


ORIGINAL ARTICLE

Chiasmatic lesions on conventional magnetic resonance imaging during the first event of optic neuritis in patients with neuromyelitis optica spectrum disorder and myelin oligodendrocyte glycoprotein-associated disease in a Latin American cohort

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Abstract

Background and purpose: Optic neuritis (ON) is often the initial symptom of neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein-associated disease (MOGAD). We aimed to compare the frequency and pattern of chiasmatic lesions in MOGAD-related ON (MOGAD-ON) and NMOSD-related ON (NMOSD-ON) using conventional brain imaging (magnetic resonance imaging [MRI]) in Latin America (LATAM).

Methods: We reviewed the medical records and brain MRI (≤ 30 days from ON onset) of patients with a first event of MOGAD-ON and NMOSD-ON. Patients from Argentina ($n = 72$), Chile ($n = 21$), Ecuador ($n = 31$), Brazil ($n = 30$), Venezuela ($n = 10$) and Mexico ($n = 82$) were included. Antibody status was tested using a cell-based assay. Demographic,

clinical, imaging and prognostic (as measured by the Visual Functional System Score [VFSS] of the Expanded Disability Status Scale) data were compared.

Results: A total of 246 patients (208 NMOSD and 38 MOGAD) were included. No differences were found in gender and ethnicity between the groups. We observed chiasmatic lesions in 66/208 (31.7%) NMOSD-ON and in 5/38 (13.1%) MOGAD-ON patients ($p = 0.01$). Of these patients with chiasmatic lesions, 54/66 (81.8%) and 4/5 had associated longitudinally extensive optic nerve lesions, 45/66 (68%) and 4/5 had bilateral lesions, and 31/66 (47%) and 4/5 showed gadolinium-enhancing chiasmatic lesions, respectively. A positive correlation was observed between VFSS and presence of bilateral ($r = 0.28, p < 0.0001$), chiasmatic ($r = 0.27, p = 0.0001$) and longitudinally extensive lesions ($r = 0.25, p = 0.0009$) in the NMOSD-ON group, but no correlations were observed in the MOGAD-ON group.

Conclusions: Chiasmatic lesions were significantly more common in NMOSD than in MOGAD during an ON attack in this LATAM cohort. Further studies are needed to assess the generalizability of these results.

KEYWORDS

magnetic resonance imaging, myelin oligodendrocyte glycoprotein-associated disease, Neuromyelitis optica spectrum disorder, optic neuritis, prognosis

INTRODUCTION

Optic neuritis (ON) is often the initial symptom of antibody-mediated conditions such as neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein-antibody-associated disease (MOGAD) [1–3]. Additionally, an overlap of paraclinical and neuroradiological features can be found in clinical practice [1–4]. Differentiating NMOSD from MOGAD is often a challenge, particularly in lower-income countries where the availability of diagnostic tests is, in general, low [5,6]. The ultimate diagnosis is crucial, as prognosis and treatments differ between the two conditions [2,7–9]. Currently, MOGAD is defined as an oligodendrocytopathy, while NMOSD seropositive for aquaporin-4 antibody (AQP4-ab) is considered an astrocytopathy [10]. A proportion of NMOSD seronegative patients have MOGAD, reaching up to 42% in Europe [11] and up to 27% in Latin America (LATAM) [12,13]. In this context, MOGAD is increasingly recognized as a nosological entity distinct from classic NMOSD seropositivity [14,15].

Although conventional brain magnetic resonance imaging (MRI) is not required for the diagnosis of isolated, bilateral or recurrent ON, it may help to detect optic nerve or chiasmatic lesions in patients with MOGAD-related ON (MOGAD-ON) and NMOSD-related ON (NMOSD-ON) [16]. Additionally, MRI is crucial to exclude differential diagnoses as well as for the evaluation of inflammatory lesions during follow-up [17]. While brain MRI lesions in both NMOSD and MOGAD have been described [9–18], only a few previous studies have evaluated the radiological features of NMOSD-ON versus MOGAD-ON, focusing on optic chiasm involvement [19–23]. Typically, NMOSD-ON affects the posterior segment, often with

