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ARTICLE

Neuromyelitis optica: phenotypic characteristics in a Brazilian case series

Neuromielite óptica: características fenotípicas em uma série de casos brasileiros

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ABSTRACT

The definition of neuromyelitis optica (NMO) is still evolving. In 2015, the International Panel for NMO Diagnosis was convened to develop revised diagnostic criteria. There have been few studies on NMO in the Brazilian population. **Objective:** To describe the characteristics of 34 Brazilian NMO patients. To evaluate the contribution of the 2015 criteria to the diagnosis of NMO spectrum disorders (NMOSD) in 40 patients with longitudinal extensive transverse myelitis (LEMT). **Methods:** This is a retrospective, descriptive and analytic study. **Results:** Among NMO patients, there was a predominance of women, with onset in the fourth decade of life, and AQP4-IgG seropositivity in 73.5%. The diagnosis of NMOSD was established in 37.5% of LETM patients according to AQP4-IgG positivity and in 5% of LETM patients if the AQP4-IgG result was unknown. **Conclusions:** The characteristics of this series are similar to those of other Western populations. The AQP4-IgG testing assists in the diagnosis of NMOSD.

Keywords: neuromyelitis optica; epidemiology; cross-sectional studies. enzyme-linked immunosorbent assay.

RESUMO

Neuromielite óptica (NMO) é um conceito em evolução. Em 2015, o Painel Internacional para o diagnóstico de NMO apresentou novos critérios diagnósticos. Poucos são os estudos em NMO na população brasileira. **Objetivos:** Descrever as características de 34 casos brasileiros de NMO. Avaliar a contribuição dos critérios de 2015 para o diagnóstico de desordens do espectro NMO em 40 pacientes com mielite transversa longitudinal extensa (MTLE). **Métodos:** Estudo retrospectivo, descritivo e analítico. **Resultados:** Predomínio do sexo feminino, início na quarta década e anticorpo anti-AQP4 positivo em 73,5% dos casos de NMO. Diagnóstico de desordem do espectro NMO estabelecido em 37.5% dos casos de MTLE com positividade do anticorpo anti-AQP4 e em 5% se o resultado sorológico fosse desconhecido. **Conclusões:** Esta série de casos de NMO tem características semelhantes às de outras séries ocidentais. A pesquisa do anticorpo anti-AQP4 é relevante para o diagnóstico das desordens do espectro da NMO.

Palavras-chave: neuromielite óptica; epidemiologia; estudo transversal, ensaio enzimático.

The association between optic neuritis (ON) and transverse myelitis (TM) has been known since the 19th century. The term neuromyelitis optica (NMO) was first used in 1894 by Eugène Devic when describing the case of a female patient with bilateral ON and TM with severe functional deficits and subsequent death[1]. First considered a variant of multiple sclerosis, NMO is currently regarded as a distinct disease, because it has clinical manifestations and radiological and pathological features that differ from multiple sclerosis[2].

The first diagnostic criteria for NMO were formulated in 1999 and intended to distinguish NMO from multiple sclerosis. At that time, exclusive clinical dysfunction of the optic nerves and spinal cord was considered mandatory for diagnosis. Suggestive findings in diagnostic tests and clinical characteristics emphasizing the severity of disease were considered major and minor criteria, respectively[3].

The discovery of a highly specific antibody for NMO in 2004[4] and of its target antigen, aquaporin 4 (AQP4) in the following year[5], allowed the recognition of limited forms of the disease and the characterization of dysfunction at other sites in the central nervous system. These developments led to a revision of the diagnostic criteria for NMO in 2006[6].

In 2007, the term NMO spectrum disorders (NMOSD) was introduced to extend to AQP4-IgG-seropositive patients with limited forms of NMO who were at high risk for future attacks[7].

The refinement of the list of non-opticospinal disease characteristics and the presence of AQP4-IgG-seronegative patients or those with unknown serostatus have rendered the 2006 criteria inadequate for contemporary practice and

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research. The term NMOSD has also been used variably in the literature and requires clarification. In 2015, the International Panel for NMO Diagnosis was convened to develop revised diagnostic criteria and to define the nomenclature. The panel recommends prospective validation of the criteria[8].

There appear to be differences among NMO patients according to serostatus. Some studies suggest that AQP4-IgG-seronegative patients are younger, less frequently female, and less likely to relapse[9].

