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Case Report

Akinetic mutism and status epilepticus due to Epstein Barr virus encephalitis

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ABSTRACT

Neurological complications of Epstein Barr virus (EBV) infection are infrequent and may include occasionally encephalitis, usually with a benign evolution. We here report on an aggressive case of EBV encephalitis in a 14-year-old boy with extensive basal ganglia involvement, and to a lesser degree of brain cortex who presented atypically with akinetic mutism and non-convulsive status epilepticus, requiring intensive care but showed a favorable outcome. EBV encephalitis is uncommon and its best management is unclear. Its pathophysiology is not well understood but could include autoimmunity. Onconeuronal and synaptic antibodies were negative in serum and cerebrospinal fluid, including the dopamine D2 receptor. To the best of our knowledge, this is the first report to evaluate antibodies to D2 receptors in EBV encephalitis. Corticosteroid therapy is usually recommended but the use of acyclovir is controversial. Intensive care is required in severe cases to assure a favorable outcome.

1. Introduction

Epstein Barr virus (EBV) usually causes mild or asymptomatic infections in children. Neurological complications develop, mostly in immunocompromised patients, in 1–5% of patients [1].

EBV encephalitis presents with non-specific symptoms and its diagnosis is based on the detection of heterophile IgM antibodies (Paul Bunnell test), a positive IgM serology against the viral capsid antigen (VCA), and/or a positive PCR in CSF [2].

We report on an aggressive case of EBV encephalitis in a 14-year-old boy with extensive basal ganglia involvement, who presented atypically with akinetic mutism and non-convulsive status epilepticus requiring intensive care but showed a favorable outcome.

2. Case report

A 14-year-old healthy boy presented at the Emergency Room with fever, odynophagia and tonsillar fibrinous exudate. Blood tests showed elevated liver enzymes and a positive Paul Bunnell test. Serology for Epstein Barr virus (EBV) was IgM (VCA) positive and IgG (EBNA) negative. He was diagnosed with infectious mononucleosis and discharged with symptomatic treatment.

Four days later, he developed poor spontaneous language and hypokinesia. A cranial CT scan was normal. A lumbar puncture showed lymphocytic pleocytosis (19 cells/ul) with normal glucose and proteins, and a positive PCR for EBV. He was admitted to the Intensive Care Unit with a diagnosis of viral encephalitis.

Magnetic Resonance Imaging (MRI) showed bilateral swelling of basal ganglia (Fig. 1). The EEG showed anterior bilateral electrical status. Intravenous (IV) acyclovir (10 mg/kg/8 h for 14 days) and methylprednisolone pulses (10 mg/kg for 3 days) were administered. Perfusion of midazolam (12 mcg/kg/min) was started, as well as IV levetiracetam (1500 mg/12 h). An EEG 48 h later showed persisting irritative discharges and IV phenytoin was added (1 g followed by 100 mg/8 h). The patient worsened to an akinetic mutism state with decerebrate posturing and upper extremities myoclonus and required orotracheal intubation. Midazolam was replaced by IV thiopental (5 mg/kg/h for 72 h) to achieve burst suppression. Subsequent EEGs showed no further epileptiform activity.

Considering his lack of improvement after therapy, the second course of methylprednisolone 500 mg daily was started on day 20 and administered for four days. A panel of onconeuronal and surface