longitudinally extensive lesions or chiasmatic involvement of the optic pathway [1–3]. By contrast, MOGAD-ON is associated with the optic nerve sheath or extends into the orbital fat with gadolinium-enhancing lesions more than half of the length of the optic nerve in 80% of patients [19,24]. Optic chiasm lesions on MRI have been reported in up to 64% of NMOSD-ON patients seropositive for AQP4-ab, while in MOGAD-ON they were reported in up to 16% [19–23]. Thus, frequency rates vary widely between distinct populations worldwide. Considering that a lack of data in the LATAM population exists, we aimed to compare the frequency and pattern of chiasmatic lesions in NMOSD-ON and MOGAD-ON patients, at the time of their first ON, using conventional brain MRI. Additionally, we correlated imaging predictors associated with visual impairment at the last follow-up.

METHODS

We conducted a retrospective observational multicenter study in consecutive patients from Argentina ($n = 72$), Chile ($n = 21$), Ecuador ($n = 31$), Brazil ($n = 30$), Venezuela ($n = 10$) and Mexico ($n = 82$) with a first event of MOGAD-ON or NMOSD-ON attack. NMOSD patients were diagnosed according to the 2015 NMOSD criteria [3]. MOGAD was diagnosed in patients with ON associated with serum myelin oligodendrocyte glycoprotein antibody (MOG-ab) positivity [10]. Each patient's medical record and brain MRI (≤ 30 days from ON onset) was reviewed locally. All patients were evaluated by at least one neurologist and/or ophthalmologist during and after this first attack. In addition, all MRI scans were rated by one neuroradiologist and/

or neurologist with expertise in demyelinating disorders. ON was defined as follows: visual acuity loss and at least two of the following criteria: (i) cecentral field defect; (ii) afferent pupillary defect; (iii) pain with eye movement; (iv) color vision abnormalities; and/ or (e) abnormal visual evoked potentials [25]. Visual outcomes at last follow-up were evaluated using the Visual Functional System Score (VFSS; rated from 0 to 6) of the Expanded Disability Status Scale (EDSS) [26], as shown in Table S1. Poor visual outcome was defined as a VFSS ≥ 4 at the last follow-up [27]. Data on demographic characteristics (gender, ethnicity and age at disease onset), clinical features (symptoms at onset, clinical course, disease duration and disability), treatment (acute and long-term) and AQP4-ab and MOG-ab status (positive and negative) at diagnosis were collected. AQP4-ab and MOG-ab were determined by means of a cell-based assay (transfected immunofluorescence cell-based assay) in each participating center as this is the gold standard for accurate detection of these autoantibodies [3,28,29]. All patients underwent brain MRI with and without gadolinium on a 1.5-T or 3.0-T scanner for typical diagnostic workup. Although MRI protocols could have varied between centers, standard clinical sequences such as T1-weighted and T2-weighted and/or fluid-attenuated inversion recovery sequences were included and reviewed locally in all patients to ensure a homogeneous sample. Of note, MRI was obtained within 30 days from ON onset (with or without prior administration of high-dose intravenous methylprednisolone). No dedicated orbital MRI was included in the analysis. Axial, coronal and sagittal views were evaluated.

Optic nerve lesions on MRI, at the time of ON attack, were classified as follows: (i) unilateral lesion; (ii) bilateral lesions; and (iii) chiasmatic lesions (affecting any part of the optic chiasm). Additionally, uni- or bilateral lesions were subclassified into: orbital (anterior) optic nerve lesion; canalicular (posterior) optic nerve lesion; and/ or longitudinally extensive optic nerve lesion (extending over 50% optic nerve length) [22,28]. Presence or absence of gadolinium-enhancing lesions was also reviewed (Figure 1).

This study was approved by the local ethics committee of each participating center and informed consent for the use of their anonymized MRI scans for investigation purposes was obtained from all participants.