In this study, we describe the demographic, clinical, and paraclinical characteristics of a Brazilian series of patients with NMO, and search for differences as a function of serostatus. We also evaluate the contribution of the 2015 criteria to the diagnosis of NMOSD in a series of patients with longitudinal extensive transverse myelitis (LETM).

METHODS

This is a retrospective, descriptive and analytic study.

Patients of any age diagnosed with NMO, according to the 2006 Wingerchuk et al.[6] criteria, or with LETM (three or more contiguous spinal segments, without other known etiology), subjected to AQP4-IgG testing at the Brasilia unit of the Sarah Network of Rehabilitation Hospitals from November 2009 to July 2012, were included.

The AQP4-IgG testing was performed using a commercial ELISA-R kit (recombinant human AQP4, M1 isoform), with a cutoff of 5 U/ml.

The variables were gender, age at initial event, skin color (white/non-white), initial clinical event (isolated TM, isolated ON, simultaneous TM and ON, and brainstem syndrome), time from first relapse to first appointment, time interval between index events (ON and TM), duration of the disease, presence and total number of recurrences, score on the Expanded Disability Status Scale at last assessment, associated immune disease, AQP4-IgG serostatus, findings on spine magnetic resonance imaging (MRI) (the presence of extensive spinal cord injury, central lesions, and affected spinal cord segments), findings on brain MRI (normal, nonspecific lesions, or typical NMO lesions according to Kim[10]), the presence of other autoantibodies (antinuclear antibody, anti-Sjögren's-syndrome-related antigen A, and anticardiolipin), whether AQP4-IgG testing was performed during an attack, and whether testing occurred before or after immunosuppression.

For the statistical analyses, the variables are expressed as means ± standard deviations and were compared between groups using Student's t-test or the Mann-Whitney test. For variables expressed as frequencies, the groups were compared using the chi-square test or Fisher's exact test. P-values < 0.05 were considered significant.

The study was approved by the research ethics committee of the Sarah Network of Rehabilitation Hospitals.

RESULTS

A total of 34 patients diagnosed with NMO according to the Wingerchuk et al.[6] 2006 criteria were identified. Most patients were female (7.5 females:1 male), and the average disease onset had occurred by the fourth decade of life (34.6 ± 17.2 years of age; range: 4–68 years of age). Six patients exhibited late disease onset, after 50 years of age, and five patients experienced onset before 16 years of age. Approximately 45% of the patients were non-white. The average time from the first attack to the first appointment was 23.7 ± 26,5 months (0–108 months). The initial clinical event was ON or TM in approximately 60% of the patients; simultaneous ON and TM (interval of up to one month between each event) occurred in 23.5% of the patients; and brainstem syndrome, mainly uncontrollable vomiting and persistent hiccups, was observed in 17.6% of the patients. Recovery after the initial clinical event was complete in slightly more than 25% of the patients and absent in almost 20%. The time between the index events was highly variable (mean: 14.7 ± 29.5 months; range: 0–108 months). The mean duration of disease was 8.1 ± 5.5 years, and 73.5% of the patients were classified as recurrent NMO. In 73.5% of the patients, AQP4-IgG seropositivity was detected by ELISA. Spinal cord lesions were central in approximately 90% of the patients, and the cervicothoracic segment was the most often affected site. Brain MRI examinations exhibited typical NMO findings in 26.5% of the patients. An association with another autoimmune disease was found in approximately 30% of the patients (an association with thyroiditis was observed in 62.5% of these patients). Other autoantibodies were detected in more than 50% of patients and, in most instances, corresponded to ANA in low titers.

The average time from the last attack to the serologic test was 28.4 ± 34,6 months (0–108 months). Only six patients (18%) had AQP4-IgG testing less than one month after relapse. Twenty-four patients (70%) were on immunosuppressive drug treatment (prednisone and azathioprine 12 patients, azathioprine 12 patients) when serological testing was performed. Neither factor significantly affected the results of AQP4-IgG testing (Table 1). Thirty-three patients (97%) remained free of attacks during immunosuppressive therapy.

In a comparison of recurrent and monophasic NMO, the latter showed a greater prevalence of isolated TM and of simultaneous ON and TM as the initial clinical event, and of other autoimmune diseases (Table 2).

