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SHORT COMMUNICATION

Epileptic encephalopathy after HHV6 post-transplant acute limbic encephalitis in children: Confirmation of a new epilepsy syndrome

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Summary Generalised epilepsy and cognitive deterioration were recently described in three children following human herpesvirus 6 (HHV6)-associated post-transplant acute limbic encephalitis (PALE). Magnetic resonance imaging (MRI) showed bilateral signal change and/or atrophy in the medial temporal structures and there was no evidence of an ongoing viral or immune-mediated process.

We report another child who developed this condition after cord blood transplantation for congenital neutropenia at the age of three. He presented with epileptic spasms four months after HHV6-associated PALE. Cognitive regression, prominent electroencephalographic abnormalities and different types of generalised seizures ensued during the following months and proved refractory to antiepileptic and immunomodulating treatment, which included steroids, immunoglobulin and rituximab. MRI was normal at onset of epilepsy but subsequently showed the development of right hippocampal sclerosis. Results from serial blood and cerebrospinal fluid (CSF) analyses were inconclusive, including lack of patient's CSF and serum reactivity with cultures of dissociated rat hippocampal neurons.

This report confirms the existence of a new epilepsy syndrome featuring generalised seizures and epileptic encephalopathy after HHV6-associated PALE in children. Presentation with epileptic spasms, lack of CSF and serum reactivity with cultured rat hippocampal neurons, and rituximab inefficacy are novel features that contribute to delineate the syndrome and argue against an immune-mediated basis of this condition.

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Introduction

Primary human herpesvirus 6 (HHV6) infection is a common trigger of febrile seizures, including febrile status epilepticus, and cases complicated by encephalitis have been reported. Experimental and clinical studies suggest that HHV6 may increase the risk of hippocampal injury and temporal lobe epilepsy in these patients but this issue remains unproven (Theodore et al., 2008; Epstein et al., 2012).

HHV6 reactivates in up to 50% of hematopoietic stem cell transplantation (HSCT) recipients and, although most patients remain asymptomatic, HHV6 is a major cause of post-transplant acute limbic encephalitis (PALE). Some patients show full recovery but most will be left with various degrees of neurological dysfunction, especially memory disturbances and temporal lobe epilepsy (Sakai et al., 2011).

Recently, Howell et al. described three children who underwent cord blood transplantation and developed generalised epilepsy and cognitive deterioration after HHV6-associated PALE. Magnetic resonance imaging (MRI) showed bilateral signal change and atrophy in the medial temporal structures and blood and cerebrospinal fluid (CSF) analyses failed to demonstrate an ongoing viral or immune-mediated process (Howell et al., 2012). We describe a child with this condition and add clinical, diagnostic and therapeutic features that were not mentioned in the original report.

Case report

The patient is a six-year-old Caucasian child who underwent unrelated cord blood transplantation for congenital neutropenia in March 2010 at the age of three. Neurological exam was normal before transplantation. Conditioning regimen comprised busulfan, cyclophosphamide and antithymocyte globulin and antiviral prophylaxis included oral acyclovir.

Acute graft-*versus*-host disease appearing on post-transplant day (PTD) eight was treated with steroids, cyclosporine and mycophenolate. Neutrophil engraftment was on PTD 18. On PTD 35 he developed acute confusion and somnolence. He was afebrile and neurological exam was otherwise normal. No seizures were recalled. Laboratory findings included hyponatremia (122 mequiv./L) and thrombocytopenia. HHV6 DNA (5000 viral DNA copies/mL) was detected by quantitative polymerase chain reaction (PCR) in the blood but severe thrombocytopenia precluded CSF analysis. Symptoms resolved within 48 h and he received a one-week course of ganciclovir until PCR negativization. MRI was consistent with acute inflammation in the right hippocampus that resolved in the study performed 12 days later (Fig. 1A). Electroencephalogram (EEG) on PTD 50 was normal. He was treated with high-dose steroids for immune thrombocytopenia, which finally responded to a four-week course of rituximab in June 2010. Follow-up blood PCRs were negative and he remained asymptomatic until discharge.

