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DEMYELINATING DISEASE IN ADOLESCENTS: A DIAGNOSTIC CHALLENGE THAT SHOULD NOT BE IGNORED. CASE REPORT

Keywords: Demyelinating Diseases; Multiple Sclerosis; Immunotherapy; Headache; Pediatrics.
Palabras clave: Enfermedades Desmielinizantes; Esclerosis múltiple; Inmunoterapia; Cefalea; Pediatría.

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RESUMEN

Introducción. Los eventos desmielinizantes del sistema nervioso central en menores de 18 años pueden representar la aparición de tres tipos de enfermedades del espectro desmielinizante: esclerosis múltiple, enfermedad asociada anticuerpos de glucoproteína de mielina-oligodendrocitos y trastorno del espectro de la neuromielitis óptica asociado a anticuerpos. La incidencia de este tipo de enfermedades se reporta en 0.87 por cada 100 000 niños al año.
Presentación del caso. Mujer de 17 años que inicialmente asistió a una institución de cuarto nivel de complejidad en la ciudad de Bogotá (Colombia) por sintomatología consistente en cefalea súbita y parestesias en la mitad izquierda del cuerpo, los cuales se resolvieron espontáneamente, por lo que se tuvo una impresión diagnóstica inicial de cefalea primaria tipo migraña. Sin embargo, un año después consultó nuevamente por un segundo episodio. La resonancia magnética cerebral reveló hallazgos sugestivos de enfermedad desmielinizante, por lo que se llevaron a cabo estudios adicionales que finalmente confirmaron el diagnóstico de esclerosis múltiple. Se inició tratamiento modificador de la enfermedad con fingolimod, con buena respuesta por parte de la paciente. No se evidenciaron reacciones adversas ni recaídas desde su inicio, y la carga lesional se mantuvo estable en las neuroimágenes de control.
Conclusión. El abordaje en el diagnóstico diferencial de las enfermedades desmielizantes es particularmente complejo, por lo que se deben considerar múltiples diagnósticos diferenciales teniendo en cuenta la sintomatología. La migraña constituye uno de los motivos de consulta más comunes en la población pediátrica, en casos como estos, las pistas semiológicas y los hallazgos clínicos desempeñan un papel crítico, así como la realización de estudios complementarios como la resonancia magnética cerebral y el análisis de líquido cefalorraquídeo. Dada la baja frecuencia de presentación de estas patologías en la población pediátrica, es crucial sensibilizar a los profesionales pediátricos sobre la necesidad de mantener un alto grado de sospecha clínica.

ABSTRACT

Introduction: Demyelinating episodes of the central nervous system in children under 18 years of age may involve the occurrence of three types of demyelinating diseases: multiple sclerosis, myelin oligodendrocyte glycoprotein antibody disease, and antibody-associated neuromyelitis optica spectrum disorder. The incidence of these types of diseases is reported to be 0.87 per 100 000 children per year.
Case presentation: A 17-year-old woman initially attended a quaternary care center in the city of Bogotá (Colombia) due to a sudden headache and paresthesia in the left half of the body, which resolved spontaneously, leading to an initial diagnostic impression of primary headache. However, one year later, she consulted again due to a second episode. Magnetic resonance imaging of the brain revealed findings suggestive of demyelinating disease, so additional studies were performed, finally confirming the diagnosis of multiple sclerosis. Disease-modifying treatment with

fingolimod was started, obtaining a good response. No adverse reactions or relapses were evidenced since its initiation, and the lesion load remained stable in follow-up neuroimaging studies.
Conclusions: The differential diagnostic approach to demyelinating diseases is particularly complex, so multiple differential diagnoses should be considered taking into account the symptomatology. Migraine is one of the most common reasons for consultation in the pediatric population and, in cases such as these, semiology clues and clinical findings play a critical role, as well as the performance of complementary studies such as brain MRI and cerebrospinal fluid analysis. Given the low frequency of presentation of these diseases in the pediatric population, it is crucial to sensitize pediatric professionals to the need to maintain a high degree of clinical suspicion.

INTRODUCTION

Demyelinating diseases are rare diseases in patients under 18 years of age. This group of diseases includes multiple sclerosis (MS), myelin oligodendrocyte glycoprotein antibody disease (MOGAD), and neuromyelitis optica spectrum disorder (NMOSD) associated with AQP4 antibodies. The incidence of this type of disease is reported to be 0.87 per 100 000 children per year. MOGAD is most commonly observed in 30% of cases, followed by MS in 20%, and NMOSD associated with AQP4 antibodies in less than 5% (1).

