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NMO in pediatric patients

Brain involvement and clinical expression

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ABSTRACT

Objective: To analyze the clinical, neuroimaging characteristics and positivity of the aquaporin water channel (NMO-IgG) in pediatric patients with neuromyelitis optica (NMO). This disorder could have a variable clinical expression. To address such variability, the term NMO spectrum has been suggested. **Method:** We evaluated six pediatric patients, with a median age of 11 years at the time of the study, with the diagnosis of NMO by the Wingerchuck criteria. **Results:** All the cases exhibited bilateral optic neuritis (ON). Four patients had abnormalities on brain MRI from the onset, although only three of them developed symptoms correlated to those lesions during the course of their disorder. NMO-IgG was positive in 80%. **Conclusion:** Optic neuropathy is the most impaired feature in NMO patients. Brain MRI lesions are not compatible with multiple sclerosis and positivity of the NMO-IgG are also present in NMO pediatric patients, confirming the heterogeneity in the expression of this disorder.

Key words: neuromyelitis optica, multiple sclerosis, optic neuritis, transverse myelitis, pediatric patients.

NMO en pacientes pediátricos: afectación del cerebro y expresión clínica

RESUMEN

Objetivo: Analizar las características clínicas y de neuroimagen, y la positividad del canal de agua acuaporin (NMO-IgG) en pacientes pediátricos con neuromielitis óptica (NMO). Este trastorno puede tener una expresión clínica variable. El término espectro de NMO ha sido propuesto para poder incluir la variabilidad. **Metodo:** Evaluamos seis pacientes pediátricos, con una mediana de edad de 11 años al momento del estudio, con el diagnóstico de NMO de acuerdo a los criterios de Wingerchuck. **Resultados:** Todos los casos exhibían neuritis óptica bilateral (ON). Cuatro pacientes tuvieron anomalías en la RM cerebral desde el inicio, aunque solo tres de ellos desarrollaron síntomas relacionados con las lesiones durante el curso de la enfermedad. NMO-IgG fue positiva en el 80%. **Conclusión:** Neuropatía óptica es la característica mayormente observada en los pacientes con NMO. Lesiones cerebrales en la RM cerebral no compatibles con esclerosis múltiple y positividad de la NMO-IgG están también presentes en los pacientes pediátricos con NMO; lo cual confirma la heterogeneidad en la expresión clínica de este trastorno.

Palabras-claves: neuromielitis óptica, esclerosis múltiple, neuritis óptica, mielitis transversa, pacientes pediátricos.

Neuromyelitis optica (NMO) is an uncommon inflammatory demyelinating disorder characterized by severe acute transverse myelitis (TM) with bilateral simultaneous or sequential optic neuro-

is (ON). Usually reported in adults and rarely in children, NMO has been considered an exceptional manifestation of multiple sclerosis (MS)¹⁻⁵. However, it seems to be a distinct entity with different underlying

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ing pathogenesis, and more severe course^{6,7}. This disorder could have a variable clinical expression which makes difficult its identification during its initial stages. To address such variability the term of neuromyelitis optica spectrum has been suggested^{6,8}.

The 1999 diagnostic criteria for NMO required fulfillment of three absolute criteria: optic neuritis, acute myelitis, and no symptoms and/or MRI findings beyond the optic nerves and spinal cord⁹. The Pediatric Multiple Sclerosis Study Group adopted the modified criteria from 2005¹⁰ excluding patients with brain lesions; however, the Study Group acknowledged that these criteria¹¹ were also applicable to the pediatric patients^{8,10}. In 2006, a new revised diagnostic criteria for definite NMO were defined due to the description of a sensitive and specific serum antibody which was called NMO immunoglobulin G (NMO-IgG)^{12,13}. These criteria included the occurrence of optic neuritis and transverse myelitis and at least two of three supportive criteria: MRI demonstrating involvement of a three or more contiguous spinal cord segments, brain MRI with lesions not compatible with multiple sclerosis or NMO-IgG seropositivity¹¹.

The introduction of the new criteria brought some difficulties to the NMO pediatric group (also to the adult group) due to the acceptance of white matter lesions seen in brain MRI¹¹.

Although spinal cord lesions are considered the landmark of NMO in children, it has been suggested that around half of the children with the diagnosis of NMO have neuroimaging evidence of brain lesions as well¹⁴⁻¹⁶. Furthermore, several lesions located in the hypothalamus, brainstem or diffuse cerebral white matter have been described in children with typical features of NMO^{14,16}.

