5.3	5 (7.57)	ON (11)
Hypothalamus	0	—	4 (6.06)	ON (12)
Thalamus	0	—	2 (3.03)	ON (9); APS (1)
Third ventricle	2 (7.66)	TM (11)/ON (22)	6 (9.09)	ON (13); TM (12)
Tumefactive hemispheric white matter	1 (3.84)	TM (17)	10 (15.09)	ON (14); TM (15)
Corticospinal tracts	2 (7.66) 1 (3.84)	ON (22) 17 ± 4.2 TM (8)	2 (3.03)	ON (8) ON (5); TM (4); CS (1)
Nonspecific (dot-like) Other	0	—	4 (6.06)	0

LETM = longitudinally extensive transverse myelitis; TM = transverse myelitis; ON = optic neuritis; CS = cerebral syndrome; APS = area postrema syndrome; BS = brainstem syndrome; STM = short-segment myelitis; MRI = magnetic resonance imaging; SD = standard deviation.
*number of relapses; **preceding time of relapse before identifying the asymptomatic lesion.

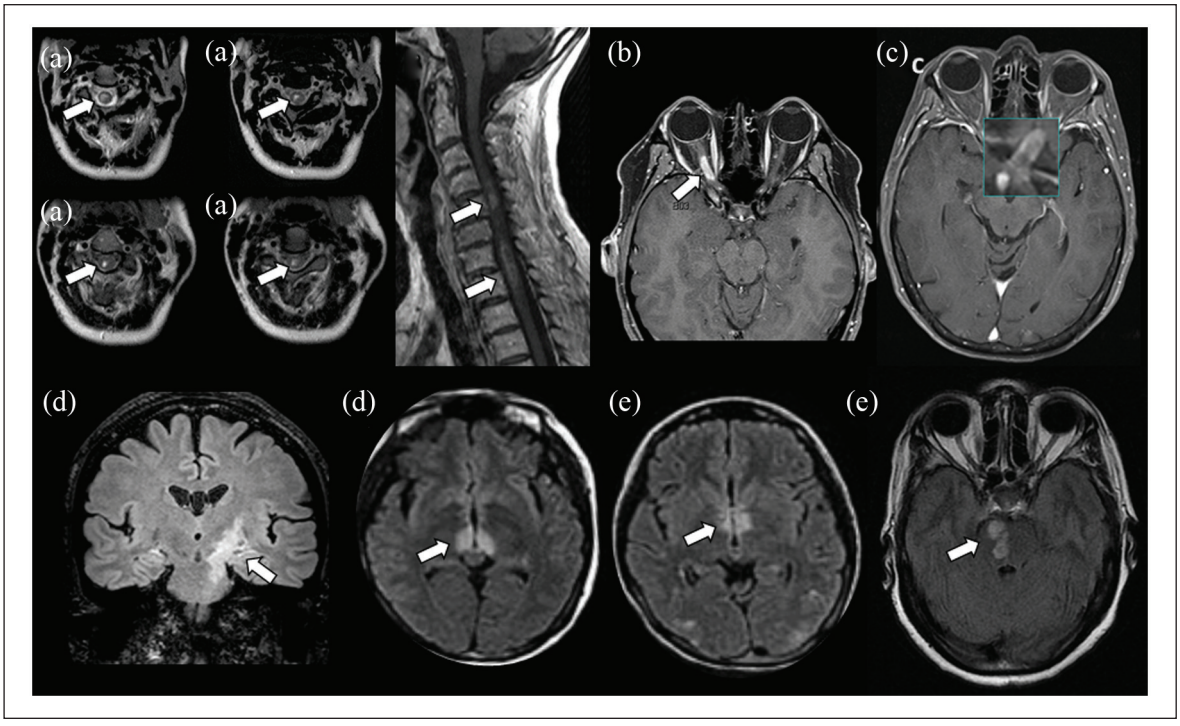

Figure 2. Asymptomatic MRI brain and spinal cord lesions during the relapse-free period:
(a) spinal cord lesions on axial T2-weighted images, (b) multisegmental spinal cord T1 gadolinium-enhancing lesions (sagittal images), (c) unilateral intraorbital right optic nerve T1 gadolinium-enhancing lesion and left-sided chiasmatic T1 gadolinium-enhancing lesion (axial images), (d) left corticospinal fluid-attenuated inversion recovery (FLAIR) hyperintensity (coronal images), (e) diencephalic (thalamus and hypothalamus) FLAIR hyperintensity lesions (axial images), and (f) brainstem (pons) FLAIR hyperintensity lesions (axial images). MRI = magnetic resonance imaging.