Statistical analysis

Results are reported as count (percentage) and mean \pm standard deviation (SD). We compared optic nerve MRI lesions in NMOSD versus MOGAD, particularly focusing on chiasmatic lesions in these disorders. We used Fisher's exact test or the chi-squared test for categorical information (when appropriate) and Student's *t*-test or the Mann-Whitney *U*-test for continuous data, depending on data distribution. Spearman's correlation was used to analyze associations between visual outcome and bilateral lesions, longitudinally extensive optic nerve lesions and optic chiasm lesions on brain MRI. The statistical analysis was performed using GraphPad Prism 8. Due to the exploratory nature of this study, no formal

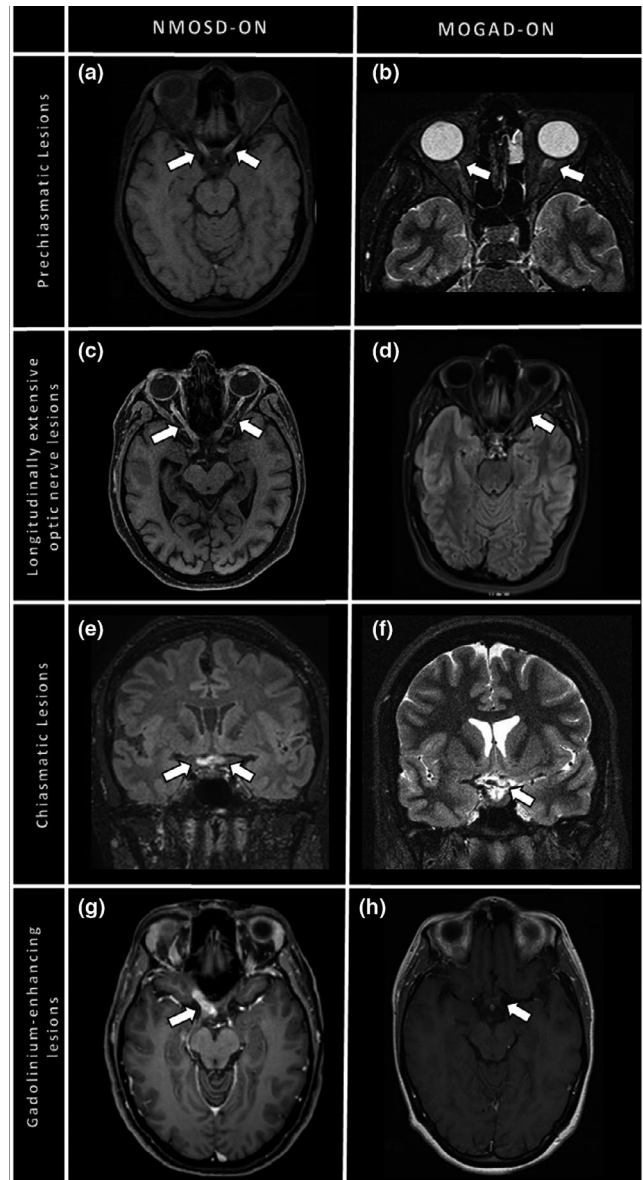


FIGURE 1 Optic nerve and chiasmatic lesions in patients with neuromyelitis optica spectrum disorder-related optic neuritis (NMOSD-ON) and myelin oligodendrocyte glycoprotein-associated disease-related optic neuritis (MOGAD-ON) using conventional brain magnetic resonance imaging. (a) Bilateral acute posterior (canalicular) optic nerve T1 hyperintensity (axial images). (b) Bilateral anterior (orbital) optic nerve T2 fat suppression hyperintensity (axial images). (c) Bilateral longitudinally extensive optic nerve T1 hyperintensity (axial images). (d) Unilateral longitudinally extensive left optic nerve fluid-attenuated inversion recovery (FLAIR) hyperintensity (axial images). (e) Chiasmatic FLAIR hyperintensity (coronal images). (f) Chiasmatic left T2 hyperintensity (coronal images). (g) Unilateral posterior right optic neuritis and right-sided chiasmatic T1 gadolinium-enhancing lesion (axial images). (h) Chiasmatic T1 gadolinium-enhancing lesion (axial images). Panels (a), (c), (e) and (g) correspond to NMOSD-ON seropositive patients and panels (b), (d), (f) and (h) correspond to MOGAD-ON patients

sample-size calculation was made and no adjustment for multiple testing was applied. The significance level was established as $p < 0.05$.

