Clinical, Paraclinical and Imaging Characterization of a Population of Colombian Patients with Neuromyelitis Optica Spectrum Disorder at the Hospital Universitario San Ignacio, Bogotá, Colombia

Caracterización clínica, paraclínica e imaginológica de una población de pacientes Colombianos con espectro de Neuromielitis óptica del Hospital Universitario San Ignacio

SUMMARY

INTRODUCTION: Neuromyelitis Optica (NMO) is an inflammatory syndrome of the central nervous system, different from multiple sclerosis, that is associated with aquaporin-4 IgG antibodies (AQP4-IgG). The new nomenclature defines a unified term of Neuromyelitis Optica Spectrum Disorder (NMOSD), seropositive or seronegative according to the AQP4-IgG positivity.

OBJECTIVES: Demographic, clinical, imaging and cerebrospinal fluid (CSF) cytochemistry characterization of patients diagnosed with NMOSD at the Hospital Universitario San Ignacio (HUSI), Bogotá, Colombia, during 2006-2017.

METHODS: A descriptive observational longitudinal study of patients diagnosed with NMO according to the International consensus diagnostic criteria for neuromyelitis optica spectrum disorders 2015 evaluated in HUSI during 2006-2017. An analysis of quantitative variables was performed with mean, standard deviation, median and interquartile range (IQR), and of qualitative variables with absolute numbers and percentages. A Wilcoxon sign-rank sum test was performed for paired data to evaluate the correlation between visual acuity (VA) and EDSS disability scale at admission and discharge after treatment.

RESULTS: Data was collected for 37 patients. The mean age was 42 years-old. The form of presentation was optic neuritis (ON) in 81.1% of the cases. In patients who presented as ON, it was typical in 21.6%, atypical in 43.2% and bilateral in 18.9% of them. An average of 4.6 plasmapheresis (PPH) were performed; at discharge 45.9% presented a visual acuity (VA) lower than 20/800. The mean Expanded Disability Status Scale (EDSS) on admission was 2.8 (SD 1.4) and 2.2 (SD: 1.4) at discharge.

CONCLUSION: Colombian NMOSD patients have shown an increasingly frequent phenotype variability Including a higher proportion of patients with bilateral optic neuritis, smaller number of patients with oligoclonal bands pattern II and with typical lesions of multiple sclerosis (MS) in MRI with seropositive NMO and a greater number of cases debuting with partial segment partial myelitis.


RESUMEN

INTRODUCCIÓN: La Neuromielitis óptica (NMO) es un síndrome inflamatorio del sistema nervioso central diferente a la esclerosis múltiple que se asocia con anticuerpos IgG aquaporina-4 (AQP4-IgG). La nueva nomenclatura define el termino unificado de trastornos del espectro de Neuromielitis óptica (NMOSD), seropositiva o negativa de acuerdo a la positividad de AQP4-IgG.

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INTRODUCTION

Neuromyelitis Optica (NMO) also known as Devic’s Disease is a central nervous system (CNS) autoimmune inflammatory disorder with a variable clinical presentation, with a monophasic course or in relapses, which predominantly affects the optic nerve and the spinal cord (SC) (1-3). NMO is more prevalent in women than in men, with a monophasic course or in relapses, which predominately affects the optic nerve and the spinal cord (1-3). The prevalence of NMO is estimated; the first study published in our country described a high prevalence of NMO, although it has not yet been published. Bichuetti published 41 cases in 2009. In Colombia there is absence of AQP4-positivity as one of the pillars that support the diagnosis; the protein water channel in astrocytes, called aquaporin 4 (AQP4), thus becoming a disease-specific biomarker. The term NMOSD was introduced in 2007 and in the 2015 update the International Society of NMO Disorders 2015 (1), classifying them as seropositive or seronegative NMOSD.

1. At least 1 characteristic clinical core: optic neuritis, longitudinally extensive acute transverse myelitis or area postrema syndrome
2. Positive serum AQP4-IgG
3. Exclusion of alternative diagnoses

>Seropositive NMOSD (must meet all of the following criteria):
1. At least 2 characteristic clinical cores that occur as a result of 1 or more clinical attacks and that meet all of the following criteria:
   A. At least 1 characteristic clinical core: optic neuritis, longitudinally extensive acute transverse myelitis or area postrema syndrome.
   B. Dissemination in space (2 or more different characteristic clinical cores).
   C. Meets imaging criteria in magnetic resonance imaging (MRI)
      (i) Acute optic neuritis: normal brain MRI or T2 lesion or contrast enhancement with extension >50% of the length of the optic nerve, or compromise of the optic chiasm.
      (ii) Acute myelitis: spine MRI with longitudinally extensive intramedullary lesion (>=3 contiguous segments) or focal spinal atrophy in patients with a clinical history compatible with acute myelitis.
      (iii) Area postrema syndrome: requires spinal cord injury/area postrema syndrome.
      (iv) Acute brain stem syndrome: requires peripherally brainstem lesions.
2. Serum AQP4-IgG-AB test negative or not available
3. Exclusion of alternative diagnoses

Additionally, patients should have the following data in the clinical history:
1. Demographic variables.
2. Clinical characteristics (visual acuity at admission and discharge).
3. EDSS (Expanded Disability Status Scale).
5. Obligaline bands.
6. Treatment received for acute attack.

