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Clinical and Radiological Evaluation of Neuromyelitis Optica in Children: Report on a Case Series

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Authors' contributions

This work received the collaboration of all authors. Author ACBK designed the methodology and followed the first manuscripts, contributed to the discussions and corrections. Author LCST designed the initial statistical program of the main cohort from which the population studied in this article arose and did the final revision of the methodology and the discussion of this article. Authors PRDVB and LAMDS read the MRI exams of the initial population. Author RMPA is the medical neurologist of the patients and made the epidemiological revisions of the tables used. All authors read, discussed and approved the final manuscript.

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Short Research Article

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ABSTRACT

Objective: To describe patterns for conventional magnetic resonance imaging (MRI) of the cranium in pediatric patients with neuromyelitis optica (NMO).
Methods: A retrospective, descriptive study of cephalic lesions and classification of abnormality patterns on MRI of the cranium in pediatric patients with NMO was conducted using the criteria established by Wingerchuck and colleagues, 2006. There viewed cases were from patients treated between 1999 and 2015 at the Center for Demyelinating Disease in Rio de Janeiro, Brazil.
Results: Of 55 patients treated for NMO at our center, 12 (21.8%) had their first neurological symptoms before the age of 18 and were thus included in this study. Nine (75.0%) were female and of African descent. IgG-NMO test were positive in 8 patients (66.7%) and negative in 4 (33.3%). The average age of the onset of neurological problems was 11 years old. Transverse myelitis was documented in 7 patients (58.3%), unilateral optic neuritis (ON) in 3 (25.0%), and bilateral ON in 2 (16.6%). The types of MRI patterns were: *Absence of a lesion in the cerebral hemispheres and brain stem* - The only patient AQP4-seropositive (8,3%) without a lesion detected by head MRI. *Unespecific hemispheric lesions* - They were found in 2 patients AQP4-seropositive (16,6%). Lesions in the ependyma infratentorial, brainstem and bulbomedular junction associated were present in only one. *Hemispheric lesions similar to MS in conjunction with lesions specific to NMO* - They were found in 2 patients (16,6%), one was AQP4-seropositive and the other AQP4-seronegative. Lesions in the ependyma supratentorial and brainstem were associated in both cases. *Lesions specific to NMO* – This type was revealed by MRI in 5 patients (41,6%). Two patients had no lesions in the cerebral hemispheres, but the brainstem was involved in both. In patient AQP4-seronegative there was lesion in the medulla oblongata and the patient AQP4 seropositive there was an extensive lesion in the brainstem, area postrema and infratentorial ependyma. In 3 patients there were lesions in corticospinal tract and the brainstem. Lesion in the ependima supratentorial was found in only one. *Extensive hemispheric lesions* were demonstrated by MRI in 2 patients AQP4-seronegative (16.7%). Others lesions in 1 patients were found in medulla oblongata and bulbomedular junction.
Conclusion: We observed five patterns of conventional head MRI findings in pediatric patients with NMO. Typical signs of NMO, using current criteria, were found with in all of the imaging patterns and were present in patients regardless of their AQP4 status. This case series showed a wide range of clinical and imaging MRI presentations of NMO. Conventional MRI protocols for the study of the brainstem, optic nerves and corticospinal tract showed specific signs and should be included in routine NMO diagnosis protocols.

Keywords: NMO spectrum disorder; neuromyelitis optica; pediatric patients; magnetic resonance imaging.

1. INTRODUCTION

Neuromyelitis optica (NMO) is an immune-mediated, inflammatory, demyelinating and necrotizing disease of the central nervous system that is characterized by serious involvement of the optic nerve, unilaterally or bilaterally, and the spinal cord. Its manifestation can be acute or subacute, and the disease course may be monophasic or recurrent. There is a range of NMO-related disorders with the communal it of IgG-NMO serum antibody which constitute a disease cluster termed NMO spectrum disorder. Generally, NMO affects adults during their 3rd or 4th decade of life and it is most common in women of Asian and African descent [1,2]. The prognosis for NMO is unfavorable with atypical evolution towards amaurosis and brainstem deficits [1,2]. When NMO presents in childhood, it is difficult to distinguish from other acute demyelinating diseases for this age band in terms of clinical and imaging characteristics. The initial diagnostic criteria for NMO, described in 1999, included optical neuritis (ON), longitudinally extensive transverse myelitis (LETM), and an absence of

symptoms or lesions detectable by magnetic resonance imaging (MRI) in areas other than the optic nerve and spinal cord [2]. From the knowledge of the high specificity of IgG-NMO in much the serum of patients with NMO and distribution of AQP4 the optic nerve, the spinal cord, diencephalon and periventricular regions, the presence of brain MRI to lesions associated or not the brain clinical manifestations, are now better understood [3]. Pittock and colleagues have described the morphology and location of these lesions in APQ4-rich areas, including around the third and fourth ventricles, lateral ventricles, periaqueductal grey matter, and hypothalamus [4]. The typical signs observed by conventional MRI of the head in patients with NMO were described current imaging criteria for NMO [5]. The current diagnostic criteria for NMO in adults, described by Wingerchuck and colleagues, can also be applied to children, with certain reservations in terms of LETM, which can also occurring in multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM) [5].