Acute neurological deficits attributable to demyelinating lesions are similar in MS, MOGAD and NMOSD, so establishing a clinical approach to these diseases, outlining the clinical features of each one, together with the alterations reflected in neuroimaging and laboratory tests, is useful. The pathophysiology of these diseases is still under study (1).

It should be noted that, depending on the clinical characteristics, several phenotypes may be found in each of these diseases. In NMOSD, it is common to find disorders such as optic neuritis (ON) and transverse myelitis, while in patients with MOGAD it is also common to find transverse myelitis and acute disseminated encephalomyelitis (ADEM) (2,3).

Initial management follows a similar therapeutic approach for all these diseases, with corticosteroids being the first line of treatment, followed by immunomodulatory therapy, which allows controlling the disease in order to avoid relapses. The most commonly used drugs in this type of therapy are fingolimod, interferon beta, glatiramer acetate, natalizumab, or rituximab. The drug is selected taking into account the severity of the disease and the characteristics of each patient (4-6).

A confirmed clinical case of demyelinating disease of the central nervous system (CNS) of the MS type in a 17-year-old adolescent girl is described below. A review of the differential diagnoses and the overall approach available for the treatment of demyelinating disease in pediatric patients is presented.

CASE PRESENTATION

On February 7, 2020, a 17-year-old mestizo woman, right-handed, was admitted to the emergency department of a quaternary care center in the city of Bogotá D.C. (Colombia) after a 4-day history of symptoms consisting of unilateral pulsating headache on the right side of progressive intensity (reaching a maximum of 8/10 on the analogue pain scale), associated with phonophobia and photophobia, but without nausea or vomiting. The episode was preceded by phosphenes of approximately 10 minutes duration. No significant disease or perinatal history was reported. Physical examination showed no change in pain upon postural changes, nor an increase in pain when Valsalva maneuvers were performed. The symptomatology was not associated with sleep or mood disorders. Following the headache, she presented paresthesia sensation on the left side of the body, without weakness or sensory alteration; it was not associated with precipitating, aggravating or extenuating factors. In the review of systems, no previous symptomatology was found.

Neurological examination showed a decrease in strength 4+/5 on the Medical Research Council (MRC) scale in the left upper limb (LUL) as the only positive finding, with no alteration in the objective sensory pattern. On admission, a simple computed axial tomography (CT) scan of the skull was performed, which was normal (Figure 1). The assessment made by the neurology department concluded that the symptoms were compatible with primary migraine headache, so the patient was discharged the same day when the pain subsided, although the subjective sensation of paresthesia was persistent. An outpatient follow-up was also requested.

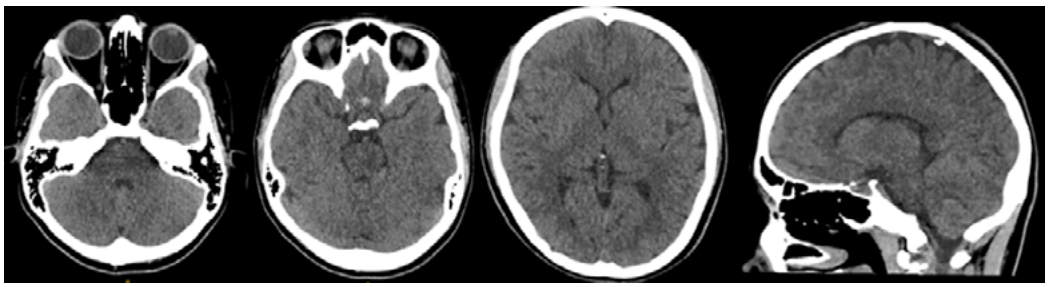

Figure 1. Simple CT showing adequate cortico-subcortical differentiation, centered midline, without intraparenchymal lesions.
Source: Images obtained while conducting the study. Archives of the Radiology Service of the Hospital Militar Central.