Another controversial diagnostic issue is related to the role of the serologic findings in pediatric NMO concerning the specific serum antibody NMO-IgG. The aquaporin 4-specific (AQP4) water channel autoantibody NMO-IgG is detected in 73% of adults with NMO. However, Banwell, Tenembaun, and cols.¹⁶ reported that NMO-IgG in pediatric patients is a sensitive marker only for relapsing NMO.

The reports of NMO in children are limited and more complexity is added to the disease characterization. Ten years ago, in 1999, the diagnostic criteria for NMO were first described and ever since two other criteria have been developed. These changes, linked to the low prevalence of the disorder in pediatric ages, have made more difficult the study of the true nature of NMO in children. Due to the dearth of information regarding pediatric NMO we aim to describe the clinical presentation as well as the neuroimaging characterization and the presence of the NMO immunoglobulin G antibody in a cohort of pediatric patients with NMO.

METHOD

The patients described in this study were children seen in two different cities in Venezuela: [1] the Neuropediatrics Service of the JM de los Rios Pediatric Hospital, in Caracas, and [2] The University Hospital in Maracaibo. Maracaibo and Caracas are the most populated cities in the country. All patients in Maracaibo were examined by the principal author (Dr. Peña), and those in Caracas by the second author (Dr. Ravelo). The children were first seen between December 2002 and December 2008. The diagnosis of inflammatory demyelination encompassing the spectrum of neuromyelitis optica was based on clinical symptomatology, MRI and serologic analysis, which are in compliance with the most recent pediatric NMO diagnostic criteria¹¹, which states that for a NMO diagnosis a child needs: optic neuritis and transverse myelitis and at least two of three supportive criteria (MRI demonstrating involvement of a three or more contiguous spinal cord segments, brain MRI with lesions not compatible with multiple sclerosis or NMO-IgG antibody seropositivity). Patients' information concerning age, symptoms in each bout, number of bouts, laboratory findings, MRI results and treatment were reviewed for each patient.

The brain and spine MRI scans of each patient were reviewed by radiologists who were blind to the diagnosis within the MS spectrum. Most of the scans were performed within two months from the onset of the symptoms and the criteria for the revision were: number, location, size, and enhancement characteristics of the lesions. For the spinal cord scans the spinal segment length was also recorded.

Serum samples from all but one child were analyzed for NMO-IgG antibody in the Mayo Clinic Neuroimmunology Laboratory. For each child, oligoclonal IgG bands in cerebrospinal fluid were tested in the Neuroimmunology Laboratory of the Universidad Central de Venezuela. This study was usually requested after the first MRI scan was performed. Parents and guardians filled out an Informed Consent.

Six patients, five females and one male, were evaluated. Age at symptoms onset ranged from five to 13 years and the median age at the time of the study was 11 years old. They all presented three or more different bouts of a demyelinating disorder with brain and/or vertebral MRI confirmation. Five patients were white / non-Caucasian, and one was Amerindian. All children were of Venezuelan origin, with no family history of any demyelinating disorder.

RESULTS

Patients' characteristics, clinical, laboratory and MRI findings are exhibited in Table.

Table. Clinical and demographic characteristics of the sample.

Case	1	2	3	4	5	6
Age	12	13	13	12	8	8
Gender	Female	Female	Female	Male	Female	Female
First attack	Vision loss	Vision loss, cephalaea	Vision loss, paresthesias, right arm weakness	Paresthesia, paraparesis	Vision loss	Vision loss, paraparesis, somnolence, irritability
Interval between 1 st and 2 nd attacks	7 months	5 months	2 months	6 months	8 months	2 months
Current treatment	AZT	AZT, Prednisone	Prednisone, AZT	Prednisone	AZT, Prednisone	AZT, Prednisone
MRI/spine	C2-C5, C7-T4	C6-D8, D10-D11	C2-C6, D1-D3	C1-T5	C6-D8, D10-D11	C2-C5, D1-D10
Brain	PV	PV, CR			PV, CR, CC	PV, CR, Cerebellum
No. of attacks	5	7	3	3	4	3
Outcome	Bilateral vision loss, paraparesis	Bilateral vision loss, paraparesis	Bilateral vision loss, paraparesis	Bilateral vision loss, paraparesis	Bilateral vision loss, paraparesis	Bilateral vision loss, paraparesis
NMO-IgG (y)	Pos (19)	Pos (15.2)	Pending	Neg (13)	Pos (12.5)	Pos (11)

AZT: azathioprine; PV: periventricular; CR: corona radiate; CC: corpus callosum; ON: optic neuritis.

