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Case report

ANTI-MOG ASSOCIATED ENCEPHALITIS: WHEN STEROID THERAPY IS NOT ENOUGH

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ABSTRACT

MOG-antibodies are consistently identified in a variety of acquired demyelinating syndromes. In children, the most common presenting phenotype is acute disseminated encephalomyelitis, an immune-mediated disease characterized by demyelination and multifocal neurologic symptoms which typically occur after a preceding viral infection or recent immunization. Herein, we report the case of a 7-year-old boy who developed the first episode of MOG associated encephalitis, which was treated with steroid therapy, and after 6 months, presented a relapse of ADEM in which steroid treatment was not decisive, as he presented new symptoms with unchanged MRI lesions. For this reason, we decided to submit the boy to immunoglobulin intravenous therapy each month. The child has been followed up for 1 year and no new episodes have been reported.

1. Introduction

Myelin oligodendrocyte glycoprotein (MOG) is a glycoprotein expressed selectively on oligodendrocytes, which are glial cells of the central nervous system (CNS). Although MOG is a minor constituent of myelin, its expression at the surface of the myelin sheaths makes it accessible for antibodies and a candidate for CNS-targeted autoimmune responses [1]. In children, several studies have shown that MOG antibodies are associated with acquired demyelinating syndromes such as optic neuritis, myelitis, or acute disseminated encephalomyelitis (ADEM), which are often monophasic. There are cases, however, in which MOG antibodies are associated with relapsing optic neuritis, multiphasic ADEM, ADEM followed by optic neuritis (ADEM-ON), or neuromyelitis optica spectrum disorder (NMOSD), raising the question of whether these patients might benefit from chronic immunotherapy [2], as in the case reported.

In this case, we report a young boy with ADEM resistant to steroid treatment and rapid resolution of the disorder with the use of cyclic intravenous immunoglobulin.

2. Case report

A 7-year-old boy was the second child of healthy and unrelated parents and the family history was negative for neurologic disorders. The boy was born at 38 weeks of gestation with a birthweight of 3800 g, and he suffered from convergent strabismus on the right eye since the age of 3. At the age of 7, some days after the onset a fever during gastroenteritis, his mother noticed a worsening of the strabismus for which an ophthalmological examination was performed in which bilateral abduction deficiency was detected.

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Additionally, the onset of ataxia with frequent falls and difficulty in swallowing solid foods was noticed for several days. After accessing the Emergency Room, a brain CT was performed with normal results. At the time of the neurologic examination, there was evidence of convergent strabismus in the right eye with paresis of lateralization movements, positive cerebellar tests, ataxic walking only with support, and brisk patellar reflexes with no meningeal signs. Routine blood laboratory analyses were normal (including ESR, CRP and procalcitonin). No abnormalities were found in the chemical analysis of CSF, and both serum and CSF were negative for the most common infectious agents. We did find, however, both in the serum and CSF, a positive title (1:640) of oligodendrocytic anti-glycoprotein myelin antibodies (anti-MOG). Brain MRI showed signs of hyperintensity in the T2-weighted and FLAIR sequences on the peri- and supraventricular cerebral white matter of the midbrain and bridge, with involvement of the upper, middle and lower cerebellar peduncles, dental cores and periaqueductal site (Figure 1a). Based on the clinical and laboratory data, the previous medical history, and the radiological lesions, ADEM diagnosis was determined and the child was treated with a steroid therapy: Methylprednisolone (30 mg/kg intravenous) for five days followed by oral Prednisone tapering for a period of five weeks. At discharge, good general conditions were documented with regular walking. A brain MRI performed after three months showed marked decrease of the brain lesions described above, in particular in the cerebellar peduncles, the midbrain and the bridge, while the peri-ventricular lesions remained unmodified (Figure 1b).

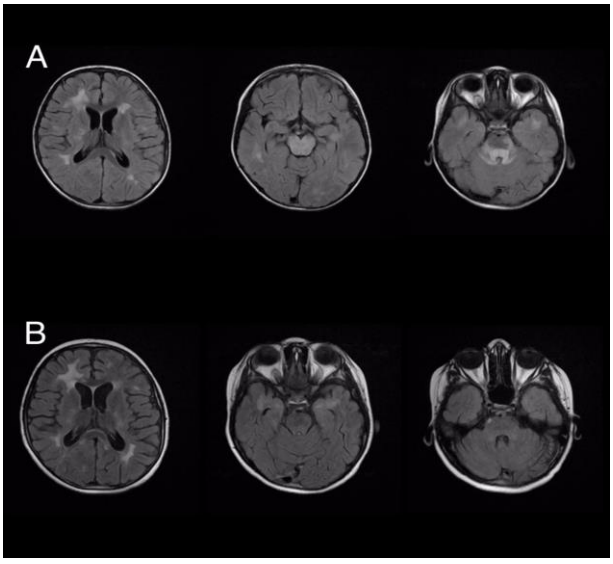

Figure 1. A) Brain MRI of the patient in the first episode. FLAIR axial sequences showing hyperintensity of cerebellar white matter, deep involvement of pons and mesencephalon, as well as periventricular and subcortical white matter. B) Same exam performed after the infusion of the first intravenous Ig cycle. The involvement of cerebellum and mesencephalon is less pronounced. Periventricular and subcortical white matter hyperintensity is still appreciable. In particular in right anterior and left posterior regions.