The relevance of this work is exactly to detect in the study population a subgroup with a different epidemiological behaviour of others and also with inhomogeneous radiological presentation, with that found in adult population.

2. PATIENTS

We collected the records of patients tracked by the Center for Demyelinating Diseases in Rio de Janeiro/Brazil between 1999 and 2015 for being treated for NMO. A total of 55 such patients were found, of which 12 were under 18 years of age at the time of their diagnosis. We conducted a retrospective analysis of the records and conventional head and spinal cord MRI examinations of those 12 children with NMO using the criteria established by Wingerchuck and colleagues (2006). We analyzed the following clinical variables: age, sex, ethnicity, attack symptoms, number of attack, anti-AQP4 antibody status, duration of the disease, and classification of lesions observed by MRI.

3. METHODS

The MRI scans reviewed were produced by an 1.5-T scanner with a T2 weighting sequence before and after intra venous administration of gadolinium (Gd), 1~2 ml/kg body weight, including T2 FLAIR (fluid attenuated inversion recovery) images in the axial and sagittal planes of the head and spinal cords can as well as STIR (short T1 inversion-recovery) sequence coronal-plane images of the optic nerves. In 2 patients, diffusion tensor imaging (DTI) studies were also obtained to evaluate anisotropy of the corticospinal tracts.

Two neuroradiologists, with a minimum experience of 15 years and with a prior history of consensual diagnosis, analyzed imaged brain and spine lesions in terms of their location, morphology, enhancement features and pattern classification. The MRIs were classified as normal, nonspecific, specific for NMO, similar to MS and atypical for MS, based on previously published guide lines, by Wingerchuck and colleagues et al., 2006 and 2015. They classified ON, detected as hyperintensitities in T2-weighted MRI, in terms of extent and laterality. Detected ON was characterized as active if there was enhancement in the post-Gd T1-weighted sequence and characterized as chronic if hyperintensity was observed in the T2-weighted and STIR sequences, with a reduction in the thickness of the optic nerve [6,7,8]. Extensive transverse myelitis was indicated by the presence of a lesion with hyperintensity in the T2-weighted sequence that involved three or more vertebral bodies. Active myelitis shows enhancement in T1-weighted sequences after Gd administration and chronic myelitis is characterized by atrophy in T1-weighted sequences [9,10]. White matter lesions appear as hyperintensities in T2-weighted images, and those that are active show enhancement in post-GdT1sequences.

The ethics committee at the Gafreée and Guinle University Hospital of the Federal University of the State of Rio de Janeiro (Universidade Federal do Estado do Rio de Janeiro, UNIRIO) approved this study (no.713.048) on july, 2014. Patients or their guardians signed informed consent forms in person.

4. RESULTS

4.1 Patients

The sample consisted of 3 children (ages at the time of this study: 2 years, 4 years, and 9 years) and 9 adults (≥18 years at the time of this study) who presented with their first clinical signs of NMO before 18 years of age. Hence, all 12 are considered pediatric patients with respect to their age at the time there viewed records were produced. The age of onset of the first

neurological event was highly variable, ranging from 2 years old to 17 years old, with the highest frequencies of age of onset being 10 years old (N=2) and 16 years old (N=2). Of these 12 pediatric patients, 9 (75.0%) were female and of African descent. The demographics of the patients are summarized in Table 1.

4.2 Clinical

The number of neurological events in the course of the disease ranged from 3 to 20 attacks. Transverse myelitis was present in the initial event in 7/12 patients (58,3%) and ON was present in 5/12 patients (41,6%) and it was bilateral in 2/12 (16,6%). One patient (Case 4) did not report any visual symptoms, but a clinical exam showed bilateral vision changes. Four patients (33.3%) had initial symptoms not directly related to ON, including 1 patient (8.3%) with encephalopathy and 3 patients with brainstem syndrome. Two patients had a head MRI after reporting cephalic symptoms characterized by a generalized convulsive crisis followed by a rapid evolution to loss of consciousness. Regarding frequency of neurological manifestations in the course of the disease, LETM occurred 38/71 times (53.5%), bilateral ON 22/71 events (30.9%), encephalopathy 11/71 events (15.4%), and brainstem syndrome 8/71 events (11.2%). The inter-index interval was less than 24 hours in one patient and as high as 24 years in another. The duration of the disease from the initial manifestation to the date of the latest MRI ranged from 2 years to 39 years. The APQ4 status (IgG-NMO test results) and clinical characteristics of the patients are summarized in Table 2.

4.3 MRI Features

The distribution and morphological appearance of lesions in supratentorial and infratentorial regions, the extent of brainstem lesions, are summarized in Table 3.