The basic data of the patients were taken from the Neurology Service database, search of medical records in the HUSI SAHI system. Through the DISEARCH system, the user request and access key was made through the institutional form for requesting information on medical record code E1A-R-18.

The demographic data for each patient were recorded in a database (age at diagnosis, race, sex, years of follow-up, diagnosis of the clinical presentation), brain MRI with number and location of lesions, anti AQP4 AB, and in case of having it, information on its positivity or negativity, result of cerebrospinal fluid cytology including: cellularity (absolute count), differential count (lymphocytes, neutrophils, eosinophils), proteinorrachy in mg/dL, glycorrhachia in mg/dL, oligodendal bands, number and type of relapses, EDSS score at admission and discharge, treatment received (type and number).

Exclusion criteria:
Patients with a medical records lacking the aforementioned data were excluded.

Patients were recruited at the Hospital Universitario San Ignacio, Bogotá, with the authorisation of the Research and Ethics Committee, in accordance with the ethical standards of the Declaration of Helsinki of 1964, clinical research must conform to the moral and scientific principles that justify medical research, no risk given that a review of clinical histories was carried out.

Statistical analysis
A 95% confidence interval was used, significant p value <0.05, variables according to nature: continuous variables: mean, standard deviation; categorical variables: classification by sub-groups according to the EDSS score (mild, moderate or severe disability). The quantitative variable analysis was performed with mean, standard deviation, median and interquartile range, the qualitative variables with absolute numbers and percentages. Wilcoxon sign-rank sum test was performed for paired data to evaluate the correlation between visual acuity (VA) and EDSS disability scale at admission and discharge after treatment. All analyses were performed with R statistical package, version 3.4.4.

RESULTS

Sociodemographic characteristics
37 patients participated, with an average age of 42 years old (IQR 29-51 years), 78.4% were women, most of urban origin (94.6%), high school education (43.2%), and employed 83.6% (table 1).

Clinical characteristics
The initial clinical presentation in 81% of the patients...
was optic neuritis (ON); 16% debuted with acute longitudinally extensive transverse myelitis (LETM), and 3% with LETM in the cervical region and 2.7% LETM in the thoracic region, cervical centromedullary 13.5%, and we were struck by the fact that 5.4% had cervical eccentric short segment myelitis, 2.7% thoracic eccentric short segment myelitis.

Laboratory characteristics
In cerebrospinal fluid (CSF) studies, the mean leukocyte count was 2.8 leukocytes/mm3, the average differential leukocyte count was: lymphocytes 9.9%, eosinophils 6.3%, and neutrophils 3.3%, with normal proteinurary and glycomuria. In the study of oligoclonal bands (OCBs) by isoelectric focusing the majority of the patients had pattern I (62.2), followed by pattern II (8.1%).

Imaging characteristics
In single and contrast MRI studies of orbits with a protocol for demyelinating diseases, the involvement of the optic nerve had an average extension of 15.9 mm (IQR 12.5–20 mm), table 2.

63% of the patients met Wingerchuck’s radiological criteria for longitudinally extensive ON and 37% for non-longitudinally extensive ON. The location was retrobulbar in 40.5% and anterior in 18.9%, simultaneous compromise of anterior and retrobulbar segment in 5.4%, equal percentage in retrobulbar + optic chiasm and optic chiasm + optic tract, 5.4% in optic chiasm. The anatomic location was distributed as follows: 40.5% intracisternal, 18.9% intratoral and intracanicular.

Single and contrast MRI studies were normal in 37.8%. Among the abnormal results non specific white matter lesions were observed in 35.1%, typical of NMOSD in 16.2% and 8.1% had typical lesions that meet the Barkhof criteria for Multiple Sclerosis (MS).

MRI studies of the cervical/thoracic spine were normal in 32.4%. Among the abnormal findings 27% presented LETM in the cervical region and 2.7% LETM in the thoracic region; cervical centromedullary 13.5%, and we were struck by the fact that 5.4% had cervical eccentric short segment myelitis, 2.7% thoracic eccentric short segment myelitis.

AQP4-IgG Abs by ELISA method were positive in 40.5% in the first sampling, it was repeated in 17 patients with clinical suspicion after discharge in a minimum time of 1 month, being positive in 35.1% of them.

