CASO CLÍNICO/CASE REPORT

Demyelinating Disorder of the Central Nervous System Mediated by Anti-MOG Antibodies: Expanding the Spectrum in Early Childhood

Doença Desmielinizante do Sistema Nervoso Central Mediada por Anticorpos Anti-MOG: Expandindo o Espectro na Infância

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Abstract

The discovery of antibodies directed against the myelin oligodendrocyte glycoprotein (anti-MOG antibodies) has allowed a very interesting diagnostic characterization of many childhood acquired demyelinating syndromes that, until the identification of those antibodies, had been described as corresponding to diseases of very different etiologies. Nevertheless, the clinical phenotypes associated with the presence of these molecules in the blood are very diverse and heterogeneous, and the notion of a spectrum of diseases of varying severity seems to be increasingly supported. It is important to note that characteristics of these conditions also seem to be very dependent on the age at which they debut. We present a clinical case of a child with a disease associated with the presence of anti-MOG antibodies in the serum and that raises an important discussion about the differential diagnosis.

Resumo

A descoberta de anticorpos dirigidos contra a glicoproteína oligodendrocítica da mielina (anticorpos anti-MOG) permitiu uma caracterização diagnóstica interessante de muitas síndromes desmielinizantes adquiridas na infância que, até à identificação desses anticorpos, foram descritas como correspondendo a doenças de etiologias variadas. No entanto, os fenótipos clínicos associados à presença dessas moléculas no sangue são muito diversos e heterogéneos e a noção da existência de um espectro de doenças de gravidade variável parece ser cada vez mais evidente. É importante notar que as características destas entidades clínicas também parecem ser muito dependentes da idade em que se manifestam. Apresentamos um caso clínico de uma criança com uma doença associada à presença de anticorpos anti-MOG no soro e que levanta uma importante discussão sobre o respectivo diagnóstico diferencial.

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Introduction

The discovery of antibodies directed against myelin oligodendrocyte glycoprotein (MOG) was an important step to increase knowledge related to acquired demyelinating diseases of the central nervous system (CNS) in children, especially in very early stages of life.[1] Since the identification of anti-MOG antibodies, several clinical situations in pediatrics have been associated with their presence in serum. The first phenotypes described were from children with an acute disseminated encephalomyelitis (ADEM)-like first episode and in children with multiple sclerosis (MS) diagnosed before 10 years of age.[2] More recently, different phenotypes have been linked to high-titers of circulating anti-MOG antibodies: they were identified in several pediatric cases with recurrent optic neuritis (ON),[3] in seronegative (meaning negative for the presence of anti-aquaporin 4 antibodies) neuromyelitis optica spectrum disorders (NMOSD)[4] and in a group of young patients starting with ADEM followed by monophasic or recurrent ON (ADEM-ON).[5]

Despite the attempt to concentrate the phenotypic description of the disorders mediated by anti-MOG antibodies in large clinical syndromes, experience has brought to medical practice a great heterogeneity of phenotypes, a situation that is particularly evident in younger children.[6] It is in them that it becomes more difficult to establish a precise diagnosis and, consequently, an assertive prognosis. Here we present a paradigmatic case addressing this clinical difficulty.

Case Report

A previously healthy 2-year-old girl was admitted to the Emergency Department (ED) of her local hospital due to a history of fever (maximum temperature of 38.9°C), somnolence, vomiting and headache with 5 days of evolution, to which a paroxysmal event very suggestive of a first febrile seizure was added, at the admission. She was observed and after discharged, with surveillance measures. Two days later, she returned the ED after a second seizure occurred at home, that was treated with rectal diazepam. A first complete blood count revealed leukocytosis with neutrophilia (leukocytes 26.6 x $10^3/\mu l$, with neutrophils 18.2 x $10^3/\mu l$) and thrombocytosis (559 x $10^3/\mu l$) and a discrete elevation in C reactive protein (3.3 μg/dL) was observed. The computerized tomography (CT) scan was unremarkable, the lumbar puncture revealed a normal profile for the cerebrospinal fluid (CSF), but the electroencephalogram (EEG) showed a diffuse cerebral dysfunction, suggestive of an encephalopathy. She was admitted at the Pediatrics Department and started on acyclovir (1500 mg/m^2/day) and ceftriaxone (80 mg/kg/day). Due to a lack of improvement, after two weeks, she was transferred to our hospital.

