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Case Report

Efficacy and tolerability of mycophenolate mofetil in a pediatric Rasmussen syndrome☆

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ABSTRACT

Rasmussen syndrome (RS) is a chronic encephalopathy with uncertain etiology and immune-mediated pathogenesis. The only definitive treatment is represented by functional hemispherectomy. We describe the case of a 6.5-year-old female patient who developed several episodes of focal, unilateral clonic seizures. Following laboratory and instrumental investigations, the patient was diagnosed as having RS. A treatment with corticosteroids, intravenous immunoglobulin, and the antiseizure medication (carbamazepine and levetiracetam) did not completely control the seizures. Therefore, the patient was treated with mycophenolate mofetil (MMF), showing a good clinical response, with reduction of the seizures, and stability of the radiological findings. This case suggests the potential utility of MMF in the immune approach to RS.

Background

Rasmussen syndrome (RS) is a chronic, progressive encephalopathy with unilateral hemispheric involvement. It is characterized by drug-resistant focal seizures including epilepsia partialis continua, hemiparesis, and progressive cognitive decline [1]. The etiology of the disease remains unknown, and the mechanisms underlying the immune-mediated pathogenesis of RS have been extensively investigated in order to improve therapeutic strategies and provide targeted therapy. The current recommended treatment for RS is functional hemispherectomy. In this paper, we describe the first case of a pediatric patient diagnosed as having RS to our knowledge who has been successfully treated with mycophenolate mofetil (MMF).

Case report

A 6.5-year-old South American girl with unremarkable history experienced her first nonprolonged, focal, unilateral clonic seizure associated with head and eye deviation to the left, during fever. A month later, she started experiencing daily seizures characterized by behavioral arrest, head and eye deviation to the left, and left hand twitching. Neurological examination revealed left hemiparesis and pyramidal tract signs (grade 2 usingat the modified Rankin scale (mRS) for children). The patient also demonstrated mild speech impairment.

Her electroencephalogram (EEG) (Fig. 1A) revealed slowing over the right hemisphere and interictal spike-and-wave discharges in right frontotemporal region. Brain magnetic resonance imaging (MRI) showed right frontal and temporal cortical atrophy with T2 hyperintensity (Fig. 2A, 2B). Positron emission tomography (PET) (Fig. 2C) scan confirmed reduced FDG uptake within the right hemisphere.

Infectious and rheumatologic blood tests were performed on cerebrospinal fluid and serum, including negative anti-NMDA; anti-VGK/LGI1; GABA B receptor; gangliosides; onconeuronal, antinucleous, cytoplasmic and peripheral antineutrophil and antiphospholipid antibodies. Search for TORCH complex, parvovirus B19, tick-borne encephalitis virus, entero–rhino virus, adenovirus, polyomavirus JC and BK, and Tuscany virus, was negative. Serum IgM tested positive for the Epstein–Barr

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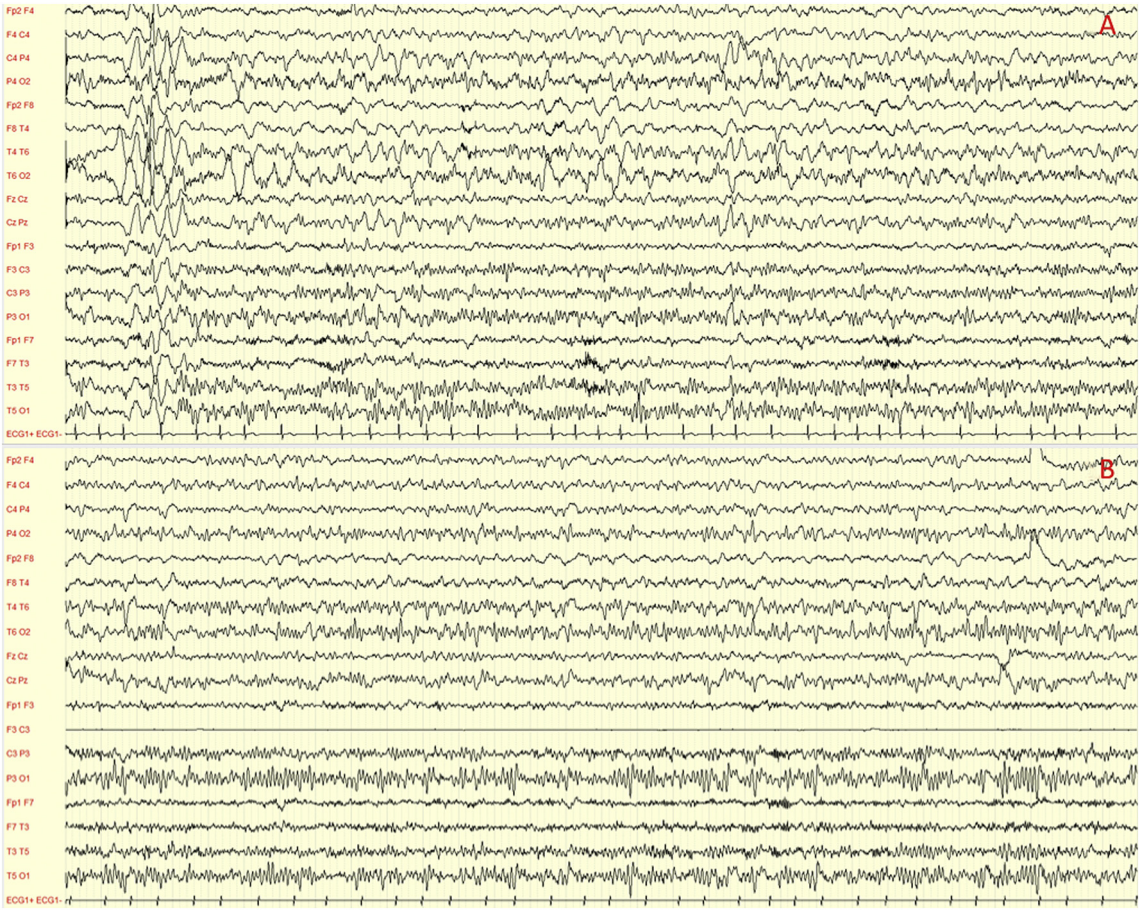