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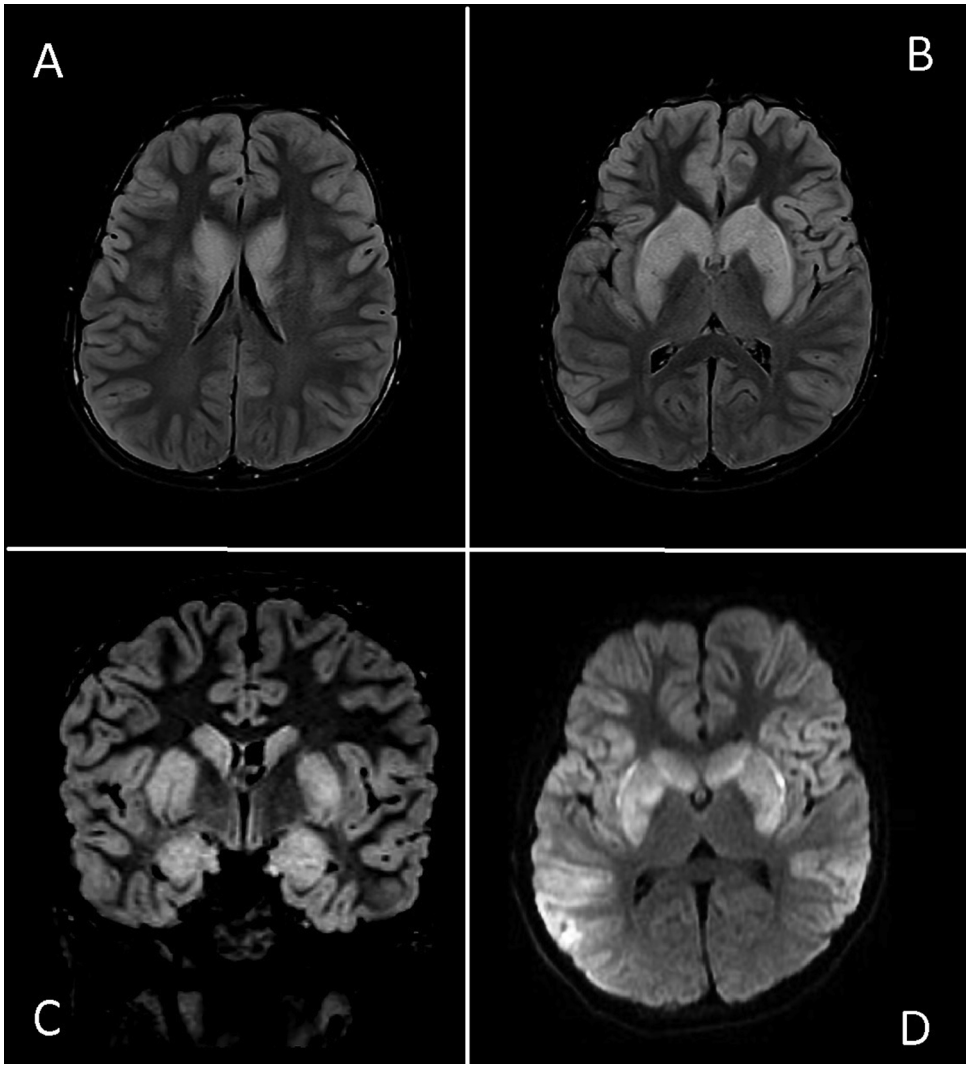

Fig. 1. Brain MRI at disease onset. Axial (A, B) and coronal (C) FLAIR, and diffusion-weighted (D) images. Bilateral, symmetrical swelling and FLAIR hyperintensity of caudate heads, lentiform nuclei, claustra, hyppocampi and frontotemporal gyri. Associated restricted diffusion in claustra, posterior lentiform nuclei and subcortical frontotemporal white matter.

autoantibodies, including anti-dopamine 2R antibodies, was performed at the Hospital Clinic in Barcelona and was negative in serum and CSF.

The day after starting methylprednisolone, a slow but progressive clinical improvement was observed. He showed spontaneous eye opening and started to vocalize words and short sentences and to respond to the environment. He could be extubated and discharged to the Neurology Department on day 29. He progressively began to communicate until reaching an elaborate language similar to baseline with progressively autonomous gait. The patient was discharged 45 days after admission.

On follow-up 7 months after admission, a brain MRI showed the resolution of corticosubcortical edema and residual involvement of basal ganglia with incipient atrophy (Fig. 2). He had regained his daily activities and had a normal neurological exam without residual cognitive impairment.

3. Discussion

Our patient had a well-documented EBV encephalitis supported by his clinical findings, serum antibodies, and CSF abnormalities, including a positive PCR. His presentation was particularly severe and had a prominent involvement of the basal ganglia as revealed by his brain MRI findings.