In our first observation, no focal neurological signs were observed, although a very important drowsiness was maintained. An EEG was firstly obtained, confirming the presence of a diffuse encephalopathy, without concomitant paroxysmal activity. This child was then submitted to a brain magnetic resonance imaging (MRI), which showed multiple parenchymal lesions in both cerebral hemispheres, involving the white matter, the basal ganglia and also the left temporo-occipital cortex (Fig. 1, A1-A3). A small lesion in the splenium of the corpus callosum was also observed. Few small foci of enhancement after gadolinium administration were present and medullary MRI was normal. The diagnosis of ADEM was then evoked. Considering this, treatment with intravenous methylprednisolone (30 mg/kg/day) was started and maintained during five consecutive days. The improvement of the state of consciousness was evident and she was then discharged home, under oral prednisolone (2 mg/kg/day), with a progressive decrease in dose over the following weeks.

At the time of the post-hospitalization reassessment consultation (3 months after hospital discharge), her mother referred that, by the time of oral prednisolone withdrawal, this child had experienced a 2-3 day episode characterized by bilateral hand tremor, predominantly upon waking, but with no negative impact on her daily activities. Due to this self-limited course, the mother did not seek medical help and the involuntary movements were not clinically evaluated. A new brain MRI was obtained 6 months after discharge and it showed regression of the lesion burden, but also several new bilateral white matter lesions were identified, namely at subcortical and periventricular levels. A lesion involving the splenium of the corpus callosum, with some mass effect, was particularly evident (Fig. 1, B2, arrow), and other lesions involving the right thalamus, the midbrain and the cerebellar hemispheres were described. After gadolinium administration, several areas of enhancement were observed, particularly at the corpus callosum level (Fig. 1, B4, arrow), reinforcing the highly active behavior of this condition (Fig. 1, B1-B4).

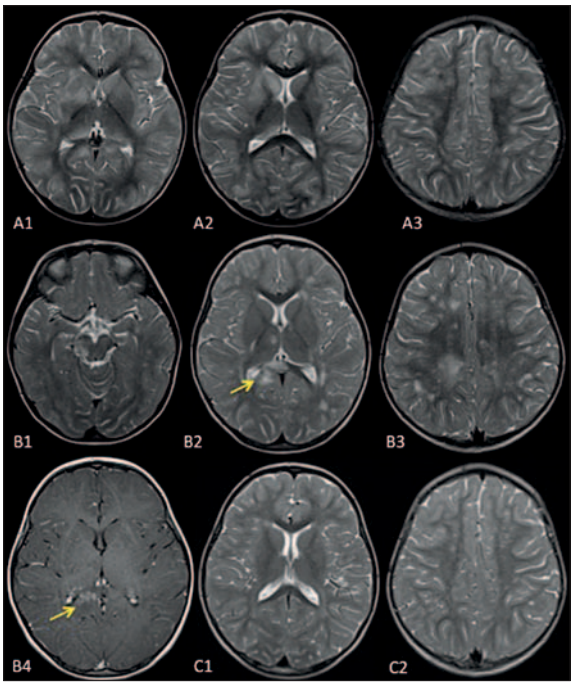

Figure 1. Brain MRI obtained during child's illness. A1-A3: first MRI, axial T2 weighted images, showing multiple parenchymal lesions, involving both white and grey matter regions, suggestive of ADEM. B1-B4: MRI obtained 6 months after ADEM diagnosis. Axial T2 weighted images (B1-B3) revealing several new lesions, involving both supra and infratentorial compartments. The arrow in B2 indicates the arch bridge lesion in the splenium of corpus callosum. Post contrast axial T1 weighted image (B4) showing that was an active lesion (arrow). C1-C2: MRI obtained 1 year after treatment with monthly IgIV. Axial T2 images show an important reduction in lesion load.

