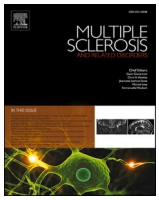
Multiple Sclerosis and Related Disorders 68 (2022) 104215

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Asymptomatic MRI lesions in pediatric-onset AQP4-IgG positive NMOSD

Renata Barbosa Paolilo [a,1,*], Carolina de Medeiros Rimkus [b,1], José Albino da Paz [a], Samira Luisa Apostolos-Pereira [a], Dagoberto Callegaro [a], Douglas Kazutoshi Sato [c]

[a] Department of Neurology. Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), São Paulo, Brazil
[b] Department of Radiology (INRAD). Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), São Paulo, Brazil
[c] Instituto do Cérebro do Rio Grande do Sul (InsCer); Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil

ARTICLE INFO

Keywords:
Neuromyelitis optica spectrum disorders (NMOSD)
Imaging
Aquaporin-4 antibody (AQP4-IgG)
Pediatric CNS demyelination
Myelin oligodendrocyte glycoprotein antibody (MOG-IgG)

ABSTRACT

Background and purpose: Around 5% of all Neuromyelitis Optica Spectrum Disorders (NMOSD) cases start before 18 years of age. Clinical and radiological manifestations of AQP4-IgG positive NMOSD were revised in 2015, and the importance of neuroimaging in the diagnosis is well recognized. Neuroimaging findings in pediatric-onset NMOSD were scarcely described, and longitudinal evaluation of NMOSD lesions was only accessed in a few adult-onset cohorts.

Methods: This study evaluated brain, spinal cord, and optic nerve MRI of sixteen pediatric-onset AQP4-IgG positive NMOSD through a qualitative evaluation of lesion evolution. Lesions were classified as symptomatic or asymptomatic in acute or chronic phase (> 30 days from last attack) MRI.

Results: Seventy MRI scans and 54 subsequent exams were evaluated. Most NMOSD lesions (74.5%) reduced, remained stable, or developed atrophy/cavitation. New brain lesions or enlargement of existing brain lesions were found in two patients (12.5%) without any clinical symptom and in five patients (31.2%) in the course of an attack from other topography (optic neuritis or acute myelitis). One patient (6.3%) presented an asymptomatic spinal cord lesion irrespective of clinical manifestation. No asymptomatic lesion was described in optic nerve MRI. In acute phase exams, longitudinally extensive transverse myelitis (13/19 vs 8/24; $p = 0.033$), cervical myelitis (15/19 vs 10/24, $p = 0.028$), lumbar myelitis (5/19 vs 0/24; $p = 0.012$), and a higher number of segments [median 8 (range 4–17) vs 3.5 (range 1–14); $p = 0.003$] were affected.

Conclusions: Asymptomatic brain and spinal cord lesions can occur in pediatric-onset NMOSD, especially in the course of acute optic neuritis or myelitis. More longitudinal studies are necessary to guide recommendations on neuroimaging frequency in pediatric patients with AQP4-IgG NMOSD.

1. Introduction

Pediatric-onset Neuromyelitis Optica spectrum disorders (NMOSD) account for about 5% of all NMOSD cases (Tenembaum et al., 2020). The frequency of antibodies against aquaporin4 (AQP4-IgG) varies in the studied populations according to ethnic background and age at onset (Jarius et al., 2020; Wingerchuk et al., 2015). In children, its frequency varies from 17 to 80% of all pediatric-onset NMOSD(Gombolay and Chitnis, 2018). A higher frequency of myelin oligodendrocyte glycoprotein antibody (MOG-IgG) associated with NMOSD has been reported in this population (Fadda et al., 2021). Aside from this, pediatric-onset AQP4-IgG positive NMOSD has a well-defined disease manifestation, sharing similar clinical and magnetic resonance imaging (MRI) presentation with adult patients (Tenembaum et al., 2020), and is associated with high disability (Paolilo et al., 2020).

Neuroimaging is crucial in NMOSD diagnosis (Kim et al., 2015a). The International Panel for NMO diagnosis (IPND-2015) included additional MRI findings in the revised diagnostic criteria (Wingerchuk et al., 2015). Typical MRI findings support the diagnosis of patients with negative or unknown AQP4-IgG results. Moreover, it is an essential tool for differential diagnosis, identifying red flag signs, and further investigating and differentiating between other demyelinating and central nervous system inflammatory disorders.

Different from multiple sclerosis (MS), disability in NMOSD is considered attack-dependent, and asymptomatic lesions indicating disease activity are considered rare. Thus, no official recommendation on

* Corresponding author.
E-mail address: renata.paolilo@hc.fm.usp.br (R.B. Paolilo).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.msard.2022.104215
Received 8 June 2022; Received in revised form 23 August 2022; Accepted 2 October 2022
Available online 4 October 2022

neuroimaging assessment in chronic patients is available to date. Longitudinal evaluation of MRI abnormalities was accessed in a few studies in adult-onset NMOSD cohorts (Chawla et al., 2020; Kim et al., 2014). Brain lesions tend to disappear or reduce at the follow-up, and asymptomatic lesions are rarely described (Kim et al., 2016; Lee et al., 2020). Brain and spinal cord atrophy have been recently described in AQP4-IgG positive NMOSD (Masuda et al., 2022; Wang et al., 2016). No study has focused on describing lesion evolution in a specific pediatric-onset population.

Wherein we described the brain, spinal cord, and optic nerve MRI findings of a pediatric-onset AQP4-IgG positive NMOSD cohort, and performed a longitudinal evaluation of lesions evolution through disease follow-up (FU).