Neurologic complications of EBV infection are rare and usually develop a few weeks after disease onset, but features of infectious mononucleosis may be absent or develop later. In our patient, encephalitis developed 4 days after the diagnosis of mononucleosis.

Brain MRI in this patient showed extensive involvement of the basal ganglia, a finding that has only been reported on a few occasions [2–4], and has led to suggest that EBV might have a particular basal ganglia tropism. Involvement of other areas (cortex, brainstem, thalamus or white matter) may also be present, however, and MRI is normal in up to 40% of cases. The lesions are usually transient with resolution in weeks to months. Despite these findings, he did not have movement disorders, and his clinical presentation was characterized by status epilepticus and akinetic mutism. The latter was likely secondary to encephalitic damage of the diencephalon or thalami.

The pathogenesis of EBV encephalitis is not well understood. Direct infectious mechanisms, as well as indirect immune reactions, may play a role. In this regard, our patient showed a direct infection of the CNS as revealed by a positive PCR in the CSF, and did not have evidence of serum or CSF autoreactivity to any of the well-known onconeuronal and synaptic antibodies implicated in autoimmune encephalitis. The absence of antibodies to dopamine D2 receptors, which could have had a pathogenic role in this patient considering his extensive basal ganglia involvement argues against a secondary autoimmune phenomenon. To