In August 2010 he was readmitted for epileptic spasms. Brain MRI was normal and EEG showed normal interictal activity during wakefulness but prominent generalised and bilateral frontotemporal slow-waves in sleep (Fig. 2A). Progressive disorganization of the EEG background activity along with complete loss of verbal abilities, disruptive behaviour and altered sleep/wake pattern ensued during the following months. Daily clusters of epileptic spasms were the only seizure type until September 2011 when he started suffering from tonic seizures, atypical absences and drop attacks that were refractory to multiple antiepileptic drugs (AED) (Fig. 2B).

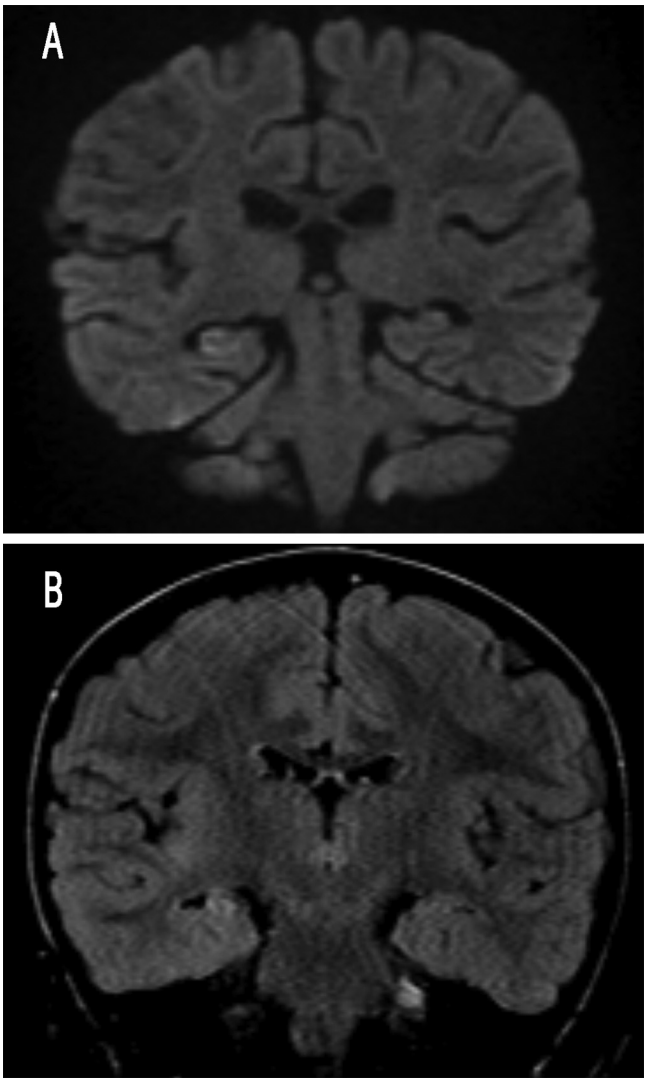

Figure 1 (A) Diffusion weighted image at diagnosis of HHV6-associated PALE showing restricted diffusion confined to the right hippocampus. (B) Coronal fluid-attenuated inversion recovery image two years after epilepsy onset showing atrophy and signal increase of the right hippocampus consistent with hippocampal sclerosis. Left hippocampus has normal size, signal and morphology.

Recurrence of thrombocytopenia two months after epilepsy onset led to a second five-week course of rituximab in November 2010 that normalised the platelet count but did not have any effect on seizure pattern, EEG abnormalities or cognition. The patient showed a slight improvement in alertness and language following five-day pulse of intravenous methylprednisolone (30 mg/kg daily) in May 2011, which was followed by monthly three-day pulses of oral methylprednisolone (10 mg/kg daily) but subsequent inefficacy led to steroid withdrawal in May 2012. Increasing doses