Table 3. Comparison between patients with and without asymptomatic MRI lesions during the relapse-free period.

	Patients with new MRI lesions ($N=26$)	Patients without new MRI lesions ($n=109$)	p
Female gender, *n* (%)	19 (73.08)	84 (77.06)	0.66
Median EDSS at study enter, IQR (years)	3 ± 1	3 ± 1	0.18
Median disease duration, IQR (years)	11.5 ± 1	9.3 ± 1	0.08
Median age at disease onset, IQR (years)	38 ± 3	38.3 ± 2	0.96
Current median age ± IQR	50 ± 3	47.1 ± 2	0.47
AQP4-IgG-positive	16 (61.5)	71 (65.1)	0.23
AQP4-IgG-negative	10 (38.46)	38 (34.8)	0.32
Serological test			
IFI	10 (38.46)	40 (36.7)	0.93
ELISA	—	1 (0.92)	—
CBA	16 (61.54)	68 (62.39)	0.87
Unknown	—	—	
First treatment for NMOSD			
Azathioprine	17 (65.38)	70 (64.22)	0.47
MMF	2 (7.69)	1 (0.91)	0.10
Rituximab	5 (19.2)	27 (24.7)	0.38
Other	0	1	—
IgG	0	0	—
None	2 (7.69)	10 (9.17)	0.65

MMF = mycophenolate mofetil; CBA = cell-based assay; IFI = indirect immunofluorescence; IQR = interquartile range; EDSS = Expanded Disability Status Scale; AQP4-IgG = aquaporin-4-immunoglobulin G; NMOSD = neuromyelitis optica spectrum disorder.

relapses were optic nerves (25.75%) followed by STM (13.63%), and no differences between AQP4-IgG-positive and AQP4-IgG-negative patients were observed (Supplemental Table 2). No differences between patients who had asymptomatic MRI lesions versus those without asymptomatic MRI lesions during relapses were observed after evaluating demographic, AQP4-IgG serostatus, and treatments.

Discussion

In this retrospective study of a large clinical cohort based on data from the RelevarEM registry, we evaluated asymptomatic MRI lesions during both relapse and relapse-free periods in 135 NMOSD patients followed up and managed in Argentina in a real-world setting. Neurologists registering patients in RelevarEM were from different regions of the country, ensuring a representative national sample of patients. In this clinical cohort, we observed that 19.26% experienced at least one asymptomatic MRI lesion during the relapse-free period and 48.88% of patients had at least one new asymptomatic MRI lesion (outside of symptomatic lesion) during relapses. No differences were observed after evaluating distinct relevant clinical factors between patients who had asymptomatic MRI lesions versus those without asymptomatic MRI lesions in both during the relapse-free period and relapses nor after applying regression models. In addition, KM analyses and cumulative hazard risk of subsequent relapses in patients with versus without new asymptomatic MRI lesion during the relapse-free period did not show differences.

While typical or suggestive MRI lesions were reported in up to 53% of NMOSD patients[16] (even at disease onset),[17] there is an extensive debate on the frequency and the impact of asymptomatic MRI lesions, and the need of routine MRI at follow-up in patients without relapses is still controversial.[18–20] In this context, studying the longitudinal evolution of MRI lesions after an initial attack may improve our understanding on subclinical activity of the disease and may help to plan specific strategies for monitoring disease activity and treatment. Although there is no consensus worldwide on MRI use during follow-up, a Latin American NMOSD consensus recently published,[21] using formal methodology (RAND/UCLA), has recommended annual brain MRI use among NMOSD patients after initiating specific treatment as a complementary control at clinical follow-up. However, there was no consensus regarding spinal cord MRI use during follow-up (unless a clinical relapse occurs).

Table 4. Comparison between patients with and without asymptomatic MRI lesions during relapses.