2. Materials and methods

2.1. Ethics

The study was approved by the local Ethical Committee of Hospital das Clinicas da Universidade de Sao Paulo and the National Ethical Committee (approval number: 64,539,717.5.0000.0068). All patients and/or parents provided a written informed consent.

2.2. Participants and procedures

Patients followed in the neuroimmunology clinic of Hospital das Clinicas da Universidade de Sao Paulo were retrospectively identified for the inclusion criteria: 1) diagnosis of NMOSD according to the IPND-2015 (Wingerchuk et al., 2015); 2) AQP4-IgG positive through cell-based assays (CBA); 3) age $\leq$ 18 years at first disease manifestation; 4) actively attending the neuroimmunology clinic (at least two evaluations in the last follow-up year). Patients were excluded if only one MRI scan was available for analysis.

Most of the patients enrolled in this study were included in other cohorts (Paolilo et al., 2021, 2020) and in a prospective observational study from July 2017 to July 2020 (Paolilo et al., 2021). All patients performed at least one complete MRI (brain, spinal cord, and optic nerve). Subsequent exams were analyzed when more than one exam from the same topography was available.

The relevant demographic and clinical characteristics were analyzed. The outcome was measured through the Expanded Disability Status Scale (EDSS) at the last visit. In this study, brain attack was considered either area postrema syndrome, brainstem syndrome, diencephalic syndrome, cerebral syndrome, or acute disseminated encephalomyelitis (ADEM) according to the IPND classification.

All participants were tested for AQP4-IgG and MOG-IgG by in-house cell-based assay (CBA) described elsewhere (Sato et al., 2014). No patient tested positive for MOG-IgG.

2.3. Image acquisition

Brain, spinal cord, and optic nerve MRI were requested according to clinical indication by the assistant during the patient's visits to the clinic. Exams were performed at the Hospital das Clinicas da Universidade de São Paulo (Instituto da Criança and Instituto de Radiologia) in 1.5T or 3T scanners. Two scans from one patient were performed in another institution.

Brain MRI sequences included: T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), fluid-attenuated inversion recovery (FLAIR), postgadolinium T1-weighted imaging (T1GD) and diffusion weighted images (DWI). FLAIR sequences were either 3 mm thickness without gap in the axial plane or sagittal 3D-FLAIR with 1 $\times$ 1 $\times$ 1 mm voxel.

Spinal cord MRI included: Sagittal T1, T2 and T2-short tau inversion recovery (STIR) or T2 Fat Saturated Fast Spin Echo (T2 FS-FSE) sequences (3 mm thickness) and axial Fat-saturated T2 $<$ 5 mm thickness.

Optic nerve MRI included 3 mm thick or T2FS-FSE or STIR sequences and T1GD in both axial and coronal planes. Some optic nerve images also included Fast Imaging Employing Steady-state acquisition (FIESTA) to access optic nerve thickness.

2.4. Image analysis

All exams were analyzed by a neuroradiologist with expertise in neuroimmunology disorders (CMR), blinded to the clinical status of the patients. A qualitative evaluation of lesion evolution in T2WD/FLAIR and T1GD sequences in follow-up exams (performed $>$ 30 days apart) allowed classification in four categories: lesion growth, lesion reduction, the emergence of new lesions in T2WD/FLAIR, or new enhancing lesions in T1GD. Exams were retrospectively classified, by a neuropediatrician (RBP), in acute phase MRI if performed within 30 days from an acute clinical attack or chronic phase MRI if performed more than 30 days from the last attack. New lesions were classified as symptomatic if topographically consistent with an acute attack. Asymptomatic lesions were either lesions that emerged in a chronic phase MRI or at acute phase MRI without topographic relation to last attack clinical symptoms.

Lesions were classified according to its characteristics as: cavitated if had the same intensity as the cerebrospinal fluid in all sequences including FLAIR; hypointensity if had a lower intensity compared to cortical signal in T1WD; infiltrative if borders were imprecise and measured $>$ 2 cm at larger diameter in T2WD/FLAIR; unspecific if located in the deep white matter and were smaller than 3 mm in FLAIR; focal subependymal if $<$ 2 cm or extensive if $\geq$ 2 cm in FLAIR; longitudinally extensive transverse myelitis (LETM) if spinal cord lesion involved $>$ 3 contiguous vertebral segments in T2WI/FLAIR. Brain lesions were considered characteristic of NMOSD as they presented ill-defined or partially defined margins; extensive periependymal areas of T2-FLAIR hypersignal; large or extensive corpus callosum or longitudinal extensive corticospinal tract lesions (contiguous involvement of internal capsule, cerebral peduncle or inferior segments of the corticospinal tract); lesions located in regions suggestive of NMOSD: dorsal medulla, area postrema, periependymal surface of the forth or third ventricles (affecting the hytothalamus or thalamus); or large, confluent subcortical or deep white matter; long, diffuse, heterogeneous, or edematous) (Kim et al., 2015b; Wingerchuk et al., 2015). Lesions were considered suggestive of MS if they had well defined margins, oval shape or the shape of a perivenular space of the affected compartiment, were perpendicular with an orientation perpendicular to a lateral ventricular surface; adjacent to lateral ventricle in the inferior temporal lobe; juxtacortical involving subcortical U-fibers, or cortical (Absinta et al., 2016; Thompson et al., 2018; Wingerchuk et al., 2015).

2.5. Statistical analysis

Statistical analysis was performed using IBM-SPSS (version 22). Descriptive data of demographic and clinical characteristics, outcome and MRI evaluation analysis were reported. Comparison from acute and chronic image results were performed with Fisher exact tests. Statistical significance was defined as a two-sided p value of $<$0.05.