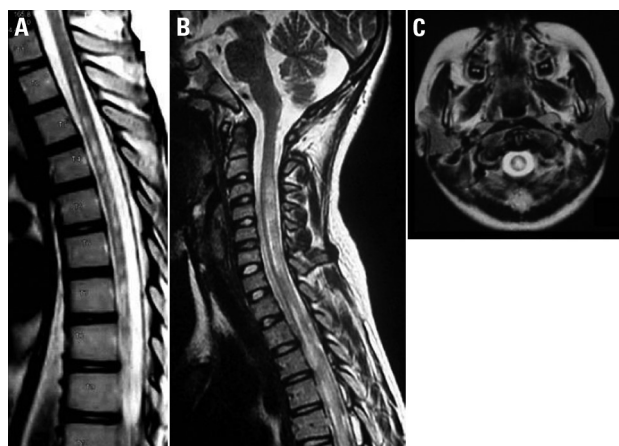


Fig 1. MRI scans of the spinal cord in patients 2 [A] and 5 [B, C] with NMO. [A] Longitudinally extensive irregular lesion from T4 to T9 levels. [B] Swollen cervical spinal cord with a longitudinally extensive lesion involving the central area of the cord. [C] Axial imaging of cervical cord showing central pattern of involvement.

Optic neuritis

In three patients ON was the initial presentation followed by TM (patients 1, 2 and 5), being apart for seven, five and eight months respectively. On the contrary, ON followed the initial presentation of TM six months later in patient 4, and ON occurred concurrently with TM in patients 3 and 6. All the cases exhibited bilateral ON with severe impairment in five of them. At the last med-

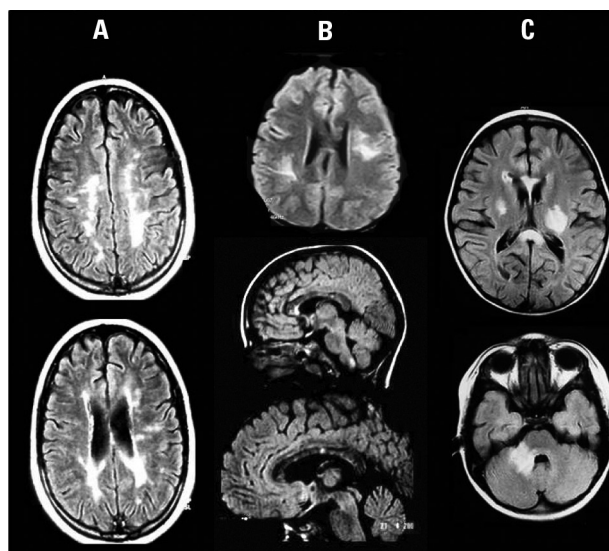


Fig 2. Abnormal brain MRI in patients with NMO. [A] Patient 1: axial T1-weighted images showing several hyperintense lesions in periventricular area. [B] Patient 5: axial T1-weighted images displaying white matter hyperintense lesions; the sagittal images show lesions in corpus callosum and pons. [C] Patient 6: axial T1-weighted images of hyperintense lesions in thalamus, corpus callosum, upper pons, and cerebellum.

ical examination, all patients showed evidence of bilateral vision loss and crural paraparesis. Patients 1, 2, 5 and 6 had complete vision loss in both eyes, and the other two children had partial vision recovery in both eyes.

Transverse myelitis

As mentioned before, only in one patient the TM was the initial presentation (patient 4); however, clinical symptoms related to TM were seen in all cases during the course of the disease, especially after the second relapse. In addition, the involvement of more than three spinal segments that included cervico-thoracic segments (Fig 1) was present in all children.

Disease course

All patients presented a relapsing-remitting course, with a median time of six months (range two to eight months) to the second relapse, and an average number of attacks of 4.16.

Brain involvement

Although the initial presentation of ON and the subsequent development of TM was the main form of the disease observed in this sample, another clinical presentations were observed, including crural paraparesis followed by ON or ON appearing concurrently with TM. Four patients exhibited abnormalities on brain MRI from disease onset, but only three developed symptoms related to brain disease during the course of the disorder (patients 2, 5 and 6). Headache, vomiting and vertigo occurred during the third clinical relapse in patient 2, while aphasia was documented among other findings in patient 5. Patient 6 exhibited seizures, somnolence and irritability as part of her second clinical relapse. Table 1 shows the distribution of the lesions. Although most of the changes were nonspecific, these three patients displayed atypical lesions which included large confluent cerebral or diencephalon lesions, periventricular lesions in the temporal horns of the lateral ventricles, and juxtacortical and central white matter lesions (Fig 2). Patients 5 and 6 had the most striking brain involvement with extensive signal abnormalities in the periventricular white matter and corpus callosum (Fig 2). The MRIs follow up displayed increased brain involvement and progressive brain atrophy in two patients (patient 5 and 6). It is important to mention that none of the images reviewed, or the recorded lesions fulfilled the Barkhof criteria for MS¹⁷.