4.3.1 Normal brain

In Case 8, the initial MRI examination was performed 88 months after the initial manifestation of NMO. It demonstrated bilateral atrophy of the optic nerves as well as extensive, active cervical and dorsal myelitis characterized by increased medullary thickness with post-Gd enhancement and an absence of supra and infratentorial hemispheric changes. A head MRI performed 6 months later again showed no changes to the brain. This patient's IgG-NMO test was positive for AQP4 antibodies.

4.3.2 Unspecific hemispheric lesions

Changes of a nonspecific nature were found in 2 patients with AQP4-positive IgG NMO test results, namely Cases 1 and 2. Punctiform (< 3.0 mm) nodular lesions were observed, the majority of which were smaller than 10 mm, without post-Gd enhancement, with juxtacortical location and in the white matter of the centrum semiovale and corona radiata. Infratentorial lesions were present in Case 2, located in the medulla oblongata and ependyma in the initial exam, as well as bulbomedullary junction in the follow-up examination. In this, the optic nerves also showed activity in the initial exam. Atrophy of the optic nerves was verified in both cases in follow-up studies over the disease course.

Table 1. Epidemiological data for pediatric patients with NMO

Case no.	Age	Sex	Ethnicity
1	7	F	A
2	10	F	A
3	9	M	A
4	2	M	W
5	4	F	A
6	12	F	A
7	10	F	A
8	16	F	A
9	16	M	W
10	17	F	A
11	15	F	A
12	14	F	A

4.3.3 Hemispheric lesions similar to MS in conjunction with lesions specific to NMO

In Cases 5 and 7, there were oval periventricular lesions, which does not meet Barkhof criteria for MS, in addition to small white matter lesions of a nonspecific pattern. In Case 7, deep white matter lesions were located on the internal capsule, compromising the anterior and posterior limbs, unilaterally and on the floor of the corpus callosum. NMO-specific hemispheric lesions characterized by periependymal hyperintensity were located on the posterior horns of the lateral ventricles in both cases. Atrophy of the frontal lobes of the cerebral hemispheres was observed in these two patients, one with a 3-year disease duration (Case 5) and the other with a 35-year disease duration (Case7) at the time of the

examination. In the latter case, atrophy of the temporal lobes was also documented. Additionally, infratentorial lesions were found in the pons in Case 5 and in the midbrain, medulla oblongata, and area postrema in Case 7. Atrophy of the optic nerves was found in both cases. The IgG-NMO test was AQP4-positive in Case 5 and AQP4-negative in Case 7.

4.3.4 Lesions specific to NMO

NMO-specific lesions (Fig. 1) were revealed by MRI in 7/12 cases (58%). In 5 cases (Cases 6, 9, 10, 11, and 12), there was no other related aspect of this findings. The IgG-NMO was AQP4-positive in case 6, 9, 10, 11 and AQP4-negative in case 12.

4.3.5 Corticospinal tract

Supratentorial and infratentorial lesions seen on MRIs, extending from the brainstem to the posterior limb of the internal capsule, provided evidence of damage to the corticospinal tract in 3/12 patients (25%; Cases 9, 10, and 11). In Case 10 and Case 11, DTI studies confirmed bilateral damage to the corticospinal trasct, showing a reduction in anisotropy due to retrograde degeneration. In Case 11, a follow-up study showed substantial atrophy of the thalamus, right cerebellar peduncle, and left cerebellum together with lesions of the midbrain, pons and left peduncle.

4.3.6 Ependyma

In 6/12 patients (50%; Cases 2, 5, 6, 7, 10, 11), T2-FLAIR MRI sequences revealed lesions affecting the topography of the water channels in the SNC, characterized by the presence of linear hyperintense signals around the cerebral ventricles and aqueduct. In Cases 5, 7, and 11, the damage was supratentorial, mainly in the lateral ventricles; in Cases 2, 6, e 10, the damage was infratentorial, affecting both the aqueduct and the 4^{th} ventricle. Supra-and infratentorial ependymal damage were present in Case 11. In 3/12 cases (25%); Cases 6, 9, and 10), infratentorial ependymal lesions with a diffuse pattern were associated with lesions in the brainstem.

4.3.7 Brainstem

Two patients (Cases 6 and 12) without any lesions in the supratentorial white matter had infratentorial lesions. In Case 6, the lesions were coalescing, affecting the midbrain, pons, left cerebral peduncle, medulla oblongata, area postrema, and periependymal areas of the aqueduct and of the fourth ventricle and extending to the brainstem. The other patient (Case 12) had a small lesion on the right bulbar pyramid, which was confirmed by DTI to have a punctiform appearance. Additionally, 7 patients (Cases 2, 3, 6, 7, 10, 11, 12) had a lesion in the medulla oblongata. Furthermore, 4 of these 7 patients (Cases 6, 7, 10, 11) also had a lesion in the area postrema.

4.3.8 Medulla oblongata

Lesions characterized by hyperintensity from the central area of the cervical spine extending to the medulla oblongata, revealed in T2-weighted sequences with FLAIR, were present in the axial and sagittal slices of 5 patients (Cases 2, 3, 6, 7, 11).