3. Results

Twenty individuals were identified and enrolled after providing a written informed consent. Two patients were unable to complete clinical follow-up. Two patients did not perform subsequent MRI due to underlying disorder (one patient diagnosed with Noonan Syndrome associated with Arnold-Chiari I malformation) or patient desire (one patient).

Demographic and clinical data from the sixteen included patients are disclosed in Table 1. Most patients were girls (93.5%) and from non-white ethnicity (14 Brazilian-mixed background, 2 caucasians). Median age at disease onset was 9 years. A total of 87 attacks were

Table 1
Demographic and clinical characteristics of the study cohort.

	$N = 16$
Age at onset, years, median (IQR)	9.0 (7.2–11)
Female sex, n (%)	15 (93.5)
Non-white ethnicity, n (%)	14 (87.5)
Number of attacks, median (IQR)	4.5 (3.2–7.7)
Total number of attacks	
Brain attacks, n (%)	23/87 (26.4)
Spinal cord attacks, n (%)	43/87 (49.4)
Optic nerve attacks, n (%)	49/87 (56.3)
Follow-up (from the first visit In the clinic), years, median (IQR)	9.5 (5–12.5)
EDSS at last FU, median (range)	3.5 (3.0–4.7)

Abbreviations: EDSS, Expanded Disability Status Scale; FU, follow-up; IQR = interquartile range.

analyzed, including the inaugural symptom. Twenty-eight attacks combined different clinical syndromes. Optic neuritis was the most common syndrome in the onset and follow-up. All patients were under chronic immunosuppression since the NMOSD diagnosis. At last visit, half of the patients were using anti-CD20 therapy (rituximab), four patients were using azathioprine, and four patients were using mycophenolate mofetil.

A total of 70 MRI scans were analyzed, five from the inaugural attack (performed within 30 days from the first clinical manifestation). Supplementary Table 1 summarizes the dates of clinical attacks and performed exams and Supplementary Table 2 summarizes all analyzed MRI findings.

Fifty-four subsequent exams were evaluated: 47 brain MRI, 36 spinal cord MRI, and 31 optic nerve MRI. Excluding the first attack, most exams were performed in chronic phase (58.1%). Median interval from disease onset and first available MRI scan was 18.5 (IQR 2.5–66; range 0–222) months. Median interval from the last clinical event and follow-up scan was 4 (IQR 0–23, range 0–168) months. Median interval from one scan to its follow-up scan was 12 (IQR 4.2–28.5, range 2–92) months. The comparison of qualitative lesion evolution according to acute or chronic phases is shown in Table 2.

All brain lesions were considered characteristic of NMOSD or unspecific, and no patient had lesions suggestive of MS. Comparison of acute and chronic phase exams did not reveal statistical differences in brain lesions' localization or characteristics. Brain cavitated lesions just appeared in follow-up exams in three patients (18.7%). Two patients (12.5%) showed new lesions or enlargement of old lesions without any clinical symptom. Five patients (31.2%) had new lesions or enlargement of old lesions in the course of an attack from other topography (optic neuritis or acute myelitis). Fig. 1 exemplifies these findings.

Table 2
Categories of lesion evolution according to acute and chronic phases exams.

	Acute phase MRI	Chronic phase MRI	p
Brain MRI ($N = 47$, from 16 patients)			
Emergence of new lesions in T2WI/FLAIR, n (%)	5/20 (25)	2/27 (7.4)	0.119
Lesion growth in T2WI/FLAIR, n (%)	3/20 (15)	2/27 (7.4)	0.638
Lesion reduction in T2WI/FLAIR, n (%)	1/20 (5)	7/27 (25.9)	0.114
New enhancing lesion in T1GD, n (%) ($N = 46$)	1/20 (5)	0/26	0.435
Spinal cord MRI ($N = 36$, from 15 patients)			
Emergence of new lesions in T2WI/FLAIR, n (%)	8/15 (53.3)	4/21 (19)	0.071
Lesion growth in T2WI/FLAIR, n (%)	4/15 (26.7)	1/21 (4.8)	0.138
Lesion reduction in T2WI/FLAIR, n (%)	1/15 (6.7)	2/21 (9.5)	>0.999
New enhancing lesion in T1GD, n (%) ($N = 32$)	10/13 (76.9)	2/19 (10.5)	<0.001
Optic nerve MRI ($N = 31$, from 16 patients)			
Emergence of new lesions in T2WI/FLAIR, n (%)	5/13 (38.5)	1/18 (5.6)	0.059
Lesion growth in T2WI/FLAIR, n (%)	1/13 (7.7)	0/18	0.419
Lesion reduction in T2WI/FLAIR, n (%)	0	0	–
New enhancing lesion in T1GD, n (%) ($N = 27$)	5/11 (45.5)	1/16 (6.3)	0.027

Abbreviations: MRI: Magnetic resonance imaging; T2WI: T2-weighted imaging (T2WI), FLAIR: fluid-attenuated inversion recovery; T1GD: postgadolinium T1-weighted imaging.

Asymptomatic growth of a left lateral periventricular lesion (A). Enlargement of a cerebellar peduncle lesion during an acute myelitis attack (B). Enlargement of a pons lesion during an acute myelitis attack (C). New right insular lesion during an optic neuritis attack (D).

Comparison of acute and chronic phase spinal cord exams reveled LETM was more common in acute phase exams (acute 13/19 vs chronic 8/24; $p = 0.033$). Cervical myelitis was more commonly seen in acute phase exams (acute 15/19 vs chronic 10/24, $p = 0.028$). Lumbar myelitis was just seen in acute phase exams (acute 5/19 vs chronic 0/24; $p = 0.012$). A higher number of segments were affected in acute phase exams compared to chronic phase [acute median 8 (range 4–17) vs chronic 3.5 (range 1–14); $p = 0.003$]. Overall, new lesions or enlargement of lesions were symptomatic and compatible with patient's clinical symptoms in acute phase MRI. New enhancing lesion in T1GD was more common in acute phase exams. Two patients presented with persistent enhancement after up to 90 days from the attack.