RESULTS

A total of 246 patients (208 NMOSD-ON and 38 MOGAD-ON) were included. AQP4-ab was detected in 84.7% of NMOSD patients. All the included NMOSD seronegative patients ($n = 31$) were MOG-ab negative. Non-White patients comprised 39.8% of the total cohort. No differences were found in gender and ethnicity between groups. As expected, age at onset, number of relapses, neurological disability, poor visual outcome at last follow-up and, plasma exchange and rituximab use were significantly associated with NMOSD-ON patients as compared to MOGAD-ON patients. Demographic and clinical features of the studied cohort are summarized in Table 1.

At the time of ON attack, we observed chiasmatic lesions on brain MRI in 66 out of 208 (31.7%) NMOSD-ON patients and in 5 out of 38 (13.1%) MOGAD-ON patients ($p = 0.01$). Of the NMOSD-ON and MOGAD-ON patients who had chiasmatic lesions, 54/66 (81.8%) and 4/5 had associated longitudinally extensive optic nerve lesions, 45/66 (68%) and 4/5 had bilateral lesions, and 31/66 (47%) and 4/5 had gadolinium-enhancing chiasmatic lesions, respectively. Additionally, no differences were found when we compared only seropositive NMOSD-ON patients versus MOGAD-ON patients (Tables S1–S4). The MRI features of the studied cohort are summarized in Table 2.

A positive correlation was observed between VFSS and presence of bilateral lesions ($r = 0.28$, 95% confidence interval [CI] 0.14–0.40; $p < 0.0001$), chiasmatic lesions ($r = 0.27$, 95% CI 0.13–0.39; $p = 0.0001$) and longitudinally extensive optic nerve lesions ($r = 0.25$, 95% CI 0.10–0.38; $p = 0.0009$) in NMOSD-ON patients. In contrast, no significant correlation was observed between VFSS and bilateral, chiasmatic and longitudinally extensive optic nerve lesions in MOGAD-ON patients (Table 3).

DISCUSSION

Aiming to distinguish the frequency and pattern of chiasmatic lesions in NMOSD-ON versus MOGAD-ON at the time of ON attack and to evaluate the visual outcomes at last follow-up, we compared MRI lesions in a LATAM cohort of NMOSD and MOGAD patients in a real-world setting. In this study, we found that the frequency of chiasmatic lesions was significantly higher in NMOSD-ON when compared to MOGAD during the first attack of ON at disease onset. A positive correlation was also found between VFSS (visual outcome at last follow-up) and presence of bilateral, chiasmatic and longitudinally extensive optic nerve lesions at disease onset in NMOSD-ON patients, but this was not observed for MOGAD-ON patients.

Two recent studies from China (MOG-ON = 20 and AQP4-ON = 45) [30] and the United States (MOG-ON = 80 and AQP4-ON = 74) [22] have reported a higher frequency of optic chiasm involvement (15% and 16%, respectively) in MOGAD patients, in line with our findings (13.1%), which is higher than previous studies that reported chiasm involvement to be as low as 0%–5% [19,20]. However, information on whether ON was the first attack or not

in these studies is unavailable. Additionally, the rate of chiasmatic lesions on MRI in NMOSD-ON seropositive patients was reported to be between 10.5% and 64%, these being more frequent in the Australian cohort (64%; MOG-ON = 19 and AQP4-ON = 11) than in the Thai cohort (10.5%; AQP4-ON = 50) and LATAM cohort (16%; NMOSD-ON = 112). Our results are slightly higher than those observed in both the US [22] and Chinese [30] cohorts (31.7%, 20% and 22.2%, respectively). Of note, as in the Australian and Thai cohorts, the present study focused on both first-ever NMOSD-ON and MOGAD-ON at disease onset. Also, this was the only study including exclusively LATAM patients.