The patient returned to the emergency department a year later after experiencing for five days symptoms of paresthesia and decreased strength in the LUL, especially in the distal region, with progression of the symptoms and migration to the left lower limb and generalized fatigue. In the examination performed by the pediatric neurology service, the patient was found to be alert, conscious, with an adequate mental status for her age, and without cranial nerve alterations. Hemiparesis was observed in the left half of the body with an intensity of 4/5 on the MRC scale, and in the remaining limbs with an intensity of 5/5, with a positive Lhermitte's sign. Due

to focal neurological deficit, on the same day of admission, a simple brain magnetic resonance imaging (MRI) was requested, revealing alterations due to hyperintense lesions in the T2-weighted sequence, localized periventricular and pericallosal, related to demyelinating disease (Dawson's fingers) (Figure 2).

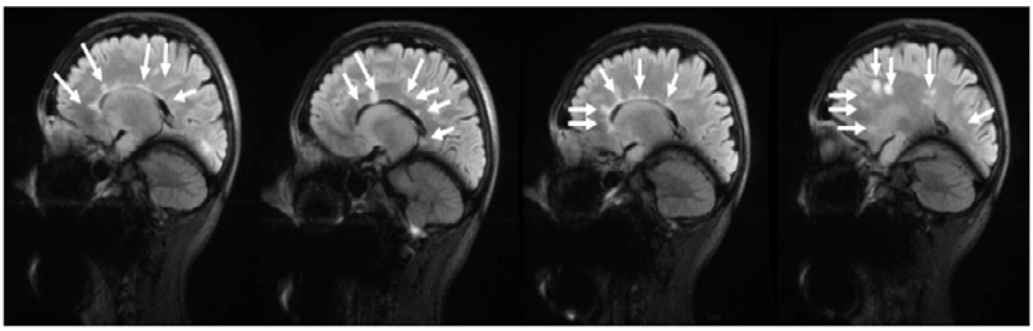

Figure 2. Simple brain magnetic resonance imaging. T2-weighted sequence showing periventricular and pericallosal hyperintense lesions related to demyelinating disease.
Source: Images obtained while conducting the study. Archives of the Radiology Service of the Hospital Militar Central.

Considering the symptomatology, the findings of the neurological examination and the results of the imaging studies, demyelinating disease was considered as the first diagnostic option because a clinical-radiological correlation was documented for bilateral periventricular hyperintense lesions in the frontotemporal region, which explained the appearance of the sensory-motor symptomatology with a migratory component that followed the somatotopic organization in the cerebral cortex.

In order to confirm the diagnosis, several studies were performed during the following 12 days of hospitalization. A contrast-enhanced MRI of the neuroaxis and orbit was requested, showing multiple demyelinating plaques located in the periventricular white matter, in the callosal-septal interface, in the white matter of the semioval center in the supratentorial region, in the corpus callosum splenium and in the right middle cerebellar peduncle, as well as a small demyelinating plaque (longitudinally anteriorly oriented) at the level of the T10 and T11 vertebrae, radiologically inactive, without contrast medium (Figure 3).

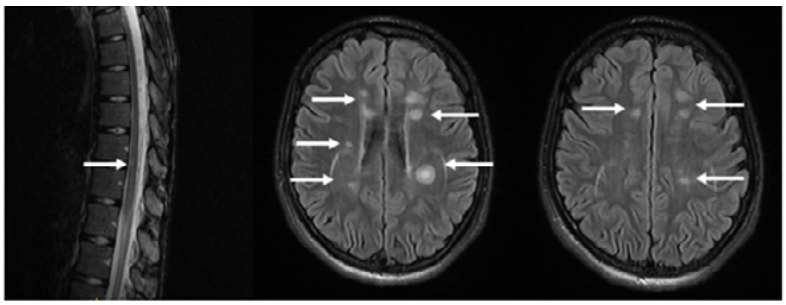

Figure 3. MRI of the neuroaxis with contrast. T2-weighted sequence with multiple hyperintense periventricular and pericallosal lesions, as well as lesion at the level of the T10 and T11 vertebrae (without contrast medium).
Source: Images obtained while conducting the study. Archives of the Radiology Service of the Hospital Militar Central.

Given the imaging findings described above, serum MOGAD and anti-AQP4 antibodies tests were requested, with negative results. Furthermore, an oligoclonal banding study was performed in cerebrospinal fluid (CSF), which showed a positive pattern in 2 bands, with no other relevant findings. During her hospital stay, an evaluation by the ophthalmology department was requested but no ocular involvement was reported. Likewise, during her stay, McDonald clinical criteria were applied with positive results for MS diagnosis, so treatment was started with intravenous methylprednisolone at a dose of 1 g/kg/day for 5 days with subsequent improvement of symptoms.