Three patients disclosed asymptomatic lesions in chronic phase exams. The first patient had a new lesion after a recent optic nerve attack (> 30 days) without myelitis symptoms. The second patient presented with a new lesion after a motor attack not seen or treated in our service. The third patient disclosed a new asymptomatic lesion with gadolinium enhancement without correlation with an attack from other topography or change in EDSS. The enhancement persisted for years without new clinical manifestations. Fig. 2 illustrates the spinal cord evolution of a patient.

Longitudinally extensive transverse myelitis in acute phase (A). Reduction of the lesion after three months (B). New lesion after six years (C) with bright spotty sign in axial evaluation (D). Reduction of the lesion and spinal cord atrophy after two years (E).

No difference was found in acute and chronic optic nerve MRI. Fig. 3 illustrates the optic nerve lesion's evolution of a patient.

The left top T1-Gd enhanced image (A) shows an acute episode of optic neuritis with optic chiasm enhancement (A) and T2 hypersignal (B), greater in the right side. Five months later, the optic chiasm is atrophied (F ang G) and without Gd-enhancement (F). The Fast Imaging Employing Steady-state acquisition (FIESTA) in the axial plane(A) shows a slight atrophy of the right optic nerve already during the acute attack of optic neuritis showed in A and B, characterized by an enlargement of the optic nerve sheath. The patient has had a previous right optic neuritis episode, three years earlier. Five months later (H), it is possible to observe a greater atrophy from the right optic nerve and also a slight atrophy in the left optic nerve. In the axial plane at the level of the optic chiasm, it is also evident the reduced thickness of the cisternal segment of the right optic nerve and the optic chiasm in I, compared to D. The proximal post chiasm segment of the optic nerves also shows a reduced thickness and a greater signal in T2 (J), five months after the acute attack, with an almost cystic appearance, compared to the more solid and mild T2 hypersignal showed during the acute attack (E).

Table 3 outlines the details of demographic and clinical characteristics of patients with asymptomatic lesions in brain and spinal cord MRI.

4. Discussion

In this pediatric-onset AQP4-IgG positive NMOSD cohort, we described asymptomatic new brain lesions related to attack from other topography (either optic neuritis or acute myelitis) in five patients and

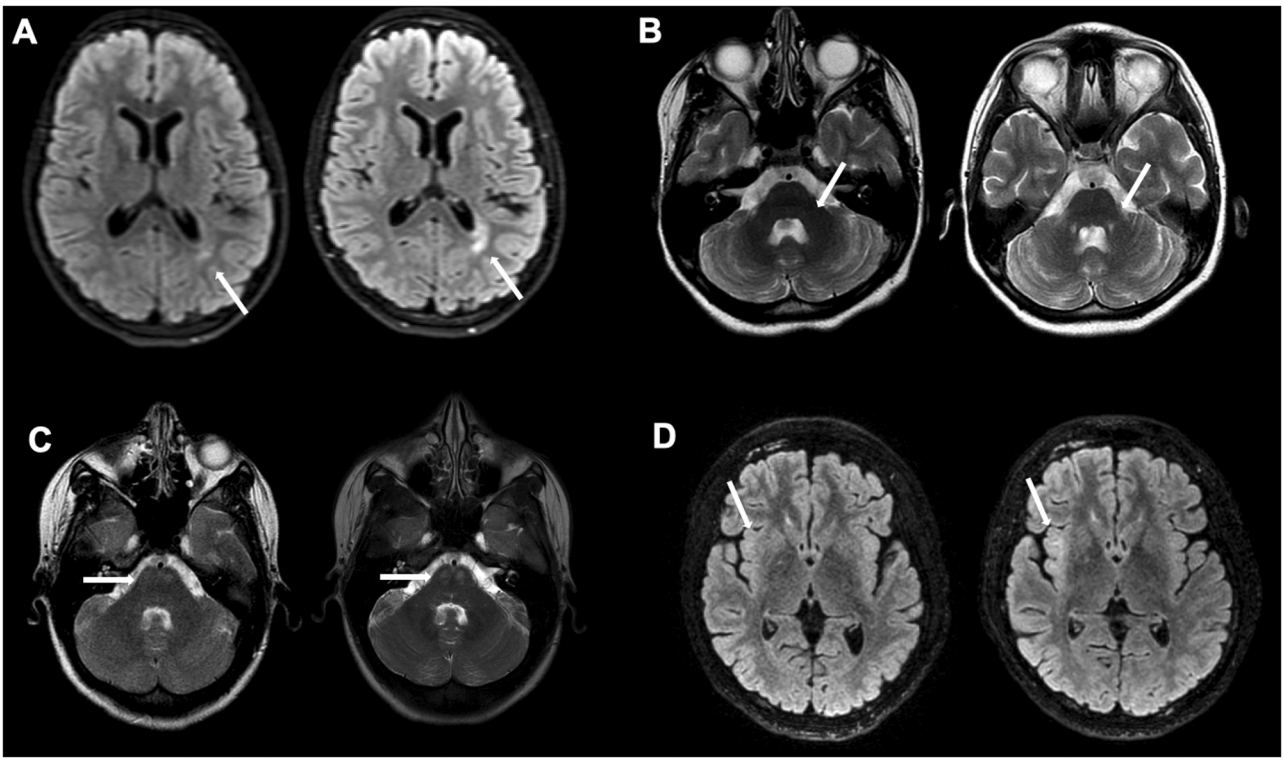


Fig 1. Evolution of brain MRI lesions of four patients.