In the present study, NMOSD-ON patients experienced more posterior lesions, and chiasmatic lesions (47% had gadolinium-enhancing lesions) were associated with longitudinally extensive optic nerve lesions and bilateral lesions in 82% and 68% of cases, respectively. Although no significant differences between NMOSD-ON and MOGAD-ON in posterior and longitudinally extensive optic nerve lesions were found in the present cohort, due to the low number of MOGAD-ON patients included, the presence of posterior and longitudinally extensive optic nerve involvement, in addition to chiasmatic lesions, should raise clinical suspicion for NMOSD-ON. Previous studies [19–23,30] reported posterior lesions in between 35% and 80% of the studied cases. Furthermore, longitudinally extensive optic nerve involvement was reported in 13%–100% [19–23] of NMOSD-ON patients. In a European study, longitudinally extensive optic nerve lesion and/or involvement of the optic chiasm was observed in 6/26 and 4/26 patients, respectively, but only 8/26 (30.8%) MRI scans were obtained during acute ON [31]. In another study from the United States [22], the authors observed that longitudinally extensive optic nerve involvement was significantly more frequent in MOGAD-ON than NMOSD-ON (54% vs. 13%; $p = 0.04$). By contrast, in the China study [30], longitudinally extensive optic nerve involvement was significantly more frequent in NMOSD-ON than in MOGAD-ON (57.8% vs. 30%; $p = 0.03$), this being lower than the rate observed in this cohort (82% in NMOSD-ON). In the present study, MOGAD-ON patients had more anterior involvement than NMOSD-ON patients (39% vs. 14%; $p = 0.02$), consistent with previous reports [19–23,30], with a similar percentage (~40% for both) of longitudinally extensive optic nerve lesions on MRI. In this sense, the presence of anterior involvement associated with longitudinally extensive optic nerve lesions, in the absence of chiasmatic lesions, suggests clinical suspicion of MOGAD-ON, supporting previous reports [19–23,30]. Given that resolution of T2-hyperintense lesions have been reported in MOGAD (72%) and NMOSD seropositive patients (14%) in a cohort from the United States [32], a strength of our study was that brain MRI was obtained at the time of ON attack in all patients in the studied cohort. Thus, all T2-hyperintense lesions represented lesions at the acute stage and not only contrast-enhancing lesions were included, increasing the detection yield. Additionally, taking into account that ON is the most frequent symptom at disease onset in both antibody-mediated diseases in LATAM [12,18], our results may have a high impact in clinical practice in this region. The present study differs from previous studies because it is the largest

TABLE 1 Demographic and clinical features

	NMOSD-ON	MOGAD-ON	<i>p</i> value
Patients, <i>n</i>	208	38	
Age at onset, years	38.5 ± 14.6	32.2 ± 14.2	0.01
Disease duration at last follow-up, months	36.6 ± 37.5	19.3 ± 23.1	0.007
Female gender, <i>n</i> (%)	175 (84)	30 (78.9)	0.47
Ethnicity, <i>n</i> (%)			
White	129 (62)	19 (50)	0.20
Non-White ^a	79 (38)	19 (50)	
Clinical course at last follow-up, <i>n</i> (%)			
Recurrent	171 (83)	24 (63)	0.01
Relapses after first attack	3.2 (±1.7)	2.2 (±1.4)	0.02
Time to second relapse, months	23.7 (±33.2)	11.3 (±15.8)	0.06
Optic neuritis, <i>n</i> (%)			
Isolated ON	175 (84)	31 (81)	0.63
ON plus any other clinical manifestation ^b	33 (16)	7 (19)	
Autoimmune comorbidity, <i>n</i> (%)	35 (17)	5 (13)	0.81
Outcome at last follow-up, <i>n</i> (%)			
Median (range) EDSS at last follow-up	4 (0–9)	2 (0–6)	0.0001
EDSS ≥ 4 at last follow-up, <i>n</i> (%)	101 (48)	6 (15.8)	0.0001
VFSS	3.6 (±2.1)	1.7 (±1.7)	0.0001
VFSS ≥ 4, <i>n</i> (%)	108 (55.3)	8 (20.1)	0.0001
Brain and spinal MRI at onset, <i>n</i> (%)			
Brain typical lesions and ON	37 (17)	6 (15)	1
Spinal cord lesions (LETM) and ON	49 (23)	9 (23)	1
Acute treatment, <i>n</i> (%)			
PLEX	85 (40)	5 (13)	0.001
Corticosteroid + PLEX	88 (42)	5 (13)	0.001
Initial chronic therapy, <i>n</i> (%) ^c			
Azathioprine	60 (29)	12 (31)	0.70
Mycophenolate	16 (7)	3 (7)	1
Rituximab	128 (61)	15 (39)	0.01