4.3.9 Extensive hemispheric lesions

Extensive areas of hyperintensity on deep white matter area surfaces with well-defined limits, hypointense in T2 and hyperintense in T2 with FLAIR (see Fig. 2), were present in 2/12 patients (16.6%; Cases 3 and 4). In Case3, the patient's MRI showed a white matter lesion with moderate edema, without restriction of diffusion, with a thick and irregular hyperintense halo and no enhancement after Gd administration. In Case 4, the patient's MRI showed a frontal lobe lesion located near the precentral gyrus with a small cortical area of restricted diffusion, without a tumefactive effect and with a discrete, incomplete halo enhancement after Gd administration.

5. DISCUSSION

Pediatric NMO is rare. NMO accounts for approximately 4% of demyelinating disease cases in children [6], with most affected children experiencing their first manifestation at 10–14 years of age [7,8]. In our case series, we observed minor peaks of higher incidence at the ages of 10 years and 16 years. Epidemiological studies have found that pediatric NMO is more common in children of Latin American and African descent [9]. In this study, all of the NMO patients were Brazilian, the majority being female and of African descent. Two of the three male patients in this cohort had encephalic manifestations and extensive lesions revealed by MRI.

Table 2. Clinical and laboratory data for patients with NMO in the pediatric age range

Case no.	Initial manifestation	Event 1 index	Event 2 index	Interval between events	Frequency of the events			Encephalopathy	Number of neurological events	Length of disease (months)	AQP4
					ON	TM	BS				
1		TM	BON	216 months	3	12	3	2	20	468	P
2		TM	BON	24 months	5	2	1		8	228	P
3	Encephalopaty	TM	BON	< 24 hours	1	2		1	4	24	N
4		TM	BON	42 months	1	1	1	1	4	120	N
5		MY	BON	12 months	1	2		3	3	48	P
6	BS	UON	TM	23 months	1	2	1	4	3	96	P
7		UON	TM	288 months	1	2			3	420	N
8		BON	TM	88 months	4	3			7	96	P
9	BS	TM	BON	< 1 month	2	6			8	336	P
10	BS	TM	BON	< 7 days	1	2	1		4	60	P
11		BON	TM	324 months	1	2	1		4	348	P
12		UON	TM	12 months	1	2			3	168	N

Key: AQP4: Aquaporin 4; P: Positive; N: Negative; U: Unknown TM:Transverse Myelitis; BON:bilateral optic neuritis; UON: Unilateral optic neuritis ; BS: Brainstem syndrome

Table 3. Distribution of brain injuries, spinal cord and brain MRI classification in pediatric patients with NMO

Patients	1	2	3	4	5	6	7	8	9	10	11	12
Distribuitions of the ledions												
Supratentorial												
White matter justacortical	X	X			X		X					
Deep white matter:												
centrum semiovale	X				X		X		X			
radiata crown	X				X		X					
Periventricular	X				X		X				X	
internal capsule					X		X		X	X	X	
Cortico spinal tract									X	X	X	
Corpus calosum					X		X					
Septal calosum interface	X											
Diencephalon											X +	
Gliosis					X				X	X	X	
Encephalomalacia					X							
Atrophy					X		X				X+	

Patients	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Extensive hemispheric lesion			X	X								
Ependymal supratentorial					X		X				X	
Infratentorial												
Midbrain						X	X			X	X	
Pons					X	X				X	X	
Peduncle middle cerebellar						X			X	X	X	
Área postrema						X	X			X	X	
Medulla oblongata		X	X			X	X			X	X	X
Cerebellum										X	X	
Ependyma infratentorial		X				X				X	X	
Atrophy											X ++	X+++
Bulbomedulary junction		X	X						X	X	X	
Optic nerve												
Unilateral						X	X					X
Bilateral	X	X	X	X	X			X	X	X	X	
Acute		X										
Chronic (Atrophy)	X	X			X	X	X			X	X	X
Spinal cord	C3-C7	C2-D8	C4-D1		D1-D12	C5-C7	C2-C6	C3-C5 e C7-D7	C1-C2 e D2-D12	C1-C7 e D1-D8	C1-C2	C2-C3 a C7-D1
Acute (Enhancement)										X		X
Swelling without enhancement								X				X
Chronic (Atrophy)												
Classification of the MRI brain	UHL	UHL	EHL	EHL	MS LIKE + NMO-S	NMO-S	MS LIKE–NMO-S	N	NMO-S	NMO-S	NMO-S	NMO-S

Key: UHL : Unspecific hemispheric lesions; N: Normal brain; MS LIKE: Similar to MS; NMO-S: Specific for NMO;
** Thalamus; ** Cerebellum; *** Cerebral peduncle, middle cerebellar peduncle and cerebellum*