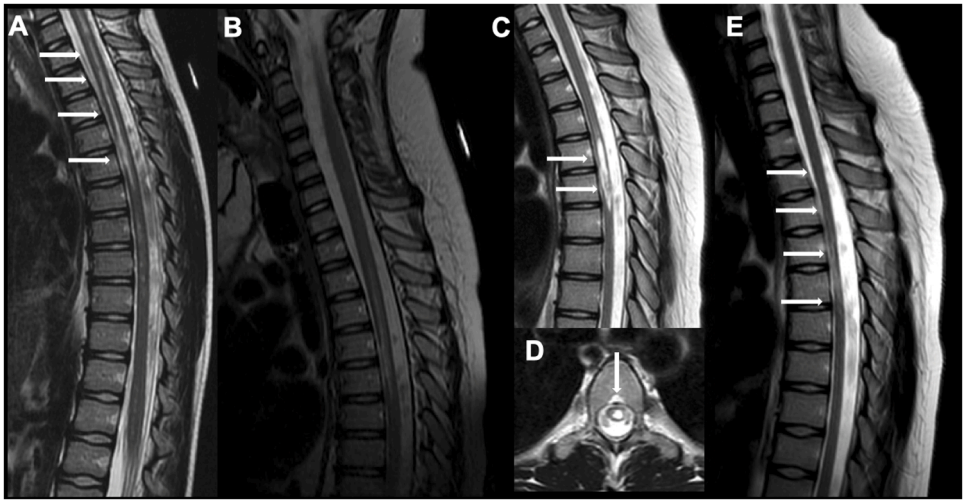


Fig 2. Evolution of spinal cord lesions in one patient.

new asymptomatic brain lesions without any associated clinical manifestation in two patients during the follow-up. Asymptomatic spinal cord lesion was found in one patient irrespective of clinical manifestation. A new asymptomatic enhancing-gadolinium asymptomatic lesion was absent.

Most NMOSD brain lesions in our cohort had either stable or reduced dimensions, with a tendency to develop atrophy or cavitating processes in the follow-up, in agreement with previous studies in the adult population (Chawla et al., 2020; Kim et al., 2014). Nevertheless, few patients had new or enlarged asymptomatic brain lesions, and even one patient had asymptomatic spinal cord lesion and persistent gadolinium enhancement.

Kim reported similar findings in his adult NMOSD cohort. Asymptomatic brain lesion associated with ON was found in 8%, and myelitis in 15% of the 165 enrolled patients (Kim et al., 2016). Recently, the same group reported new asymptomatic brain lesions in the deep white matter of 5/145 (3.4%) patients in the inter-attack analysis of 370 scans (Lee et al., 2020). In both studies and this cohort, the newly identified lesions were not responsible for changes in therapeutic strategies. Asymptomatic spinal cord lesion was described in three adult patients during an acute attack in other topography (Flanagan et al., 2015). Cervical atrophy was also described in patients without a history of myelitis, suggesting that an asymptomatic lesion could have been present or that atrophy can occur independently of prior attacks (Ventura et al., 2016). A recent paper reported an asymptomatic longitudinally extensive optic neuritis lesion associated with an asymptomatic focal cervical spinal cord lesion in a 12-year-old girl with positive serum AQP4-IgG detected after the routine ophthalmologic examination

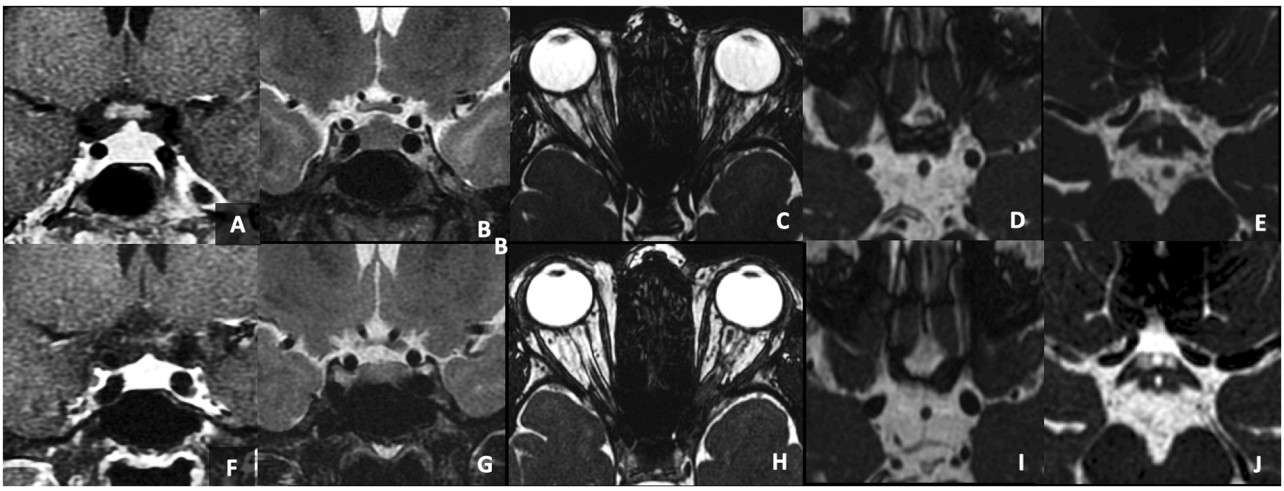


Fig 3. Evolution of optic nerve lesion in one patient.

Table 3
Description of new asymptomatic brain and spinal cord lesions.