Abbreviations: EDSS, Expanded Disability Status Scale; LETM, longitudinally extensive transverse myelitis (extending over ≥3 vertebral segments); MOGAD-ON, myelin oligodendrocyte glycoprotein-associated disease-related optic neuritis; NMOSD-ON, neuromyelitis optica spectrum disorder-related optic neuritis; ON, optic neuritis; PLEX, plasma exchange; VFSS, Visual Functional System Score.

Data are mean ± standard deviation, unless otherwise indicated.

Significant *p* values are indicated in bold.

^aMestizo = 84, Afro-descendant = 10, Aboriginal = 1, and Asian = 3.

^bNMOSD: ON + TM (*n* = 30), ON + APS (*n* = 1), ON + TM + APS (*n* = 1); MOGAD: ON + TM (*n* = 6), ON + cerebellar syndrome (=1).

^c4 NMOSD patients initiated with cyclophosphamide.

to date specifically focused on chiasmatic lesions in patients with a first event of NMOSD-ON and MOGAD-ON in a LATAM population.

In line with results from a Japanese cohort (MOG-ON = 19 and AQP4-ON = 9) that showed a significant association between abnormal axial signal length of the optic nerve in the acute phase and affected visual prognosis, we found a significant correlation between visual outcome at last follow-up and bilateral, chiasmatic and longitudinally extensive optic nerve lesions at disease onset in NMOSD-ON

patients. Consistent with other large series [8,14,31–35], we observed that NMOSD-ON patients experienced a greater number of relapses, as well as more severe and sustained visual (VFSS) and neurological (EDSS) impairment at latest follow-up than MOGAD-ON patients. Thus, we confirmed that MOGAD-ON patients may have better neurological and visual recovery, and more favorable outcomes than those with NMOSD-ON [8,14,31–35]. However, adult MOGAD-ON patients may have a higher risk of relapses and worse functional recovery as

TABLE 2 Imaging features

	NMOSD-ON	MOGAD-ON	<i>p</i> value
Patients, <i>n</i>	208	38	
MRI lesions at the time of ON, <i>n</i> (%)			
Optic nerve			
Unilateral	87 (42)	17 (44)	0.85
Bilateral	90 (43)	14 (37)	0.48
Chiasm	66 (31.7)	5 (13.1)	0.01
Orbital (anterior) optic nerve lesion	30 (14)	15 (39)	0.001
Canalicular (posterior) optic nerve lesion	59 (28)	6 (15)	0.11
Longitudinally extensive optic nerve lesion	85 (40)	14 (37)	0.72
Optic chiasmal involvement	66/208	5/38	
Chiasmatic lesions with unilateral lesions	21(32)	3 (60)	0.32
Chiasmatic lesions with bilateral lesions	45 (68)	2 (40)	0.32
Chiasmatic lesions with orbital (anterior) optic nerve lesion	0	0	
Chiasmatic lesions with canalicular (posterior) optic nerve lesion	10 (15)	2 (40)	0.19
Chiasmatic lesions with longitudinally extensive optic nerve lesion	54 (82)	4 (80)	1
Gadolinium-enhancing quiasmatic lesions	31 (47)	4 (80)	0.19
Chiasmatic lesions with extra optic nerve lesions	4 (6)	0	1
Chiasmatic lesions with LETM	28 (42)	2 (40)	1
Chiasmatic lesions with STM	7 (10)	0	1

Abbreviations: LETM, longitudinally extensive transverse myelitis (extending over ≥ 3 vertebral segments); MOGAD-ON, myelin oligodendrocyte glycoprotein-associated disease-related optic neuritis; MRI, magnetic resonance imaging; NMOSD-ON, neuromyelitis optica spectrum disorder-related optic neuritis; ON, optic neuritis; STM, short-segment transverse myelitis (only one lesion < 3 vertebral segments in length).