By comparing the patients according to their serostatus, we found a greater proportion of women and non-white patients in the AQP4-IgG seropositive group and greater functional deficits, defined as higher Expanded Disability Status Scale scores, in the AQP4-IgG seronegative group. However, none of these findings were statistically significant (Table 3).

Forty patients were diagnosed with LETM (25 monophasic LETM, 15 recurrent LETM). Thirteen (32.5%) were AQP4-IgG seropositive and, as a result, defined as NMOSD. Only two recurrent NMO patients had brainstem syndrome and neuroimaging suggestive of NMOSD, matching the diagnosis of NMOSD according to the 2015 criteria, but both were AQP4-IgG seropositive.

Table 1. Characteristics of the patients when AQP4-IgG was performed.

Characteristics n(%)	Total	AQP4-IgG+	AQP4-IgG-	p-value
Time from attack				1.0000
> 1 month	28(82.4)	20 (80.0)	8 (88.9)	-
≤ 1 month	6 (17.6)	5 (20.0)	1 (11.1)	-
Immunosuppressive drugs				0.6921
No	10 (29.4)	8 (32.0)	2 (22.2)	-
Yes	24 (70.6)	17 (68.0)	7 (77.8)	-

p-value according to Fisher's test or Chi-square test.

Table 2. Demographic, clinical and paraclinical characteristics of the patients with NMO. n(%)

Characteristics n(%)	NMO	rNMO	mNMO	p-value
Gender				1.000
Female	30 (88.2)	22 (88.0)	8 (88.9)	-
Male	4 (11.8)	3 (12.0)	1 (11.1)	-
Age of onset	34.6 ± 17.2	36.3 ± 16.6	30.1 ± 19.1	0.489
Skin color				1.000
White	15 (55.6)	11 (55.0)	4 (57.1)	-
Non-white	12 (44.4)	9 (45.0)	3 (42.9)	-
Unknown	7	5	2	-
Initial clinical event				0.080
ON	10 (29.4)	9 (36.0)	1 (11.1)	-
TM	10 (29.4)	6(24.0)	4(44.4)	-
Simultaneous ON and TM	8 (23.5)	4(16.0)	4 (44.4)	-
Brainstem syndrome	6 (17.6)	6(24.0)	0(0.00)	-
Interval between events months	14.7 ± 29.5	12.5 ± 27.0	20.3 ± 36.3	0.621
Autoimmune comorbidities				0.034
No	25 (73.5)	21 (84.0)	4 (44.4)	-
Yes	9 (26.5)	4 (16.0)	5 (55.6)	-
Initial event recovery				1.000
Absent	7 (20.6)	5 (20.0)	2 (22.2)	-
Partial	19 (55.9)	14 (56.0)	5(55.6)	-
Complete	8 (23.5)	6(24.0)	2 (22.2)	-
Disease duration - years	8.1 ± 5.5	8.5 ± 5.6	6.9 ± 5.4	0.376
EDSS*	6.5 ± 2.5	6.0 ± 2.5	6.5 ± 3.0	0.565
AQP4-IgG+	25 (73.5)	19 (76.0)	6 (66.7)	0.670
Affected spinal cord segment				0.262
Cervical	5 (14.7)	5 (20.0)	0 (0.00)	-
Cervicothoracic	19 (55.9)	13 (52.0)	6 (66.7)	-
Thoracic	7 (20.6)	4 (16.0)	3 (33.3)	-
Entire spinal cord	3 (9.0)	3 (12.0)	0 (0.00)	-
Central spinal cord lesion	30 (88.2)	22 (88.0)	8 (88.9)	1.000
Brain MRI				0.678
Normal	7 (20.6)	6 (24.0)	1 (11.2)	-
Typical NMO findings	9 (26.5)	7 (28.0)	2 (22.2)	-
Unspecific findings	18 (52.9)	12 (48.0)	6 (66.7)	-
Other autoantibodies				-
ANA	16 (47.1)	11 (44.0)	5 (55.6)	0.703
Anti-SSA	1 (3.2)	1 (4.2)	0 (0.0)	1.000
Anticardiolipin	7 (21.9)	6 (26.1)	1 (11.2)	0.640

NMO: neuromyelitis optica; r: recurrent; m: monophasic; ON: optic neuritis; TM: transverse myelitis; EDSS: expanded disability status scale; AQP4: aquaporin 4; MRI: magnetic resonance imaging; ANA: antinuclear antibody; SSA: anti-Sjögren's-syndrome-related antigen A. *Values expressed as the median; ± interquartile range.