	Patients with new brain lesion during relapse ($N=66$)	Patients without new brain lesion during relapse ($n=69$)	p
Female gender, *n* (%)	53 (80)	48 (69)	0.66
Median EDSS at study enter, IQR (years)	3.0 ± 1	3.0 ± 1	0.35
Median disease duration, IQR (years)	9.3 ± 1	9 ± 1	0.46
Median age at disease onset, IQR (years)	36.8 ± 2	40.8 ± 2	0.15
Current median age ± IQR	45.7 ± 2	49 ± 2	0.21
AQP4-IgG-positive	40 (60)	47 (68)	0.23
AQP4-IgG-negative	26 (40)	22 (31)	0.18
Serological test			
IFI	21 (33)	29 (39)	0.24
ELISA	1 (1)	—	—
CBA	44 (66)	40 (61)	0.65
Unknown			
First treatment for NMOSD			
Azathioprine	40 (62)	47 (68)	0.08
MMF	2 (1.5)	1 (2)	0.43
Rituximab	17 (25.5)	15 (23)	0.67
Other	0	1	—
IgG	0	0	—
None	7 (11)	5 (7)	0.18

MMF = mycophenolate mofetil; CBA = cell-based assay; IFI = indirect immunofluorescence; IQR = interquartile range; EDSS = Expanded Disability Status Scale; AQP4-IgG = aquaporin-4-immunoglobulin G; NMOSD = neuromyelitis optica spectrum disorder.

At the interattack period, different observational retrospective studies reported a frequency of new MRI lesions between 2.6% and 8%,[6,8] which is lower than that described in this study (19%). A preliminary analysis from the N-MOmentum randomized placebo-controlled trial (inebilizumab study) in NMOSD patients found that approximately 51%, 3%, and 18% of MRI showed asymptomatic optic nerve, brain, and spinal cord Gd-T1 MRI enhancement during an interattack surveillance MRI (in the absence of adjudicated attacks), respectively.[9] These results yielded lesion appearance frequencies higher than those described in a recent study from the United States (Mayo Clinic) where asymptomatic optic nerve enhancement occurred in 16.8% of patients with preceding ON and new asymptomatic enhancement was observed only in 1.8% of patients,[22] suggesting that intermittent blood–brain barrier breakdown or subclinical ON might occur. However, in this study, asymptomatic optic nerve MRI lesions were detected in 38.46%, in line with findings from N-MOmentum trial in which data management or monitoring is specific. Most recently, a European study reported that asymptomatic MRI lesions were detected in 7 out of 269 (2.6%) patients during the remission period.[8] Furthermore, median time from MRI to next relapse was shorter in patients experiencing a new asymptomatic MRI lesion at remission than in their absence, suggesting that new asymptomatic MRI lesions are rare in NMOSD during remission and appear to precede imminent relapses. Conversely, our findings were not associated with an increased risk of subsequent relapses. In another Korean study,[6] authors reported new asymptomatic brain lesions in 5 out of 145 (3.4%) patients over a long relapse-free period (708 person-years; median, 2.7 person-years), and all new asymptomatic MRI lesions observed were deemed to be nonspecific in terms of their location and configuration (all lesions were less than 6 mm in size without gadolinium enhancement). Most recently, new brain lesions were observed in 8% of NMOSD patients during follow-up, which was less than detected in MS (54%) but did not differ from MOGAD (4%).[23] New spinal cord MRI lesions were rare across groups (0%–4%).[23] In our cohort, only one patient presented a new asymptomatic dot-like (nonspecific) lesion, but the remaining lesions were typical or suggestive of NMOSD[1] such as those in area postrema,

optic chiasm, and corticospinal tracts.[3,24] Of note, all images were reviewed by NMOSD expert neurologists and/or neuroradiologists, who took into consideration their location and configuration, for which reason misinterpretation would be rare. Interestingly, a complete resolution of all the specific T2 abnormalities at MRI follow-up has been described for MOGAD, but not in NMOSD (only 10% on axial brain MRI and 0% on sagittal spinal cord MRI).[25] However, a Korean study reported that 24% of the acute brain lesions in NMOSD patients resolved completely on T2-weighted images, and a decrease in size ⩾50% on T2-weighted was found in 58% of lesions on follow-up MRI.[26]