After six months, there was onset of hetero-aggression and a new feverish episode followed by loss of appetite, drowsiness with worsening strabismus and uncertain gait. For this reason, a new hospitalization was arranged and an emergency brain MRI was performed, which showed a different distribution of the areas of altered signal, in particular, in the frontal and temporal white matter and in the limbic cortex, characterized by marked hyperintensity in the long TR sequences. The relapse of ADEM was confirmed by the radiological and clinical features, and by a further analysis of serological values of MOG-Ig. The patient was underwent another cycle of steroid therapy, without a clinically notable response. The brain MRI check-up, about a month after discharge, showed that the lesions remained unmodified. For this reason, we decided to submit the boy to immunoglobulin intravenous therapy at the initial dose of 2g/kg (first three months) followed by 1g/kg (months 4 to 12) every 4 weeks for one year. The child responded with good general conditions and without side effects and has been followed up for 1 year. No new episodes have been reported and brain lesions, at the last MRI control, performed after 1 year of IVIG treatment, were noticeably reduced.

3. Discussion

MOG-Abs are consistently identified in a variety of acquired demyelinating syndromes in adults and in up to 50% of children. ADEM and neuromyelitis optica are the most common presenting phenotypes in children. ADEM is an immune-mediated disease that typically occurs after a viral infection with an average onset between ages 5 to 8 years old, and with an incidence of 0.4 per 100,000 per year among people younger than 20 years old [3]. Multifocal neurologic abnormalities at presentation are common and can include: ataxia, hemiplegia or hemiparasthesia, cranial nerve palsies, visual changes, seizures, and speech impairment [4]. Although MOG-Abs were initially reported in predominantly monophasic disease, a recent report of 210 children with ADSs who were followed up for at least 2 years observed that 22 of 65 MOG-Ab–positive children (33.8%) experienced clinical relapse and were diagnosed with multiphasic disseminated encephalomyelitis (MDEM), recurrent optic neuritis (RON), acute disseminated encephalomyelitis followed by optic neuritis (ADEM-ON), or neuromyelitis optica spectrum disorder (NMOSD) [5].

The patient in this report has been diagnosed as affected by multiphasic pediatric ADEM according to the clinical criteria: two distinct clinical events of ADEM, with MRI patterns of diffuse large T2-FLAIR hyperintensities in white matter and basal ganglia that occurred ≥3 months after the initial event and associated with new or reemergence of previous clinical and MRI findings. Children with MOG-Ab may present with four MRI patterns: multifocal hazy/poorly marginated lesions, involving both gray matter and white matter and typically involving the middle cerebellar peduncles; spinal cord and/or optic nerve involvement with normal intracranial appearance, or non-specific white matter lesions; extensive and periventricular white matter lesions, resembling a “leukodystrophy-like” pattern; and cortical encephalitis with leptomeningeal enhancement [6]. At the present, there is no standardized treatment for children affected by relapsing or multiphasic MOG-encephalitis. In the acute phase, the majority of children respond well to intravenous steroids (i.e. methylprednisolone for 3 to 5 days with a dose of 20 to 30 mg/kg/day, followed by oral prednisone at 1 to 2mg/kg per day for 1 to 2 weeks with a subsequent 2 to 6 weeks taper).

On the other hand, patients who relapse are typically treated with immunosuppressive protocols which may include immunoglobulins, anti-CD20 agents, rituximab [7]. Hacohen et al. treated 52 patients with relapsing Demyelination Syndrome with regular IVIG, infusion of rituximab, mycophenolate mofetil, and azathioprine in descending order, and this treatment was associated with a reduction in the Annualized Relapse Rates (ARRs). In these children, unresponsive to the initial steroid therapy, IVIG was the most useful maintenance therapy, with the greatest improvements in ARR [8]. Further confirmations came from the study by Hacohen et al, who highlighted that the only treatment that appears to prevent relapses, particularly in children with multiple yearly relapses, is repeated IVIG (every 4 weeks); the authors stated that IVIG is the only treatment that modifies the disease without leading to immunosuppression and risk of infection-triggered relapses [9]. According to these reports, we treated our patient at first with steroids and then with IVIG. The child had good general conditions after the dosage of immunoglobulin and we have evaluated his outcome for one year. No new episodes have been recorded thus far.

Even if our treatment choice was supported by several sources of evidence, recent reports [7,10], highlight that patients with MOG-encephalitis continue to relapse, sometimes despite maintenance treatment. It maybe that the treatment-resistance represents a selected group of patients who are biologically or immunologically different. However, to achieve this, studies must initially elucidate many key aspects of the MOG–associated disorders, such as disease heterogeneity, early biomarkers of relapsing and/or severe disease, and therapeutic efficacy of immunosuppressant treatment.

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