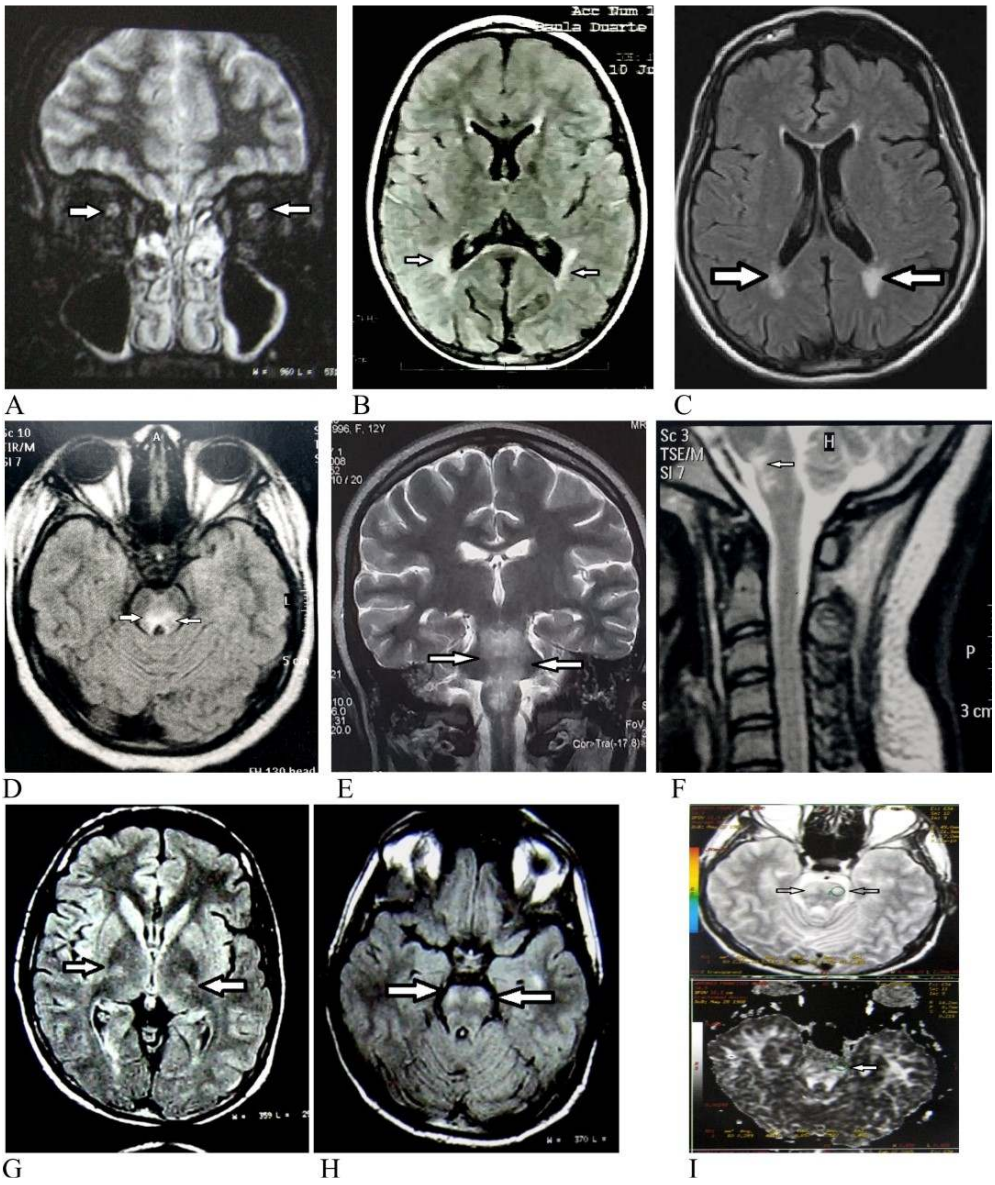

Fig. 1. A (Case 10) - T2 sequence, coronal plane: bilateral atrophy of the optic nerves.
B (Case 5), C (Case 7), D (Case 6) and G (Case 9) - Sequences FLAIR, axial planes: In B, C and G: periependimárias lesions with hyperintensity in subsequent extensions of the lateral ventricles (arrows). D - periependimária hyperintense lesion with the fourth ventricle extending to the midbrain (arrow).
E (Case 6) - T2 sequence, coronal plane: coalescing lesions with hyperintensity in brainstem.
F (Case 6) - T2 sequence, coronal plane: hyperintense lesion in the area postrema.
G (Case 9) - Sequence FLAIR, axial plane: Bilateral lesions with hyperintensity in the posterior limb of the internal capsule in the path of the corticospinal tract.
H (Case 9): T2 sequence axial: bilateral lesions in the midbrain, following the path of the corticospinal tract.
I (Case 9): diffusion tensor sequences, axial planes G and H, indicating a reduction of anisotropy in corresponding locations to the corticospinal tract