Whether progressive subclinical brain atrophy in NMOSD similar to MS exists or not is another important point in NMOSD, but it was not studied in this paper.[27] In this regard, brain atrophy is uncommon in NMOSD at follow-up,[28,29] including LATAM population.[25] In MS, the presence of widespread abnormalities in normal-appearing tissues is frequently observed.[30] However, such changes in NMOSD seem to be limited to tracks that connect to lesions, such as the optic nerve and spinal cord pathways, consistent with our results.[28] In contrast, a recent study reported that silent progression of brain atrophy was present in NMOSD patients, similar to what is observed in MS patients, as the annualized atrophy rate of normalized brain volumes was not different between NMOSD and MS patients even in the age-matched analysis.[30]

First myelitis attack can be associated with asymptomatic spinal cord MRI lesions in seropositive NMOSD patients (STM rather than LETM), but these silent lesions have also been described in patients with ON in the absence of prior myelitis.[31] In this study, we found that one-quarter of patients experienced asymptomatic STM lesion during the relapse-free period. In addition to this, spinal cord atrophy and reductions of mean upper cervical cord area have been reported in seropositive NMOSD, even in the absence of a clinical history of relapses or previous spinal cord MRI lesions.[32] Likewise, a recent study has reported an association between spinal cord atrophy and an increased number of clinical myelitis relapses.[33] Recently, a graph theory-based multimodal network analysis in NMOSD patients, evaluating associations of optic coherence tomography, clinical measures, MRI total brain and deep gray matter volumes, cortical thickness, and spinal cord atrophy has reported potential evidence of neurodegeneration in nonrelapse localized topographies. An association between decreased nucleus accumbens and caudate nucleus volumes with higher combined relapse type count and longer disease duration, respectively, was found, demonstrating that subclinical pathological processes may make symptoms worse.[33,34]

The presence of asymptomatic MRI lesions during a relapse has been previously published in different cohorts of NMOSD patients. A Korean study based on 165 seropositive NMOSD patients found that acute asymptomatic NMOSD-typical brain lesions were detected in 8% of patients during an attack of ON and 15% during an attack of myelitis. Interestingly, the median time to diagnosis using the 2015 NMOSD diagnostic criteria was shortened from 28 to 6 months if asymptomatic NMOSD-typical brain lesions were considered as evidence for dissemination in space,[7] even in the absence of AQP4-IgG data. More recently, new asymptomatic MRI lesions were detected in 88 of 470 (18.7%) relapses.[8] In addition, a preliminary analysis from the N-Momentum trial reported that during an ON relapse, 29% and 7% experienced simultaneous asymptomatic Gd-T1 MRI enhancement in spinal and brain, respectively. Furthermore, 27% and 14% of patients suffering a relapse of myelitis had simultaneous new asymptomatic Gd-T1 MRI-enhancing lesions in optic nerves and brain, respectively.[9] In this study, an increased frequency of new asymptomatic MRI lesions during relapses was found (48%), and optic nerves and spinal lesions being the most frequently affected regions.

This study has several limitations that should be noted. It is a retrospective cohort study with the possibility of bias and confounders typical of this design, and therefore, findings should be interpreted with caution. The unintentional selection bias could have occurred given the relatively small numbers of patients included in the different subgroups, thus reducing statistical power. Another important limitation is the lack of standardized MRI assessment of MRI lesions at a regular time interval on the same MRI scanner with variable magnetic field intensity (1.5 vs. 3.0 T). The use of nonconventional MRI sequences may potentially improve the detection rate of new asymptomatic MRI lesions not spotted on conventional studies. However, strength of this research is that this information reflects real-world evidence of clinical practice. Finally, the role of immunosuppressant treatment was not studied, and it could have impacted on the results, it being another limitation.

In this cohort from Argentina, and despite the limitations described above, our findings showed that new asymptomatic lesions are relatively frequent.

However, the presence of new silent MRI lesions during the interattack period and at relapses does not seem to be a concern, as these findings were not associated with a shorter time to developing subsequent relapses. To the best of our knowledge, this is the first large cohort study from a Latin America (LATAM) region. These results serve to add information to the international data set, for comparison with previously published results from North America, Asia, and Europe. As shown, patients in LATAM are expected to present differences in comparison with patients in these other regions. Further prospective studies, employing regular intervals with MRI identical field intensity in patients receiving equal treatments, with a larger number of participants are needed to assess the generalizability of our conclusions, thus determining whether performing MRI outside of relapses (at follow-up) as a complementary subclinical activity control in NMOSD patients is relevant in clinical practice, especially in the current era of newly approved immunotherapies.[35]

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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