Serology

NMO-IgG antibody was tested in five patients, with positive results in four of them (80%). At different stages of the disorder, five patients underwent cerebrospinal fluid (CSF) analysis, two had pleocytosis (35 and 20 cells/mm³), while other two had normal cell count. Oligoclonal bands were negative in all cases, and none of the patients had serologic evidence of other autoimmune antibodies or disorders.

Treatment

All patients received high-doses of methylprednisolone for the treatment of the acute attacks. One patient was treated with intravenous immunoglobulin for one acute attack (patient 2). Four patients were treated with prednisone and azathioprine simultaneously (patients 2, 3, 5 and 6). Three of the patients were initially diagnosed as MS, and for that reason they received Interferon b1a until the final diagnosis was achieved (patients 1, 5 and 6).

DISCUSSION

As an uncommon entity in pediatric ages, the clinical features of NMO are still being characterized. The demographic features of this sample were similar to those of other cohorts with adults or children, most of the cases were female and all children were from non-white populations, one of them being Amerindian^{6,8,17,18}. Recently, race has been considered an important demographic variable for NMO in children, with a predominance of Latin American and African ancestry⁶, and occurring also more frequently in non-white racial groups^{16,19}. Race-related findings might indicate that Northern European ancestry is not as determinant in pediatric-onset demyelinating disorders as it is in the adult NMO population^{8,19}.

The clinical manifestations in this small sample point toward a diverse initial presentation of NMO in Hispanic children. The optic involvement was bilateral in all patients, leading to bilateral optic atrophy. We consider this an important finding, not only for being the most common presentation of the disease in this sample, but also because of the ON sequelae: 60% of the children were blind and 40% had some kind of visual impairment. It seems then, that ON is the most impairing feature in NMO.

Spinal cord lesions evidenced by spinal MRI had been reported as the single most useful diagnostic feature in the NMO spectrum disorder, both in adults and children^{7,20}. For our sample, this additional criterion was observed in the entire group. However, there are patients with NMO who do not have the specific lesion length characteristic of the disorder thus stressing the supportive condition of this criterion.

Four of our cases exhibited the disseminated nature of the central white matter demyelination that extended beyond the optic nerves and spinal cord which is another supportive criteria according to the most recent classification¹¹. In fact, recent studies have reported a high frequency of brain MRI abnormalities in patients who fulfill criteria for NMO^{14,15,21}, including nonspecific lesions, atypical and thalamic or hypothalamic lesions that could be related to hypothalamic endocrinopathies, and also extensive cerebral white matter lesions^{8,22}. As mentioned before, three patients exhibited signal abnormalities in the diencephalon without apparent metabolic or endocrine findings.

Symptoms related to brain disorders, which have been reported in other pediatric series, were observed in our sample⁸⁻¹⁶. Throughout the study, one of our patients presented headache, vomiting and vertigo, another had seizures while other had symptoms of expressive aphasia in the course of the disorder, probably related to an extensive tumefactive white matter lesion in the left hemisphere. Moreover, in four patients there were an atypical brain MRI since the initial relapse with extensive brain damage on follow-up. Such evolution pattern has been well described in NMO literature and should prompt neuropediatricians to follow-up their NMO patients, with brain MRI, regardless of the initial presentation.

Inclusion of the autoantibody testing in the recently revised diagnostic criteria for NMO led to the distinction of this disorder from MS and other autoimmune CNS diseases. This antibody, which has 73% sensitivity and 91% specificity, has classified NMO as a brain blood barrier channelopathy with abnormal humoral immunity activation¹². It was positive in 80% of the patients in our sample. However, 10 to 25 % of the patients clinically diagnosed as NMO are seronegative for NMO-IgG. An important finding for our sample was that all the patients who had positive NMO-IgG were the same who showed brain lesions at the MRI. Published studies report that sites of high brain aquaporin 4 expressions seem to correspond with brain MRI abnormalities in this group of patients^{13,23}.

According to our findings, we can conclude that demographic characterization of NMO in children is similar to adults, exhibiting a higher prevalence of females and non-white populations. The characterization of this entity in children could be done by using the new 2006 criteria, with an emphasis on the possibility of brain lesions or symptoms of brain involvement that do not meet MS criteria. The presence of ON and TM as required criteria, in addition to the three supportive criteria in pediatric samples, was also evident in this study.

This study highlights the association of seropositivity of NMO-IgG and the presence of brain lesions in the NMO pediatric group. The heterogeneity of symptoms and neuroimaging characterization suggest that the term "neuromyelitis optica" should be applied to a broader clinical syndrome in pediatric patients.

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