The patient was discharged after 12 days with a treatment plan in which the pharmacodynamic benefits that would facilitate adherence to treatment were explained. Treatment was started one month after discharge with fingolimod at a dose of 0.5 mg/day orally, which she continues to take to date with an adequate response. No new acute episodes have been reported since discharge, with no progression of lesions in neuroimaging at subsequent follow-ups, and no adverse reactions associated with the sphingosine 1-phosphate receptor modulator. She is currently being followed up by the neurology department for adults with a diagnosis of stage 1 relapsing-remitting MS on the Expanded Disability Status Scale (EDSS).

DISCUSSION

Acute neurological deficits attributable to demyelinating diseases are similar in MS, MOGAD and NMOSD associated with AQP4 antibodies, and each has its own clinical, pathophysiological and imaging features, making it difficult to fully understand their pathophysiology. Demyelinating diseases in the pediatric population have a low incidence, so they are of academic interest (4,5). Table 1 describes the most common features of demyelinating spectrum diseases.

Table 1. Common presentations of demyelinating diseases and distinctive features associated with MS, MOGAD, and NMOSD-AQP4.

	MS	MOGAD	NMOSD-AQP4
Key clinical features			
Female to Male Ratio	1.8:1	1:1	4:1
Onset before 11 years of age	Infrequent	Frequent	Rare
Autoimmunity	Variable frequency	Variable frequency	Common
Prodromal symptoms	Infrequent	Frequent	Infrequent

	MS	MOGAD	NMOSD-AQP4
Clinical phenotypes			
Optic neuritis	Frequent, only present in one eye, small bright focal lesion of the optic nerve in T2	Frequent, bilateral, long, bright T2 optic nerve lesions that rarely involve the chiasm	Frequent, bilateral, T2-bright optic nerve lesions involving the chiasm and extending into the optic tract
Transverse myelitis	Variable frequency, clinically silent	Frequent, mild symptoms despite multiple lesions, typically occurring with longitudinally extensive transverse myelitis with the H sign	Frequent, typically occurring with severe clinical deficit, poor recovery, longitudinally extensive myelitis with patchy enhancement
Posterior fossa syndrome	Well-demarcated lesions, internuclear ophthalmoplegia	Large lesions extending to cerebellar peduncles and ataxia	Focal lesions extending into the midbrain, area postrema, and diencephalon. Hiccups and vomiting are present
ADEM	Rare	Common, this is the most common phenotype in MOGAD, usually associated with optic neuritis and transverse myelitis	Occasional
Non-ADEM encephalitis	Not applicable	Common; cortical hyperintensity on FLAIR	Rare; diencephalic encephalopathy
Laboratory findings			
Oligoclonal bands	>80%	10%	10%
Anti-MOG antibodies in serum	< 5%	100%	0%
Anti-AQP4 antibodies in serum	0%	0%	100%
CSF pleocytosis	<50%	>70%	>70%

FLAIR: fluid-attenuated inversion recovery; MOG: myelin oligodendrocyte glycoprotein.
Source: Elaborated based on Fadda *et al.* (1).

In childhood and adolescence, 98% of the population diagnosed with MS has a relapsing-remitting course (6), so it is considered a progressive disease. The diagnosis of demyelinating diseases in the pediatric age is challenging, so it is necessary to perform a comprehensive anamnesis to detect it because it has a wide range of neurological symptoms that hinder early diagnosis (in the first event), as in the case presented here (7,8).

Some of the most commonly described symptoms include sensory and motor involvement. Compared to adults, children with MS have more relapses in the first 4 years after the onset of symptomatology (9) (annualized relapse rate 1.13 vs. 0.40 in adults) (10). They also show a greater number and volume of T2 lesions in spine or brain MRI; however, it is noteworthy that recovery from relapses in the pediatric age group is more noticeable and with fewer sequelae compared to adults, while permanent disability rarely develops, with an average time of one year

from the first episode to the presence of progressive disability. The risk of disease progression and secondary disability could be attenuated using disease-modifying therapies (8,9).

MRI of the brain and spinal cord is the most important test to support the diagnosis of MS in children and adults (9). MS lesions appear on T2 MRI as ovoid-shaped, high-signal defined areas. T2-fluid attenuated inversion recovery inversion recovery (FLAIR) images extend throughout the white matter (WM) in different regions such as the juxtacortical, periventricular areas, corpus callosum, brainstem, and cerebellum. Pericallosal hyperintense lesions are known as Dawson's fingers. In this case, the alterations in the first cranial MRI led to the diagnostic suspicion of the patient, and the contrast medium confirmed the lesions related to demyelinating disease (Dawson's fingers) (11,12,13).