Table 3. Demographic, clinical and paraclinical characteristics by serological status.

Characteristics n(%)	AQP4-IgG+	AQP4-IgG -	p-value
Gender			0.281
Female	23 (92.0)	7 (77.8)	
Male	2 (8.0)	2 (2.2)	
Age of onset	33.8 ± 17.3	37.0 ± 17.7	0.640
Skin color			0.219
White	9 (45.0)	6 (85.7)	
Non-white	11 (50.0)	1 (14.3)	
Unknown	5	2	
Initial clinical event			0.901
ON	7 (28.0)	3 (33.3)	
TM	9 (36.0)	2 (22.2)	
Simultaneous ON and TM	5 (20.0)	3 (33.3)	
Brainstem syndrome	4 (16.0)	1 (11.1)	
Autoimmune comorbidities			0.670
No	19 (76.0)	6 (66.7)	
Yes	6 (24.0)	3 (33.3)	
Initial event recovery			0.769
Absent	5 (20.0)	1 (11.1)	
Partial	13 (52.0)	6 (66.7)	
Complete	7 (28.0)	2 (22.2)	
Recurrences			0.425
No	6 (24.0)	3 (33.3)	
Yes	19 (76.0)	6 (66.7)	
Disease duration - years	8.0 ± 5.7	7.9 ± 5.6	0.960
EDSS*	6.0 ± 4.0	8.0 ± 1.5	0.081
Central spinal cord lesion	23 (92.0)	7 (77.8)	0.281
Affected spinal cord segments			0.320
Cervical	5 (20.0)	0 (0.0)	
Cervicothoracic	14 (56.0)	5 (55.6)	
Entire spinal cord	2 (8.0)	1 (11.1)	
Thoracic	4 (16.0)	3 (33.3)	
Brain MRI			1.000
Normal	5 (20.0)	2 (22.2)	
Typical NMO findings	6 (24.0)	2 (22.2)	
Nonspecific findings	14 (56.0)	5 (55.6)	
Other autoantibodies			0.462
Present	15 (60.0)	4 (44.4)	
Absent	10 (40.0)	5 (55.6)	

NMO: neuromyelitis optica; ON: optic neuritis; TM: transverse myelitis; EDSS: Expanded Disability Status Scale; AQP4: aquaporin 4; MRI: magnetic resonance imaging. *Values expressed as the median; ± interquartile range.

DISCUSSION

The definition of NMO is still evolving. The International Panel for NMO Diagnosis affirmed the decision to unify the terms NMO and NMOSD[8]. The index events required for diagnosis, now termed core clinical characteristics, include ON, TM, area postrema syndrome (episode of otherwise unexplained hiccups or nausea and vomiting), acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions, and symptomatic cerebral syndrome with NMOSD-typical brain lesions[8]. Bilateral and/or recurrent ON, poor recovery of visual acuity, lesions extending over half the optic nerve length or involving the optic chiasm, and the absence of visual evoked potentials are indicative of NMOSD[11]. Painful tonic spasms, sensory level, bilateral motor impairment, persistent sphincter dysfunction, extensive and central spinal cord lesions on MRI performed within the first weeks after the onset of symptoms, spinal cord cavitation and late atrophy are common findings in NMOSD[3,6].

The demographic characteristics of NMO patients are reinforced by each successive published study. Neuromyelitis optica patients are predominantly female, with a ratio higher than that of multiple sclerosis; the average age at onset is older, usually by the end of the fourth decade of life; and the prevalence of non-white patients is higher than that of other demyelinating diseases[12,13,14,15,16,17,18]. These demographic characteristics were also present in the current Brazilian NMO

case series and were similar to those reported for other case series in the country[19,20,21,22]. The exceptions include a younger age at onset in the Adoni et al.[21] series, in which only patients with recurrent NMO were analyzed, and lower female-to-male ratios in the Alves-Leon et al.[20] and Bichuetti et al.[22] series (Table 4).

All NMO patients in our series exhibited extensive longitudinal spinal cord lesions in at least one spinal MRI, and none had imaging features suggestive of multiple sclerosis. Therefore, AQP4-IgG seropositivity was not mandatory to establish the diagnosis of NMO[6,8].