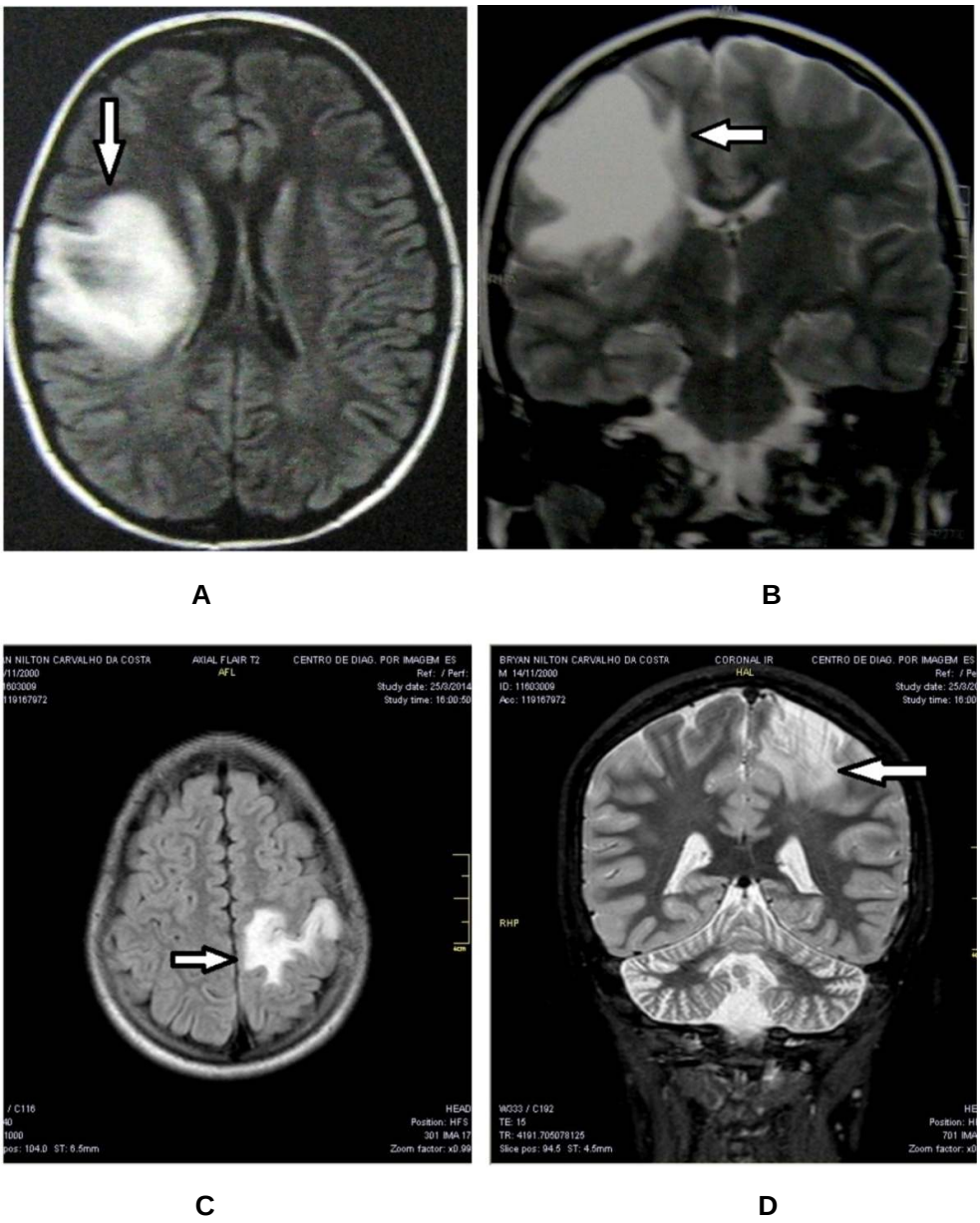

Fig. 2. A and B (Case 3) - FLAIR sequence, axial (A) and T2-weighted sequence, coronal (B): inhomogeneous hyperintense lesion with moderate tumefativo effect on justacortical and deep white matter.
C and D (Case 4) - Sequence Axial FLAIR (A), Coronal T2 (B), Injury cortico-subcortical hyperintense involving the pre-central gyrus of the left frontal lobe

By definition, ON and LETM occur simultaneously in a monophasic form. In the recurrent form, recurrence intervals are variable, with an inter-index interval of ≥ 5 years after the first event in 90% of the cases [2]. Although this clinical presentation is found in both pediatric and adult patients, among pediatric patients, the monophasic form has been associated with AQP4-seronegative status [6,8,9,10,11]. Tillema and colleagues [7] found that although the frequency of AQP4-IgG seropositivity among pediatric patients with NMO (78%) is similar to that in adults, the proportion of pediatric NMO cases that are monophasic was quite low (12.5%). Banwell and colleagues [8] reported that the AQP4-IgG antibody seropositive is a

sensitive marker in pediatric patients with NMO. Lotze and colleagues [10] have argued that seropositivity has a predictive value for recurrence and a more severe disease prognosis, and that the relationship between negative-to-positive seroconversion during an attack and its reversal during treatment is relevant. In our case series, 10/12 patients had recurrent attacks with the classic characteristics seen in adults. Two AQP4- seronegative children had encephalopathy and extensive hemispheric lesions on their MRIs. Five AQP4-seropositive children with recurrent attacks had lesions typical of NMO visible on their MRIs. An MS-like pattern with NMO-specific lesions was found in another patient with are current form and negative serology. The children whose AQP4 were positive, cases 2, 6, 9, 10 and one child with AQP4 was negative, case 12, had an nonspecific pattern in their first MRI examination, but a specific pattern in subsequent MRIs. To our knowledge, the heterogeneous aspect of AQP4 status present in this series, combined with the diversity of clinical presentations and different MRI patterns have been described in the literature consulted in this age range