Patient number / Sex	Age at onset / Age at last FU (years)	Total number of attacks	Description of asymptomatic lesion	FU duration in the clinic (years)	IST/EDSS prior to the referred MRI	IST/EDSS 1 month after the referred MRI	IST/EDSS at last visit
1 Female	10/21	4	One subcortical lesion (no clinical event, three years after last attack)	9	Azathioprine/2.0	Azathioprine/2.0	Azathioprine/2.0
2 Female	7/13	4	Growth of periventricular lesion (no clinical event associated, between attacks number 3 and 4)	5	Azathioprine/3.0	Azathioprine/3.0	Rituximab/2.0
3 Female	9/21	7	Growth of cerebellar penduncle during myelitis attack (attack number 6)	5	Rituximab/3.0	Rituximab/4.0	Rituximab/4.0
4 Female	17/27	6	New right insular lesion during optic neuritis attack (attack number 6)	6	Mycophenolate mofetil/3.0	Rituximab/3.0	Rituximab/3.0
5 Male	14/25	4	New unspecific subependymal lesion during optic neuritis attack (attack number 4)	11	Rituximab/3.0	Rituximab/3.0	Rituximab/3.0
6 Female	9/31	12	Growth of a periaqueductal lesion during a myelitis attack (attack number 12)	18	Azathioprine/5.0	Azathioprine/5.0	Mycophenolate Mofetil/5.0
7 Female	11/29	40	Growth pons lesion during a myelitis attack (attack number 35)	13	Azathioprine/8.0	Azathioprine/8.0	Rituximab/8.0
8 Female	11/24	2	Focal thoracic lesion (no history of myelitis throughout the FU)	12	Azathioprine/1.0	Azathioprine/1.0	Azathioprine/1.0

Abbreviations: FU: follow-up; IST: immunosuppressive treatment; MRI: Magnetic resonance imaging; EDSS: Expanded Disability Status Scale.

(Abdel-Mannan et al., 2022).

Different from MS (Wattjes et al., 2021), there is no consensus recommendation for MRI evaluation in adult or pediatric patients with NMOSD during the stable phase of the disease. Recently, a Latin American group publication recommended an annual brain MRI assessment to detect asymptomatic lesions and avoid severe disease attacks (Carnero Contentti et al., 2020). In opposition, most experts refuse this idea and support the concept that asymptomatic lesions are rare, as well as potential complications related to immunosuppressive drugs such as progressive multifocal leukoencephalopathy (Juryńczyk et al., 2021). Especially in the pediatric population there is a further concern in indiscriminate gadolinium usage (Wattjes et al., 2021), which must be considered before an MRI demand for a stable patient. Further multicentric studies enrolling more patients are needed to conclude this question. Still, this study's results increase the evidence that might help build new guidelines once the evidence of asymptomatic lesions resulted in no change in clinical outcome and management.

The overall characteristics of this cohort's brain, spinal cord, and optic nerve MRI abnormalities are consistent with previous descriptions of the pediatric NMOSD population and adult AQP4-IgG positive patients (Hacohen et al., 2017; McKeon et al., 2008; Zhou et al., 2019). Pediatric NMOSD patients have a high frequency of abnormal brain MRI (Tenembaum et al., 2020), but asymptomatic brain lesions have not been described in this population. Spinal cord MRI disclosed extensive and central lesions (Ciccarelli et al., 2019). Although there is no pediatric study describing optic nerve MRI abnormality for comparison, the findings in this cohort are similar to adult descriptions (Kim et al., 2015a). Even though the image acquisition protocol did not include susceptibility-weighted imaging (SWI), which could evaluate the presence of lesions highly suggestive of MS, such as central venule sign and paramagnetic rim lesions, all brain lesions fulfilled the characteristics for NMOSD MRI findings, and none fulfilled the criteria for lesions suggestive of MS.

This study has several limitations due to his single-center retrospective design, the unavailability of the MRI from inaugural attack for most patients, and the lack of serial assessment of MRI at regular intervals without standardized protocol using the same imaging acquisition techniques and scanner. As we are in a tertiary center, several patients arrive years after the first symptom without a precise diagnostic or to review diagnostic and treatment. Except for five patients with

annual exams, MRI scans were requested according to the clinical indication, and optic nerve MRI was rarely performed in asymptomatic patients. Nevertheless, we analyzed a considerable number of pediatric patients with a rare disease that is even less prevalent in pediatric populations.

5. Conclusions

Even though most NMOSD lesions tend to reduce, remain stable, or develop atrophy /cavitation, almost a third of patients in this study showed new asymptomatic lesions during acute optic neuritis or myelitis, and 12.5% of patients without a clinical symptom. In this small cohort, this finding did not influence the patient's clinical outcome or management, and clinical manifestations rather than imaging findings guided therapy. More longitudinal studies are necessary to understand the frequency and the clinical meaning of those findings that might impact new recommendations on neuroimaging surveillance in pediatric patients with AQP4-IgG NMOSD.

CRediT authorship contribution statement

Renata Barbosa Paolilo: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Carolina de Medeiros Rimkus:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **José Albino da Paz:** Conceptualization, Validation, Writing – review & editing. **Samira Luisa Apostolos-Pereira:** Writing – review & editing. **Dagoberto Callegaro:** Writing – review & editing. **Douglas Kazutoshi Sato:** Writing – review & editing.

Declaration of Competing Interest

None.

Acknowledgments

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

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

Ethical approval

The local Ethical Committee of the Sao Paulo University approved this study (approval number: 64539717.5.0000.0068).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.104215.

References

Abdel-Mannan, O., Klein, A., Zipori, A.B., Ben-Sira, L., Fattal-valevski, A., Hacohen, Y., Meirson, H., 2022. Radiologically isolated aquaporin-4 antibody neuromyelitis optica spectrum disorder. Mult. Scler. 28, 676–679.