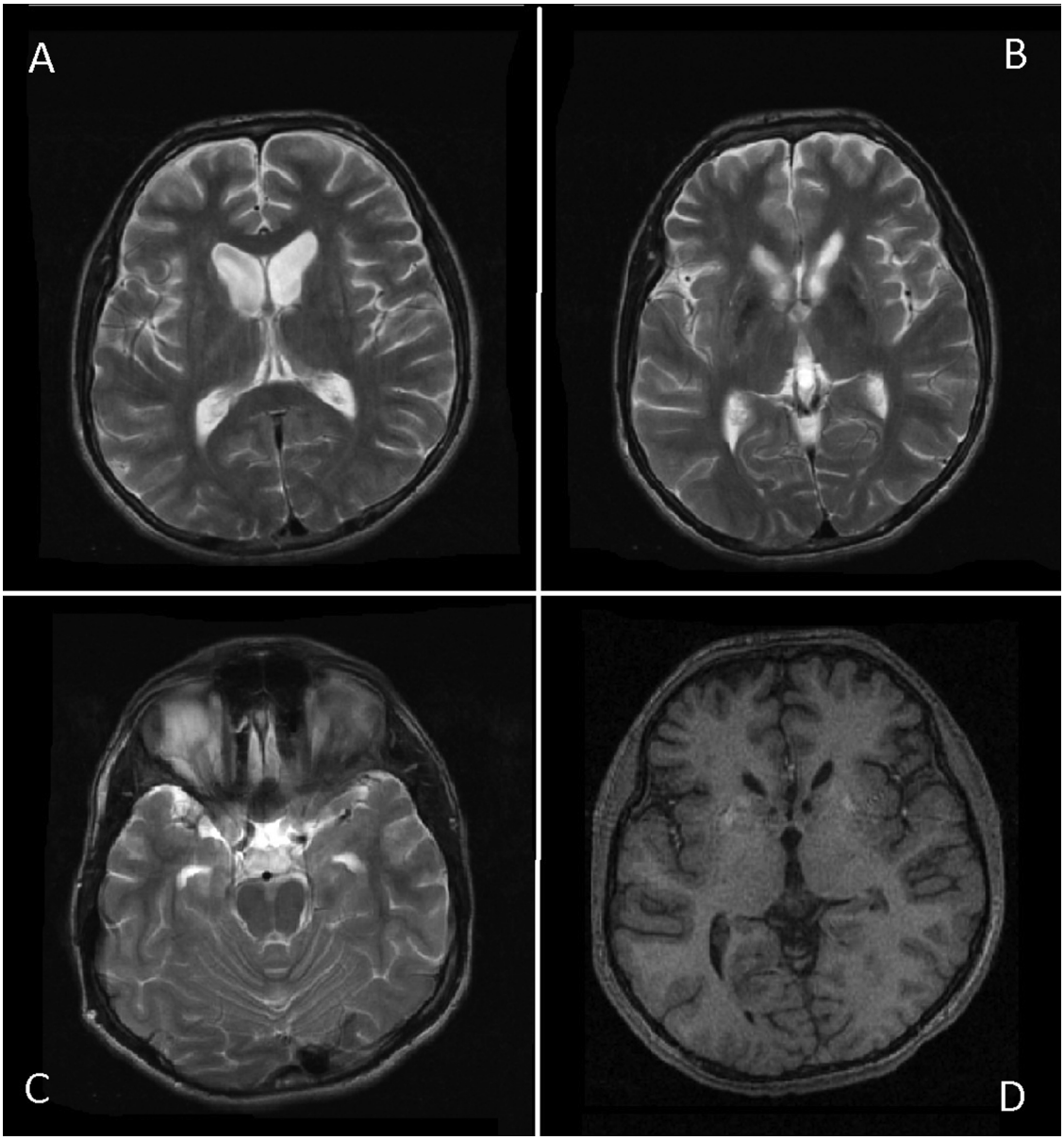

Fig. 2. Brain MRI seven months after disease onset. Axial T2 (A, B, C), T1 (D) weighted images. Resolution of edema changes. T1 hyperintensity of caudate heads and anterior globi pallidi suggestive of necrosis, associated with global T2 hypointensity of lentiform nuclei. Moderate prominence of ventricular heads and temporal horns, consistent with atrophy.

the best of our knowledge, this is the first report to evaluate antibodies to dopamine D2 receptors in EBV encephalitis.

The optimal therapy of EBV encephalitis is controversial since the available evidence is based on case reports or small case series. While steroid therapy (high dose methylprednisolone with variable duration depending on the evolution) together with IV acyclovir for 14 days has been advocated [2], the infectious Disease Society of America does not recommend acyclovir and concluded that the use of corticosteroids may be beneficial (C-III), but the potential risk must be weighed against the benefits [5]. Our patient did not show a prompt response to acyclovir and the first course of steroids and showed a delayed response. Whether this improvement was a direct effect of treatment or part of the natural evolution of the disease cannot be established.

The prognosis of EBV encephalitis is favorable on most patients with complete recovery [2]. However, even immunocompetent patients as the one here described may show a particularly severe evolution requiring prolonged intensive care.

In summary, EBV encephalitis may show a particularly severe course in immunocompetent patients and can associate an extensive symmetrical involvement of the basal ganglia that so far has not been proven to be antibody mediated. Every therapeutic effort should be made in these patients, since they may ultimately show complete recovery.

Declaration of Competing Interest

None.

References

[1] K. Mazur-Melewska, I. Brenska, K. Jonczyk-Potoczna, P. Kemnitz, I. Pieczonka-Ruszkowska, A. Mania, W. Sluzewski, M. Figlerowicz, Neurologic complications caused by epstein-barr virus in pediatric patients, J. Child Neurol. 31 (6) (2016) 700–708.

[2] A. Doja, A. Bitnun, E.L. Ford Jones, S. Richardson, R. Tellier, M. Petric, H. Heurter, D. MacGregor, Pediatric Epstein-Barr virus-associated encephalitis: 10-year review, J. Child Neurol. 21 (5) (2006) 384–391.

[3] J. Ono, K. Shimizu, K. Harada, T. Mano, S. Okada, Characteristic MR features of

encephalitis caused by Epstein-Barr virus: a case report, Pediatr. Radiol. 28 (8) (1998) 569–570.

[4] P. Phowthongkum, K. Phantumchinda, K. Jutivorakool, C. Suankratay, Basal ganglia and brainstem encephalitis, optic neuritis, and radiculomyelitis in Epstein-Barr virus infection, J. Infect. 54 (3) (2007) e141–4.

[5] A.R. Tunkel, C.A. Glaser, K.C. Bloch, J.J. Sejvar, C.M. Marra, K.L. Roos, B.J. Hartman, S.L. Kaplan, W.M. Scheld, R.J. Whitley, A. infectious diseases society of, the management of encephalitis: clinical practice guidelines by the infectious diseases society of America, Clin. Infect. Dis. 47 (3) (2008) 303–327.