Significant *p* values are indicated in bold.

TABLE 3 Results of Pearson *r* correlations between magnetic resonance imaging variables at disease onset and Visual Functional System Score at last follow-up

Variables	Visual Functional System Score					
	NMOSD-ON			MOGAD-ON		
	<i>r</i>	95% CI	<i>p</i> -value	<i>r</i>	95% CI	<i>p</i> -value
Bilateral lesions	0.28	0.14–0.40	<0.0001	0.31	–0.004–0.57	0.051
Chiasmatic lesions	0.27	0.13–0.39	0.0001	0.19	–0.13–0.48	0.23
Longitudinally extensive optic nerve lesions	0.25	0.10–0.38	0.0009	0.26	–0.07–0.54	0.12

Abbreviations: CI, confidence interval; MOGAD-ON, myelin oligodendrocyte glycoprotein-associated disease-related optic neuritis; NMOSD-ON, neuromyelitis optica spectrum disorder-related optic neuritis.

Significant *p* values are indicated in bold.

well as a shorter median time to second attack, supporting the use of effective long-term relapse prevention treatments [8–10]. Currently, there is an ongoing debate on when, how and with which drugs MOGAD patients should be treated [9,36].

This study has several limitations, such as the retrospective nature of its design and potential selection bias. However, careful data collection and patient follow-up were developed in each center to decrease the possibility of potential bias. Additionally, a slight

variability in protocols and measurements is likely. We would like to mention that all included centers have standardized MRI protocols and fully trained neuroradiologists. In addition, the relatively small numbers of patients included in the different subgroups, in particular the MOGAD-ON group, could have reduced the study's statistical power. Furthermore, seronegative patients are often a heterogeneous group of patients, which could impact the results. However, only 15.3% of seronegative NMOSD-ON patients were included in this cohort (slightly higher than in previously published studies), but this represents real-world evidence from specialized centers in LATAM. Finally, although this was a relatively large cohort from LATAM, it could not reflect the whole LATAM population. Despite these limitations, the present study adds new data to the international dataset, since previous studies have come from Asia, Europe and North America, but there were no data on any large multicenter cohort of LATAM patients, who would be expected to present differences in comparison with patients in these other regions.

In conclusion, chiasmatic lesions using conventional brain MRI are significantly more frequent in NMOSD-ON than in MOGAD-ON during an ON attack in this LATAM cohort. In addition, the presence of bilateral, chiasmatic and longitudinally extensive optic nerve lesions in NMOSD-ON patients correlated with poor visual outcome at last follow-up, but this was not observed for MOGAD-ON patients. Further studies including more MOGAD-ON patients are needed to assess the generalizability of our results.

CONFLICT OF INTERESTS

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

AUTHOR CONTRIBUTIONS

Edgar Carnero Contentti: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Supervision (equal); Validation (equal); Writing – original draft (lead); Writing – review and editing (lead). **Pablo Lopez:** Resources (supporting); Writing – review and editing (supporting). **Juan Criniti:** Formal analysis (supporting); Resources (supporting); Writing – review and editing (supporting). **Juan P Petinicchi:** Investigation (supporting); Resources (supporting); Writing – review and editing (supporting). **Edgardo Cristiano:** Resources (supporting); Writing – review and editing (supporting). **Liliana Patrucco:** Investigation (supporting); Resources (supporting); Writing – review and editing (supporting). **Elisa Bribiesca Contreras:** Investigation (supporting); Resources (supporting); Writing – review and editing (supporting). **Enrique Gómez-Figueroa:** Investigation (supporting); Supervision (supporting); Writing – review and editing (supporting). **Jose Flores:** Investigation (supporting); Writing – review and editing (supporting). **Edgar Correa:** Investigation (supporting); Writing – review and editing (supporting). **Ana Toral:** Investigation (supporting); Writing – review and editing (supporting). **Angelica Ortiz:**

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DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Table S1-S4

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