Absinta, M., Sati, P., Reich, D.S., 2016. Advanced MRI and staging of multiple sclerosis lesions. Nat. Rev. Neurol. 12 (6), 358–368.

Carnero Contentti, E., Rojas, J.I., Cristiano, E., Marques, V.D., Flores-Rivera, J., Lana-Peixoto, M., Navas, C., Papais-Alvarenga, R., Sato, D.K., Soto de Castillo, I., Correale, J., 2020. Latin American consensus recommendations for management and treatment of neuromyelitis optica spectrum disorders in clinical practice. Mult. Scler. Relat. Disord. 45, 102428.

Chawla, S., Ge, Y., Wuerfel, J., Asadollahi, S., Mohan, S., Paul, F., Sinnecker, T., Kister, I., 2020. Longitudinal ultra-high field MRI of brain lesions in neuromyelitis optica spectrum disorders. Mult. Scler. Relat. Disord. 42, 102066.

Ciccarelli, O., Cohen, J.A., Reingold, S.C., Weinshenker, B.G., Amato, M.P., Banwell, B., Barkhof, F., Bebo, B., Becher, B., Bethoux, F., Brandt, A., Brownlee, W., Calabresi, P., Chatway, J., Chien, C., Chitnis, T., Ciccarelli, O., Cohen, J., Comi, G., Correale, J., De Sèze, J., De Stefano, N., Fazekas, F., Flanagan, E., Freedman, M., Fujihara, K., Galetta, S., Goldman, M., Greenberg, B., Hartung, H.-P., Hemmer, B., Henning, A., Izbudak, I., Kappos, L., Lassmann, H., Laule, C., Levy, M., Lublin, F., Lucchinetti, C., Lukas, C., Marrie, R.A., Miller, A., Miller, D., Montalban, X., Mowry, E., Ourselin, S., Paul, F., Pelletier, D., Ranjeva, J.-P., Reich, D., Reingold, S., Rocca, M.A., Rovira, A., Schlaerger, R., Soelberg Sorensen, P., Sormani, M., Stuve, O., Thompson, A., Tintoré, M., Traboulsee, A., Trapp, B., Trojano, M., Uitdehaag, B., Vukusic, S., Waubant, E., Weinshenker, B., Wheeler-Kingshott, C.G., Xu, J., 2019. Spinal cord involvement in multiple sclerosis and neuromyelitis optica spectrum disorders. Lancet Neurol. 18 (2), 185–197.

Fadda, G., Armangue, T., Hacohen, Y., Chitnis, T., Banwell, B., 2021. Paediatric multiple sclerosis and antibody-associated demyelination: clinical, imaging, and biological considerations for diagnosis and care. Lancet Neurol. 20, 136–149.

Flanagan, E.P., Weinshenker, B.G., Krecke, K.N., Pittock, S.J., 2015. Asymptomatic myelitis in neuromyelitis optica and autoimmune aquaporin-4 channelopathy. Neurol. Clin. Pract. 5 (2), 175–177.

Gombolay, G.Y., Chitnis, T., 2018. Pediatric neuromyelitis optica spectrum disorders. Curr. Treat. Options Neurol. 20 (6), 19.

Hacohen, Y., Mankad, K., Chong, W.K., Barkhof, F., Vincent, A., Lim, M., Wassmer, E., Ciccarelli, O., Hemingway, C., 2017. Diagnostic algorithm for relapsing acquired demyelinating syndromes in children. Neurology 89, 1–10.

Jarius, S., Paul, F., Weinshenker, B.G., Levy, M., Kim, H.J., Wildemann, B., 2020. Neuromyelitis optica. Nat. Rev. Dis. Primers 22 (6), 85.

Juryńczyk, M., Messina, S., Palace, J., 2021. Spinal cord and brain MRI should be routinely performed during follow-up in patients with NMOSD – No. Mult. Scler. 27, 15–16.

Kim, H.J., Paul, F., Lana-Peixoto, M.A., Tenembaum, S., Asgari, N., Palace, J., Klawiter, E.C., Sato, D.K., de Seze, J., Wuerfel, J., Banwell, B.L., Villoslada, P., Saiz, A., Fujihara, K., Kim, S.H., Biorepository, G-JCFNICC, 2015a. MRI characteristics of neuromyelitis optica spectrum disorder: an international update. Neurology 84 (11), 1165–1173.

Kim, H.J., Paul, F., Lana-Peixoto, M.A., Tenembaum, S., Asgari, N., Palace, J., Klawiter, E.C., Sato, D.K., Seze, J., Wuerfel, J., Banwell, B.L., Villoslada, P., Saiz, A., Fujihara, K., Kim, S., Biorepository, TG-JCFNICC, 2015b. MRI characteristics of neuromyelitis optica spectrum disorder: an international update. Neurology 85, 1165–1173.

Kim, S.H., Huh, S.Y., Hyun, J.W., Jeong, I.H., Lee, S.H., Joung, A., Kim, H.J., 2014. A longitudinal brain magnetic resonance imaging study of neuromyelitis optica spectrum disorder. PLoS One 9 (9), e108320.

Kim, S.H., Hyun, J.W., Joung, A., Lee, S.H., Kim, H.J., 2016. Occurrence of asymptomatic acute neuromyelitis optica spectrum disorder-typical brain lesions during an attack of optic neuritis or myelitis. PLoS One 11 (12), e0167783.

Lee, M.Y., Yong, K.P., Hyun, J.W., Kim, S.H., Lee, S.H., Kim, H.J., 2020. Incidence of interattack asymptomatic brain lesions in NMO spectrum disorder. Neurology 95 (23), e3124–e3128.