Fig. 1. EEG findings at diagnosis (A), with improvement after 1 year of treatment (B).

virus (EBV) (268.5 kU/L, normal value < 10 kU/L) with perceptible DNA of EBV in blood (>500 copies/mL). Additionally, the IgG tested positive for the Zika virus (qualitative assay).

According to current diagnostic criteria, even in the absence of defined epilepsia partialis continua, the clinical picrain involvement allow for the diagnosis of RS [1].

The girl started antiseizure medication with carbamazepine (up to 20 mg/kg/day) and then levetiracetam as add-on (up to 50 mg/kg) without effect. The patient received two cycles of systemic corticosteroid therapy associated with intravenous immunoglobulin (IVIG). Each cycle of IVIG was composed of 2 infusions of IVIG at the dose of 1 g/kg. This resulted in a mild improvement of neurological deficits.

However, because of the persistence of the seizures, after six months from disease diagnosis, oral MMF up to 1000 mg/m^2 was started, concomitantly corticosteroids were tapered. The patient showed a dramatic response, with reduction of seizures and improved functional improvement (grade 1 according to mRS). After 1 year of treatment, a reduction of the amount of EEG slowing in the right hemisphere was evident (Fig. 1B) and brain MRI showed stable inflammatory changes (Fig. 1 D). The cognitive assessment performed one year after initial diagnosis of RS showed the absence of progression of cognitive decline. The child was seizure-free for 10 months, and continued on MMF (750 mg/m^2), carbamazepine (dose), and levetiracetam.

Discussion

The case offers interesting elements about etiology, pathogenesis, and treatment of RS. The etiology of the disease is unknown, and several potential infectious causes have been investigated, without demonstrating a clear correlation between RS and specific agents. To our knowledge, this is the first pediatric case of RS concomitant to an acute EBV infection. Although this result has to be interpreted with caution, we suggest that a virus could have represented the trigger for the disease. Viral infection has been evidenced in the encephalic tissue of pediatric patients, confirming its potential pathogenic role [2,3]. In our case, the identification of EBV in the brain tissue was not possible, as the clinical and radiological features allowed the diagnosis of RS without the necessity of a brain biopsy. Moreover, the patient exhibited positive serology for previous Zika infection. This association has not been detailed, and therefore further studies are needed to clarify the role of Zika infection in patients with RS.

The therapeutic approach to treating RS by means of agents that interfere with the immune system has been performed with different medications. These include intravenous immunoglobulins, corticosteroids, azathioprine, and tacrolimus [4–10]. The purpose of agents active on the immune system in RS is to arrest or slow down the progression of brain atrophy. It does not represent a corrective therapy.

Therefore, most patients ultimately must undergo a functional hemispherectomy. The immune mechanism underlying the disease, as evidenced by histopathological findings and cytokine expression profiles, confirms that the T-cells (CD8 cells in particular) are crucial in the development of brain damage [11]. This supports the utility of T cell-targeted therapies.

Mycophenolate mofetil acts by inhibiting purine synthesis in lymphocytes, inducing apoptosis in activated T-cells and reducing the recruitment of lymphocytes, and it has been successfully used to treat other types of immune-mediated encephalitis. Additionally, MMF is generally better tolerated than azathioprine [12].