Therapeutic characteristics
Twenty three patients (62.2%) received treatment for the attack with a combination of methylprednisolone and PPH, and 8.1% of the patients (3) only received methylprednisolone. On average, the number of PPH was 4.6. In relation to immunomodulatory maintenance management the most common treatment was prednisolone and azathioprine (56.8%), followed by rituximab in 40.5% of the patients.

Table 1. Demographic characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Count</th>
<th>%</th>
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<tr>
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<tr>
<td>Female</td>
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<tr>
<td>Male</td>
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<td>21.6</td>
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<td><strong>ORIGIN</strong></td>
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<td>Urban</td>
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<td>Rural</td>
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<tr>
<td><strong>LEVEL OF EDUCATION</strong></td>
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<td>High school</td>
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<tr>
<td><strong>OCCUPATION</strong></td>
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<tr>
<td>Employed</td>
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<tr>
<td>Unemployed</td>
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<td>Retired</td>
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Table 2. Imaging characteristics

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<th>Variables</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Median</th>
<th>Percentile 25</th>
<th>Percentile 75</th>
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<tbody>
<tr>
<td>Extension length of ON (mm)</td>
<td>15.9</td>
<td>6.8</td>
<td>3</td>
<td>30</td>
<td>16.5</td>
<td>12.5</td>
<td>20</td>
</tr>
</tbody>
</table>

Wilcoxon sign-rank sum test for paired data

The Wilcoxon rank test was performed to evaluate statistically significant differences between visual acuity or EDSS at admission and discharge and treatment with plasmapheresis. Table 3.

DISCUSSION
The epidemiology of NMOSD has been based on international studies of relatively small populations; many early studies have shown demographic, clinical, laboratory and radiological variability. This variability is due to confounding factors, including the use of non-standardized diagnostic criteria, variability in anti-AQP4 antibody assay techniques, studies with small cohorts, and the potential for selection bias. The epidemiological characteristics of patients in Colombia differ in some criteria from the usual presentation known worldwide; this makes it necessary to describe our own epidemiology and the characteristics of patients with NMOSD in Colombia.

The advent of more specific diagnostic criteria, improved tests and diagnostic methods, and a better understanding of the basic immunology of NMO and NMOSD have made it possible to talk more homogeneously about patients with NMOSD. Given the heterogeneity of the populations, it is particularly important to describe the clinical, neuroimaging and laboratory characteristics, that are particular to the Colombian population. It is striking to note the frequency of AQP4-IgG seroreversion to positivity and the frequency of association with other autoimmune comorbidities; the prevalence worldwide is 20-30%, and in our study autoimmune comorbidities were reported in 13.5% of the population.

It is interesting that the demographic variables of our study are very similar to those reported in other studies; the clinical presentation has a heterogeneity, and we emphasize that of the patients who debuted with optic neuritis in the first attack, up to 89% was bilateral, compared to the world population, which is only 5%. In paraclinical variables, three patients (8.1%) with seropositive NMOSD had oligoclonal bands pattern II, compared to the world population, which reports up to 20%. Regarding the characteristics of the cerebrospinal fluid cytometry, the literature reports that...
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REFERENCES


35% of patients present pleocytosis of less than 50 cells/mL with a differential count of 44% neurophilps and 10% eosinophils (30,33); in our study, 29.7% had mild pleocytosis with lymphocytes (9.9%), eosinophils (6.3%) and neurophilps (3.5%) predominance. It is utilizing that in radiological studies, up to 8.1% presented lesions typical of multiple sclerosis according to the Barkhof criteria, compared to 16% in the world population; unlike the world population, which reports a 7-14% short segment partial acute myelitis presentation, we noted a higher frequency in our study (21.6%) (16-25). In addition, in studies worldwide, the most common form of spinal involvement is longitudinally extensive acute transverse myelitis (80%); in our study it was not as frequent, as it was only evidenced in 29.7%. EDSS was statistically significantly lower at discharge compared to admission among patients treated with plasmapheresis (Z = 3.8, p = 0.0001).

Differences were compared to the study by Reyes et al, which were the most frequent first attack was optic neuritis (80%); in our study it was not as frequent, as it was only evidenced in 29.7%. EDSS was statistically significantly lower at discharge compared to admission among patients treated with plasmapheresis (Z = 3.8, p = 0.0001).

CONCLUSION
In Colombia there is only one study of 22 patients in 3 hospital centers. There are no more epidemiological data specific to our population, being this the first characterization of the largest number of patients NMO patients recruited in a single hospital in Bogotá. We want to emphasize that we found some differences in the presentation in comparison with the available data in the literature. However, studies with a larger number of patients are required to draw conclusions regarding differences in clinical, imaging and laboratory variables in our population.

Conflicto de interes
There is no conflict of interest regarding the publication of this article.