The most common initial events were isolated ON or isolated TM, recovery was generally partial or absent, the average time to the second core event was longer than one year, and immunosuppressive therapy appeared highly effective at reducing relapses. These findings reinforce the relevance of early diagnosis and early onset of immunosuppressive therapy. The AQP4-IgG testing may help the diagnosis of NMOSD. Diagnostic requirements are more stringent for patients in whom AQP4-IgG is not detected or for whom testing is unavailable[8]. In this series of patients with LETM, the diagnosis of NMOSD was established in 37.5%, based on AQP4-IgG positivity. If the AQP4-IgG result was unknown, only 5% would meet the diagnosis, according to 2015 criteria.

In the present case series, AQP4-IgG seropositivity was similar to that reported by Lennon et al.[4] (73%) and was higher than that found by Adoni et al.[23] in Brazilian patients with recurrent NMO; both studies used the IF method.

An AQP4-IgG seropositivity by the ELISA method reported for other Western populations varies from 60 to 76%[9,24,25]. The use of the isotype AQP4 M23 increases the sensitivity of this method[26,27]. Currently, cell-based assays are strongly recommended[8,25], but the expertise and resources required to perform those assays preclude their use in small-scale clinical diagnostic laboratories. A previous study affirms that commercially available kit assays (ELISA-R and CBA-E) are both sensitive and specific for AQP4-IgG detection, and their relative simplicity to perform allows small-scale laboratories to offer sensitive and specific AQP4-IgG testing[25].

We did not find any significant difference among NMO patients according to their serological status. The proportions of women and of people of African descent were higher in the AQP4-IgG seropositive group. The small numbers of seropositive and seronegative patients may account for the lack of significant differences between the groups.

In our series, an association with other autoimmune diseases was more frequent among the monophasic patients. Isolated TM or simultaneous ON and TM were more prevalent as initial events in that group, although this difference was non-significant. Once again, the small number of recurrent and monophasic patients reduced the statistical power of the sample.

Table 4. Characteristic of Brazilian NMO case series.

Variable	Papais-Alvarenga	Alves-Leon	Adoni	Bichuetti	Del Negro
	2002	2008	2008	2009	2014
Number of cases	24	28	28	41	34
Study period	1995–2001	2003–2005	NR	1994–2007	2009–2012
female:male ratio	05:01	03:01	08:01	2.4: 1	7.5: 1
Age of onset	32.8	29.3	26	32.6	34.6
Disease duration years	7.7	12.3	7	7.4	8.0
Final EDSS	6	3.2	5.5	5.2	6.5
Initial event %					
ON	33.3	46.4	61	34	29.4
Myelitis	37.5	28.6	39	42	29.4
ON + myelitis	29.2	25.0	0	24	23.5
AQP4-IgG+ %	Not tested	NR	64.3	41 (n = 17)	73.53
Other AI disease %	12.5	NR	21	7	26.5
Other autoAb %	NR	NR	46	34	55.9
Affected segments %					
Cervical	NR	NR	36	NR	14.7
Cervicothoracic	NR	NR	46.4	NR	55.9
Thoracic	NR	NR	17.6	NR	17.6
Entire spinal cord	NR	NR	NR	NR	8.8
Abnormal brain MRI %	38	NR	NR	59	79.4
CSF %					
Normal	52	NR	NR	NR	44.1
Pleocytosis	37.5	NR	NR	10*	32.3
Increased protein	45.8	NR	NR	NR	38.7
OB	21	NR	NR	0	3.4

NMO: neuromyelitis optica; EDSS: expanded disability status scale; AI: autoimmune; NR: non-recorded; ON: optic neuritis; AQP4: aquaporin 4; Ab: antibody; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; OB: oligoclonal bands. *more than 50 leukocytes/field

Because it is a rare disease, multicenter studies and meta-analyses are needed to achieve better epidemiological characterization of NMO and NMOSD. The establishment of databases, such as NEMOS[17] and NMO-DBr[28], is fundamental.

In conclusion, the characteristics exhibited by the present series of Brazilian patients with NMO reinforce those reported for other Western populations. The ELISA-R method exhibited satisfactory sensitivity for the detection of AQP4-IgG. The most common initial events included limited forms of the disease, which emphasizes the relevance of AQP4-IgG testing in such patients. No statistically-significant difference was found between patients as a function of their serological status, but the small sample size may have led to this result.

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