Masuda, H., Mori, M., Hirano, S., Uzawa, A., Uchida, T., Muto, M., Ohtani, R., Aoki, R., Kuwabara, S., 2022. Silent progression of brain atrophy in aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder. J. Neurol. Neurosurg. Psychiatry 93 (1), 32–40.

McKeon, A., Lennon, V.A., Lotze, T., Tenenbaum, S., Ness, J.M., Rensel, M., Kuntz, N.L., Fryer, J.P., Homburger, H., Hunter, J., Weinshenker, B.G., Krecke, K., Lucchinetti, C. F., Pittock, S.J., 2008. CNS aquaporin-4 autoimmunity in children. Neurology 71, 93–100.

Paolilo, R.B., da Paz, J.A., Apostolos-Pereira, S.L., Rimkus, C.M., Callegaro, D., Sato, D. K., 2021. Reduced quality of life in a pediatric-onset Neuromyelitis optica spectrum disorders cohort. Mult. Scler. Relat. Disord. 56, 103252.

Paolilo, R.B., Hacohen, Y., Yazbeck, E., Armangue, T., Bruijstens, A., Lechner, C., Apostolos-Pereira, S.L., Martynenko, Y., Breu, M., Rimkus, C.M., Wassmer, E., Baumann, M., Papetti, L., Capobianco, M., Kornek, B., Rostásy, K., da Paz, J.A., Ciccarelli, O., Lim, M., Saiz, A., Neuteboom, R., Marignier, R., Hemingway, C., Sato, D.K., Deiva, K., 2020. Treatment and outcome of aquaporin-4 antibody–positive NMOSD. Neurol. Neuroimmunol. Neuroinflamm. 7 (5).

Sato, D.K., Callegaro, D., Lana- Peixoto, M.A., Waters, P.J., de Haidar Jorge, F.M., Takahashi, T., Nakashima, I., Apostolos-Pereira, S.L., Talim, N., Simm, R.F., Lino, A. M.M., Misu, T., Leite, M.I., Aoki, M., Fujihara, K., 2014. Distinction between MOG antibody positive and AQP4 antibody positive NMO spectrum disorders. Neurology 82, 474–481.

Tenembaum, S., Yeh, E.A., Guthy-Jackson Foundation International Clinical Consortium, G.-I, 2020. Pediatric NMOSD: a review and position statement on approach to work-up and diagnosis. Front. Pediatr. 8, 339.

Thompson, A.J., Banwell, B.L., Barkhof, F., Carroll, W.M., Coetzee, T., Comi, G., Correale, J., Fazekas, F., Filippi, M., Freedman, M.S., Fujihara, K., Galetta, S.L., Hartung, H.P., Kappos, L., Lublin, F.D., Marrie, R.A., Miller, A.E., Miller, D.H., Montalban, X., Mowry, E.M., Sorensen, P.S., Tintoré, M., Traboulsee, A.L., Trojano, M., Uitdehaag, BMJ, Vukusic, S., Waubant, E., Weinshenker, B.G., Reingold, S.C., Cohen, J.A., 2018. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 17 (2), 162–173.

Ventura, R.E., Kister, I., Chung, S., Babb, J.S., Shepherd, T.M., 2016. Cervical spinal cord atrophy in NMOSD without a history of myelitis or MRI-visible lesions. Neurol. Neuroimmunol. Neuroinflamm. 3 (3), e224.

Wang, Y., Wang, Y., Tan, S., Lu, Z., 2016. Spinal cord atrophy in neuromyelitis optica spectrum disorders. Mult. Scler. Relat. Disord. 8, 9–10.

Wattjes, M.P., Ciccarelli, O., Reich, D.S., Banwell, B., de Stefano, N., Enzinger, C., Fazekas, F., Filippi, M., Frederiksen, J., Gasperini, C., Hacohen, Y., Kappos, L., Li, DKB, Mankad, K., Montalban, X., Newsome, S.D., Oh, J., Palace, J., Rocca, M.A., Sastre-Garriga, J., Tintoré, M., Traboulsee, A., Vrenken, H., Yousry, T., Barkhof, F., Rovira, À, Wattjes, M.P., Ciccarelli, O., de Stefano, N., Enzinger, C., Fazekas, F., Filippi, M., Frederiksen, J., Gasperini, C., Hacohen, Y., Kappos, L., Mankad, K., Montalban, X., Palace, J., Rocca, M.A., Sastre-Garriga, J., Tintore, M., Vrenken, H., Yousry, T., Barkhof, F., Rovira, A., Li, DKB, Traboulsee, A., Newsome, S.D., Banwell, B., Oh, J., Reich, D.S., Reich, D.S., Oh, J., 2021. 2021 MAGNIMS–CMSC–NAIMS consensus recommendations on the use of MRI in patients with multiple sclerosis. Lancet Neurol. 20 (8), 653–670.

Wingerchuk, D.M., Banwell, B., Bennett, J.L., Cabre, P., Carroll, W., Chitnis, T., de Seze, J., Fujihara, K., Greenberg, B., Jacob, A., Jarius, S., Lana-Peixoto, M., Levy, M., Simon, J.H., Tenembaum, S., Traboulsee, A.L., Waters, P., Wellik, K.E., Weinshenker, B.G., 2015. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 89, 177–189.

Zhou, Y., Zhong, X., Shu, Y., Cui, C., Wang, J., Wang, Y., Li, X., Chen, Z., Peng, L., Kermode, A., Qiu, W., 2019. Clinical course, treatment responses and outcomes in Chinese paediatric neuromyelitis optica spectrum disorder. Mult. Scler. Relat. Disord. 28, 213–220.