A new EEG was obtained, being unremarkable. Then, an analytical re-evaluation was requested and this included a new lumbar puncture (revealing a normal CSF profile, with no oligoclonal bands identified), the determination of serum anti-aquaporin 4 (AQP4) antibodies (negative) and anti-MOG antibodies (positive). Having this, she started treatment with intravenous immunoglobulin (IgIV), with an initial target-dose of 2 g/kg in each monthly session (that was reduced to 1 g/kg from month 6), and the overall clinical picture gradually improved. After 1 year of treatment, brain MRI shows a significant regression of the CNS lesion load (Fig. 1, C1-C2) and the clinical observation does not reveal any focal neurological deficit. In fact, this child's developmental milestones are in line with what is expected for her chronological age. She maintains a regular follow-up at the Pediatric Demyelinating Disorders consultation.

Discussion

This case illustrates the diagnostic difficulties that greatly hamper the establishment of a prognosis and the correct information of the family, at such an early stage of life. In fact, we have no doubt that this child had a first demyelinating event associated with an encephalopathic state, which was only associated with the detection of anti-MOG antibodies in the serum, *a posteriori* (they were not investigated during the first hospital admission, because the diagnosis was obvious, the laboratorial method was not totally consolidated in our institution, and the response to corticosteroid treatment was excellent). This profile, at the time, seemed to us very suggestive of the diagnosis of an ADEM.

However, looking at the clinical profile of this child's's disease, we do not have arguments to define this ADEM as multiphasic, since no clinical event compatible with an encephalopathic state has been repeated, although the mother describes the occurrence of tremor, despite not medically evaluated (we can admit that there could have been new focal neurological signs after hospital discharge, but not 3 months after that, since the reassessment consultation was done precisely at that time and the mother described the tremor as being past).

Nevertheless, this additional clinical manifestation was enough to request an imaging reassessment 6 months after hospital discharge and this allowed identifying a very significant increase of the CNS lesion load. New large lesions spread through the parenchyma were observed, and some of them allowed evoking, due to its topography and characteristics, the diagnosis of a NMOSD. In fact, the edematous lesion in the splenium of the corpus callosum, though not involving the complete thickness of that region, has an aspect similar to the "arch bridge" pattern, typical of NMOSD.[7] Nevertheless, other periependymal lesions surrounding the ventricular system were not found. Since anti-MOG antibodies were identified at this time, disease behaviour led us to consider the diagnosis of a possible NMOSD with anti-MOG antibodies (and hence anti-AQP4 negative).

It is true that this child has never had any clinical manifestation clearly suggestive of meeting major criteria for the diagnosis of neuromyelitis optica (NMO), but retrospectively, we cannot exclude that the encephalopathic state that dominated the first clinical event could eventually correspond to a symptomatic narcolepsy to diencephalic demyelinating lesions (and, thus, we would have a core manifestation of an NMOSD). In addition, what is described in ADEM associated with anti-MOG

in young children is that demyelinating lesions normally spare the corpus callosum and there is usually CSF pleocytosis (whether or not associated with the presence of oligoclonal bands). These are two other aspects in which the case of our patient reveals itself in a diametrically opposite position: the lesion load in the corpus callosum is very significant and there is no CSF pleocytosis. Therefore, we believe that the diagnosis in our patient is much closer to an NMOSD, precisely reinforcing the notion of "disease spectrum" associated with the presence of anti-MOG antibodies.

Since it is a very small child and an antibody-mediated pathophysiology has been documented, treatment with monthly IgIV has been chosen. The radiological response was good and no compromises of psychomotor development were identified, so far.

Even so, the fact that we have the most likely diagnosis of an NMOSD in mind obliges us to keep this child in a tight clinical and radiological surveillance program to, if necessary, rethink the therapeutic strategy (this does not appear to be a benign disease). This case reinforces the great clinical heterogeneity that may exist in diseases mediated by anti-MOG antibodies in early childhood. ■

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