The AQP4 antibody can also be present in the serum of patients with other disorders related to NMO, constituting NMO spectrum disorder (NMO-SD) [12]. Under the current criteria, the term NMO and NMO-SD should be unified and the others clinical manifestations in addition to ON and LMTE meet clinical criteria [5]. AQP4 positive patients, negative or unknown with SC-NMO associated with changes present on MRI of the brain and brainstems, can fulfill criteria for NMO [5]. Given the possibility for seroconversion, Wingerchuck an colleagues (5) suggest that AQP4-seronegative pediatric patients be retested for anti-AQP4 antibodies.

In MRI, active ON appears as a hyperintense lesion in T2, an enhancement in T1 after Gd administration, and as an increase in optic nerve thickness. These signs of active disease are found in both MS and NMO [13,14]. However, extensive and bilateral damage to the optic nerve up to the optic chiasm or radiations and areas adjacent to the hypothalamus are characteristic of ON in NMO [15]. Mealy and colleagues [14] demonstrated that MRI-demonsHYtrated ON was longitudinally more extensive involving at least three optic nerve segments than in a similarly sized group of patients with relapsing-remittent MS. According to Colongues and colleagues [7], NMO-related deterioration on of visual acuity is more rapid in children than in adults.

Although optic nerve atrophy is observe able by MRI, we did not find studies in the literature that analyzed how optic nerve atrophy may be related to disease duration or the number of attacks experienced. In all 12 cases in this study, we observed extensive hyperintense lesions on the T2-weighted sequence; post-Gd enhancement was observed in only 1/12 patients (Case 2). In 8/12 patients (66.6%) atrophy was verified in subsequent imaging.

One of the patients (Case 4) had not experienced a visual attack, though that patient's neurological evaluation revealed a bilateral visual deficit. In the new diagnostic criteria, this negative AQP4 patient, need a second event (ON or LETM) to fill of the requirement of the dissemination in space. And, being a child, this event was only realized after clinical examination and confirmation of atrophy on MRI. ON especially unilateral can be very difficult for pediatric patients or their family members to notice (6), making neurological MRI evidence of such optic nerve lesions critical for diagnosis of NMO.

In children, ON is related primarily to post infectious etiology [16]. In the case series studied by Peña and colleagues, 6/6 pediatric patients (100%) had bilateral ON, which is considered the most common presentation of the disease in an ethnically Latin American population [16,17]. In our series, transverse myelitis was the most common presentation, being observed in 7/12 patients (63.6%) at the time of their initial attack. Visual deficits, which were observed in all patients eventually over the course of the disease, were bilateral in 9/12 cases (75 %).

Among the typical brain lesions with hyperintense on T2 present at the skull MRI in NMO-SD, there is the long commitment of the corticospinal tract, visualized with dedicated study to the trajectory of this bundle, which passes through the internal capsule and cerebral peduncle [5]. A DTI sequence can demonstrate reduction in the anisotrophy of this bundle, which provides evidence of retrograde degeneration. To our knowledge, there have been no reports that have examined the relationship between the incidence of this lesion and age. In our case series, damage to this bundle was present in 3/12 cases (25.0%), and was bilateral in 2/12 cases (16.6%). The predominant symptoms were

spasms at the end of the limbs, hypoesthesia and hyperreflexia.

LETM can also be present in children with MS and ADEM. In NMO, lesions detected by MRI are mostly central [18,19]. Hypointensity in T1 and atrophy demonstrate the extent of injury related to recurrent attack so fold lesions. In these cases, attention should be given to the enhancement of short segments superimposed upon pre-existing lesions. In the presence of short spinal-cord lesions, other typical signs seen on head MRI should be researched before ruling out NMO [19].

Cervical lesions can be associated with medulla oblongata lesions and lesions in the area postrema; in certain patients, these lesions underlie the severe clinical presentation of a requirement for breathing support. Although their condition is serious, these patients can achieve a good clinical and radiological response owing to reversible vasogenic edema, which can also occur in hemispheric lesions [19,20,21,22]. Indeed, in our case series, we did see MRI verification of a disappearance or marked volume reduction of brainstem lesions.