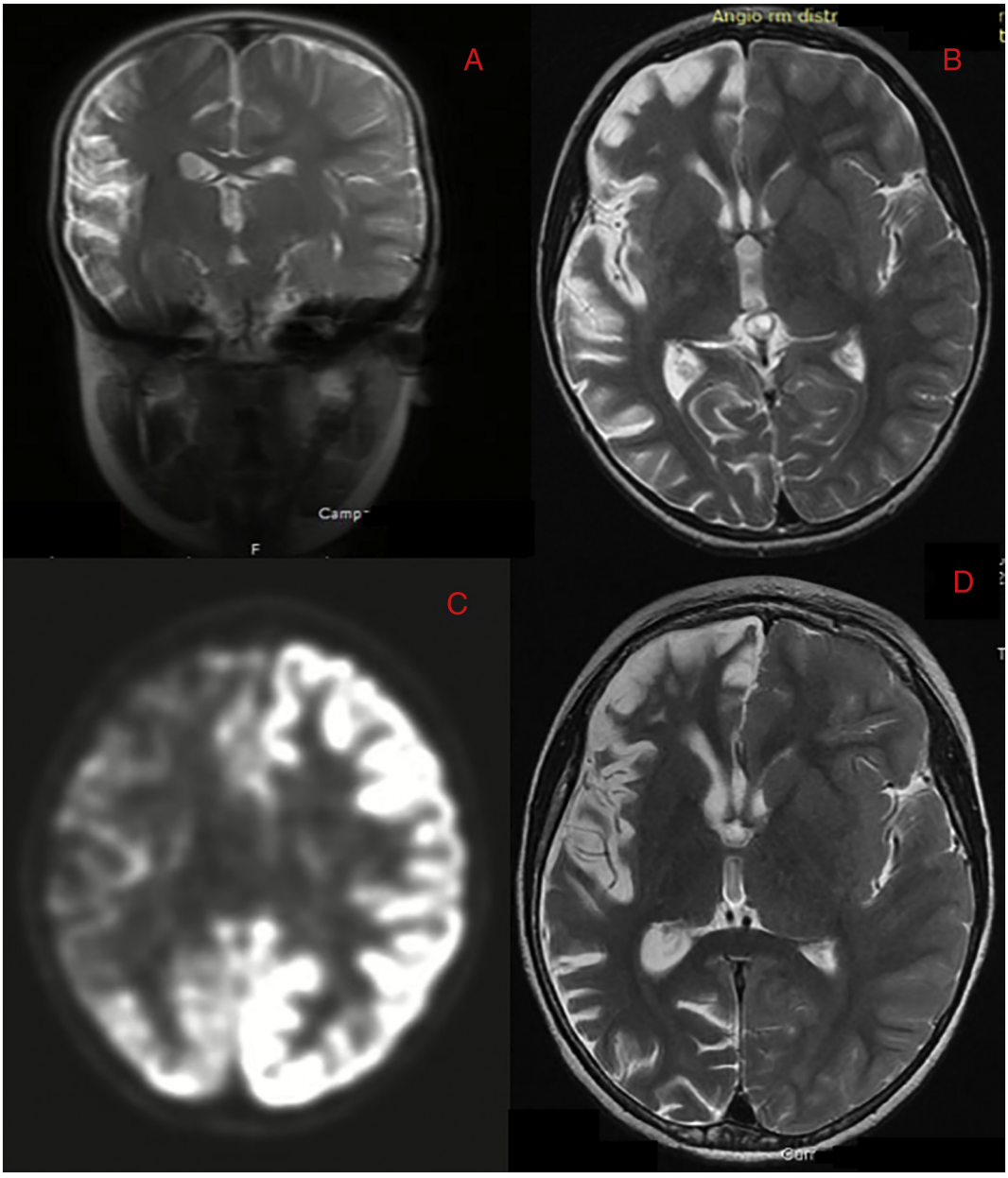

Fig. 2. MRI features at diagnosis with 1.5 T (A) and 3 T imaging (B), and after 1 year of follow-up (D), with evidence of stability for the inflammatory changes. PET performed at disease onset (C), showing reduced FDG uptake in the right hemisphere only.

Based on this rationale, we treated our patient with MMF (whose seizures showed an incomplete response to antiseizure medication and corticosteroids) with subsequent clinical and electroencephalographic stabilization. Moreover, the follow-up MRI showed an absence of progression of the cortical atrophy. To date, limited experience for patients with RS having successfully been treated with MMF exist, except for a case showing a clinical response achieved with the combination of MMF combined with corticosteroids [13].

Interestingly, in our case, MMF was effectove both as a corticosteroid-sparing agent in the acute phase, and as monotherapy with respect to control of disease progression.

Although surgery remains the only definitive treatment for patients with RS, it imparts a risk of neurological sequella including the development of hemianopia and hemiplegia. Therefore, the search for effective drugs acting on the immune system is crucial in the management of RS. Despite the single report and relatively short follow-up period, our case suggests that MMF, demostrating efficacy and safety, could represent an effective opportunity to use an immune approach to successful treatment in patients suffering from RS.

Declaration of competing interest

The authors declare no conflict of interest.

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Ethic statement

Written informed consent was obtained from the individual(s) Q8 for the publication of any potentially identifiable images or data included in this article.

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