Although pediatric patients with MS rarely exhibit permanent physical or neurological impairment during childhood, fatigue, depression, and cognitive impairment have a negative effect on quality of life. Many patients with this disease report the presence of fatigue that interferes with daily and enjoyable activities of life, triggering physical deconditioning and chronic psychiatric disorders (14). During the second consultation following the second episode of the disease, the patient in this case reported this symptom (fatigue), which is also very common in adults (11).

There are diagnostic criteria for MS such as the McDonald Criteria (Table 2), which were found (most of them) in the reported case.

Table 2. McDonald criteria (updated 2017) for the diagnosis of MS.

Number of clinical episodes	Number of lesions with objective clinical evidence	Additional data required for the diagnosis of MS
>/=2	>/=2	None
>/=2	1 (as well as previous clinical history of an episode with a lesion in a different anatomical location)	None
>/=2	1	Dissemination in space demonstrated by 1 additional clinical episode involving a site other than the CNS or using MRI
1	>/=2	Dissemination in time demonstrated by 1 additional clinical episode or by MRI, or demonstration of CSF-specific oligoclonal bands
1	1	Dissemination in space demonstrated by 1 additional clinical symptom involving a site other than the CNS and dissemination in time demonstrated by 1 additional clinical episode or by MRI, or demonstration of CSF-specific oligoclonal bands

Source: Elaborated based on Thompson *et al.* (11).

Many of the children with MOGAD experience only one demyelinating episode, as well as an increased likelihood of having a monophasic course of the disease associated with an earlier presentation of ADEM-related symptoms. When MOGAD presents with relapse-remission, the occurrence of a second episode is considered to range between 5-12 months (7). The severity of relapse is variable and most children with MOGAD recover almost completely (15). Some unfavorable disease courses with poor neurological prognosis have been documented; when the patient presents events similar to those of ADEM, the diagnosis may be leukodystrophy, which is evident due to an MRI pattern (with symmetrical, regional involvement and involvement of subcortical fibers or structures) or cortical encephalitis with cerebral atrophy (13).

Neuromyelitis optica spectrum disorders are divided into anti-aquaporin-4 (anti-AQP4-Ab) antibodies seropositive NMOSD and seronegative NMOSD (or unknown serological status) (16,17). In anti-AQP4-Ab seropositive NMOSD, optic neuritis is severe and can involve the optic system, including the chiasm and, in the case of acute myelitis, it is longitudinally extensive (involving more than 3 vertebral segments) and mainly affects the central gray matter. Seropositive NMOSD can also be associated with lesions of the area postrema with symptoms such as intractable hiccups, nausea, and vomiting (18). This symptomatology was not observed in the reported case.

A small proportion of anti-AQP4-Ab seronegative NMOSD patients are positive for anti-myelin oligodendrocyte glycoprotein antibodies (anti-MOG-Ab), and they exhibit some unique features compared to anti-AQP4-Ab seropositive NMOSD patients (fewer relapses and better prognosis) (16). In the case presented, the serological results for antibodies were negative.

Optical coherence tomography (OCT) is a key test for the diagnostic characterization and prognosis of demyelinating diseases. In this type of studies, neuronal damage is generally evidenced (16). Both MRI and OCT are useful to diagnose and evaluate both types of NMOSD associated with autoantibodies (16,18). The patient in this case did not undergo OCT; however, the main diagnosis was made by MRI. After an exhaustive analysis of the disease-modifying drugs, fingolimod was considered the best therapeutic option, showing a good performance with adequate patient tolerance and no relapses.

CONCLUSIONS

The diagnosis and therapeutic approach to this type of demyelinating diseases is a challenge both in the adult and pediatric population, so proper anamnesis, neurological physical examination and the rational and correct use of clinical and imaging tests allow an early and accurate diagnosis.

ETHICAL CONSIDERATIONS

The patient and her parents gave their informed consent for the publication of this article, demonstrating their positive attitude to contribute to the advancement of medical knowledge and, in this way, help other patients in similar situations to obtain an early and timely diagnosis.

CONFLICT OF INTEREST

None stated by the authors.

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