In pediatric patients, brainstem syndrome can impact morbidity and mortality [15,26]. In our case series, 6/12 patients had brainstem syndrome, including 3 patients in which it was an initial manifestation. Lesions of the brainstem are identified in T2-weighted FLAIR sequences as hyperintense areas with poorly defined margins, mainly in the dorsal portion of the medulla oblongata [15]. They can occur in the midbrain, pons, and medulla oblongata, with the medulla oblongata being the location highest prevalence in patients with NMO [15]. The presence of area postrema syndrome with lesions on MRI fulfills the criteria for NMO [5]. The most detailed interpretations of bulbomedullary junction lesions discovered on MRI in the present case series were from cases in which a dedicated protocol using fine T1 axial, sagittal, and coronal slices before and after Gd had been added to the basic routine to differentiate among isolated brainstem lesions, high cervical lesions with or without damage to the brainstem, and bulbomedullary junction lesions. In two cases, hyperintense brainstem lesions located on the medulla oblongata and area postrema and extensive coalescing lesions had good clinical-radiological resolution. Lesions on the brainstem seen on MRI may or may not be related to brainstem syndrome [15]. In our case study, only a single patient (Case1) had MRI-demonstrated bilateral internuclear ophthalmoplegia without a brainstem lesion.

Respiratory symptoms and vomiting may precede encephalic manifestations in NMO [6,10,18]. Encephalic symptoms (e.g., headache, narcolepsy, convulsive crisis and coma), brainstem symptoms (e.g. difficult-to-control hiccups, nausea, vomiting, and bulbar dysfunction), homonymous hemianopsia, and cerebral symptoms (e.g., ataxia) can all be present in NMO [5,23]. Pediatric patients can present with ON and LETM or encephalic symptoms after an infection or vaccination [23]. In our case series, one of the patients had extensive hemispheric lesions (Case3) with multiple manifestations including respiratory symptoms and influenza-like fever, followed by bilateral loss of vision, loss of strength in the lower limbs, a convulsive crisis, and rapid deteriorate on of consciousness. Extensive hemispheric lesions can be present in pediatric and adult patients with NMO [24]. Encephalic lesions with an MRI appearance similar to ADEM and Posterior reversible encephalopathy syndrome (PRESS) are present in 16% of pediatric patients [9,21]. In our case series, the male patients had extensive hemispheric lesions on MRI during the period rapidly evolving encephalic symptoms. In one of these patients (Case3), surgical intervention with biopsy was necessary to make a differential diagnosis versus neoplasm. The biopsy revealed brain tissue modified by notable xanthomatous infiltration of a perivascular nature, low levels of leukocyte infiltration and astrocyte reactivity, and a histopathological pattern suggestive of a pseudo-tumor demyelinating disease. Gliomas and metastases are the main differential diagnoses of extensive brain lesions [25]. Extensive demyelinating lesions can show post-Gd enhancement of the complete or incomplete annular type or with a central vessel [30]. In our case series, only one patient had post-Gd enhancement of an incomplete halo. According to the literature, isolated encephalic masses with initially acute or subacute neurological symptoms, halo enhancement, and little or no mass effects without edema should lead to a diagnostic hypothesis of an extensive demyelinating hemispheric lesion and, among other possibilities, NMO [25].

Pediatric NMO case studies have aroused interest not only because our understanding of the disease has been changing recently, but also because of its different forms of presentation,

which differ across different ethnic groups. We considerate important to describe the characteristics of this sample, despite our study's limitations, namely that it was a retrospective study based on users of a public service in which we could not establish relevant information about attack-to-MRI interval. Although a retrospective reading of the cases was performed by two neuroradiologists with prior knowledge of the diagnosis, standardization of lesion currently recognized as typical of NMO could still be established correlation with the current diagnostic criteria for NMO. There was not a standardized protocol for the detailed study of the bulbomedular junction common to all patients. It was not possible to establish the interval between the neurological attack and AQP4 test serum or the interval between this test and treatment to establish the status AQP4 in the course of the disease. Studies with larger samples of pediatric patients, particularly of Latin American and African descent, could provide further complementary information relevant to our understanding of the range of clinical and radiological expression of this disease.

Future MRI studies incorporating range of technique, including DTI among other, may improve clinicians' ability to diagnose NMO. Early diagnosis enables early treatment and thus can improve survival and quality of life of pediatric patients with NMO.

6. CONCLUSION

Five patterns of conventional brain MRI were found in the present series of pediatric patients with NMO. In this series, there was the presence of at least one typical sign in these imaging patterns. To facilitate their detection, some typical signs of NMO in the brain need dedicated protocols in conventional MRI for the study of corticospinal tracts, the bulbomedullary junction, area postrema, the whole length of the optic nerves and quiasma optic. Specific signs for NMO are part of the radiologic requirement in the current diagnostic criteria.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX

LEARNING POINTS

NMO is a disease related to the IgG-NMO antibody, which mainly affects adult women of African descent and has important neurological consequences.

It rarely occurs in childhood.

For many years, it has been thought that the absence of lesions in the brain on MRIs was a characteristic of NMO.

Imaging studies of children with NMO can show signs of the initial stages of the disease.

Recognizing the clinical signs and the appearance on imaging of the onset of the disease leads to earlier diagnosis and treatment, thereby reducing the neurological consequences for patients and improving their quality of life.

The technical aspects of MRIs in NMO:

Protocols dedicated to the study of the pyramidal tract, brainstem, bulbomedular junction, to the entire optic nerve up to the chiasm with thin slices, on the axial, sagittal and coronal planes should be used on children in NMO.

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