Brief Communication

Treatment of epileptic encephalopathy after human herpesvirus 6-induced post-transplantation acute limbic encephalitis with adrenocorticotropic hormone therapy: A case report

Kanako Maizuru, Takeo Kato, Masatoshi Nakata, Minako Ide, Keiko Saito, Takeshi Yoshida, Atsushi Yokoyama, Tomonari Awaya, Toshio Heike

1Department of Pediatrics, Graduate School of Medicine, Kyoto University, Kyoto, Japan
2Department of Pediatrics, Hyogo Prefectural Amagasaki General Medical Center, Hyogo, Japan

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Abstract

Recently, several authors have reported cases in which children with human herpesvirus 6-induced post-transplantation acute limbic encephalitis (HHV6-PALE) developed generalized epilepsy and cognitive deterioration. Here, we report an 8-year-old boy who developed HHV6-PALE one month after receiving cord blood transplant for precursor B lymphoblastic leukemia. At the age of 9 years, a series of epileptic spasms started, and his cognitive function deteriorated. An interictal electroencephalogram showed generalized epileptic discharges. The patient was diagnosed with epileptic encephalopathy after HHV6-PALE. Although his condition did not respond to various antiepileptic drugs, ketogenic diets, or immunomodulatory therapies, it improved temporarily after ACTH therapy. Considering that the prognosis of this type of epileptic encephalopathy is devastating, elucidation of the mechanisms responsible for the development of epileptic encephalopathy and development of a new strategy for its management are urgently needed.
Introduction
Human herpesvirus 6 (HHV6) is able to persist in the host and is reactivated in 50% of patients that undergo hematopoietic stem cell transplantations. HHV6-induced post-transplantation acute limbic encephalitis (HHV6-PALE) is the most severe manifestation of HHV6 reactivation, although most patients remain asymptomatic [1, 2]. Recently, Howell et al. [3] reported three cases in which children affected by HHV6-PALE subsequently developed generalized epilepsy and cognitive deterioration, and referred to this condition as epileptic encephalopathy after HHV6-PALE. Raspall-Chaure et al. [4] reported a similar pediatric case. The patient in the latter case suffered generalized seizures that did not respond to antiepileptic or immunomodulatory drugs, followed by global cognitive impairments. Here, we report a case in which a child developed epileptic spasms and electroencephalogram (EEG) abnormalities after HHV6-PALE and was temporarily treated with adrenocorticotropic hormone (ACTH) therapy. Of the four reported cases, three involved patients of Asian ethnicity, suggesting that genetic factors contribute to this condition. However, there are no reports on this type of epileptic encephalopathy from Asian countries. To the best of our knowledge, this is the first case report of epileptic encephalopathy after HHV6-PALE from an Asian country.

Case Report
This case involved a 12-year-old boy who was delivered at term with no complications. He was diagnosed with precursor B lymphoblastic leukemia at two years of age. He achieved remission after chemotherapy, but relapsed at the age of seven years. His leukemia was less responsive to the second round of remission induction therapy, and subsequently underwent cord blood transplant (CBT). As the first transplant resulted in graft failure, the patient received a second CBT at the age of seven years and nine months.

Generalized tonic seizures and disturbance of consciousness occurred on post-transplant day (PTD) 25. Quantitative polymerase chain reaction (qPCR)-based assay for HHV6-DNA in the patient’s cerebrospinal fluid (CSF) and blood produced positive results (100 and 8,800 copies/ml, respectively). Brain diffusion-weighted imaging (DWI) revealed high-intensity lesions in bilateral hippocampi and amygdalae on PTD 26 (Figs. 1A, B, and C). The patient was treated with intravenous foscarnet under a diagnosis of HHV6-PALE. A qPCR-based assay of his CSF on PTD 77 produced a negative result, but memory disturbances and behavioral problems remained as sequelae of HHV6-PALE.

Five months later (age of eight years and three months), generalized seizures started to occur in clusters. The seizures involved series of epileptic spasms (ES), which were confirmed on an ictal surface electromyogram (EMG) and an EEG (Fig. 2A), and occasional generalized tonic seizures. An interictal EEG showed generalized high-voltage spike-and-wave discharges (Fig. 2B). Brain magnetic resonance imaging (MRI) depicted atrophy of the bilateral hippocampi, and the patient’s lesions exhibited hypometabolism on 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) (Figs. 1D and F). At this time, qPCR-based assays of the patient’s
CSF and plasma did not detect any HHV6 reactivation. The frequency of ES increased from day to day. The patient’s cognitive function simultaneously deteriorated, and behavioral problems including impulsive actions, attention deficit disorder, and memory function disorder appeared. Thus, he was diagnosed with epileptic encephalopathy after HHV6-PALE. The ES did not respond to antiepileptic drugs (levetiracetam, valproic acid, topiramate, and piracetam); ketogenic diets; or immunomodulatory agents such as high-dose intravenous immunoglobulins (IVIG) (400 mg/kg for five days), tacrolimus (0.15 mg/kg), and four courses of steroid pulse therapy (to prevent graft-versus-host disease). The patient’s interictal EEG abnormalities worsened, and we finally decided to administer ACTH therapy at the age of nine years and one month. The ACTH therapy consisted of ACTH-Z at a dose of 0.01 mg/kg every day for two weeks, followed by 0.02 mg/kg every day for two weeks, before the dose was gradually reduced over two weeks. Both the tonic seizures and ES responded to a four-week course of ACTH therapy, and the patient’s cognitive impairment and behavioral problems improved significantly. The pa-

Figure 1. A, B: Diffusion weighted imaging (DWI) performed on post-transplant day 26 demonstrates high-intensity lesions in the bilateral hippocampi and amygdalae (white arrows). C: Fluid attenuation inversion recovery (FLAIR) imaging conducted at the same time shows no abnormal signals. D, E: FLAIR imaging carried out at six months and two years after the onset of epileptic spasms (ES) show atrophy of bilateral hippocampi. F: The lesions exhibit hypometabolism on fluorodeoxyglucose positron emission tomography (FDG-PET) performed at one year after the onset of ES.
Patient's Wechsler Intelligence Scale for Children (WISC) IV score was 119 at two months after the onset of HHV6-PALE (prior to the occurrence of epileptic encephalopathy), but his cognitive impairment and behavioral problems deteriorated so extremely after the onset of epileptic encephalopathy that he could not complete the WISC IV. At three months after the ACTH therapy, his score had risen to 75. His generalized epileptic discharges completely disappeared, and only focal epileptic discharges remained in bilateral central and temporal regions (Fig. 2C).

Unfortunately, ES recurred at two months after the first ACTH therapy, and memory impairment and behavioral problems were also exacerbated as ES became more frequent (Fig. 2D). As antiepileptic drugs (gabapentin and oxcarbazepine) and four courses of steroid pulse therapy were ineffective, we administered a second round of ACTH therapy. We administered ACTH-Z at a dose of 0.02 mg/kg...
kg every day for 28 days. The series of spasms disappeared on day 14, and individual spasms only occurred two or three times a day. As the ACTH therapy was also effective against the generalized EEG abnormalities (Fig. 2E) and behavioral problems, we decided to continue long-term weekly ACTH therapy. Unfortunately, ES developed six months later, and the patient’s cognitive functions and behavioral problems gradually worsened.

Discussion

We report a case in which patient child developed epileptic encephalopathy after HHV6-PALE. The clinical course and MRI and EEG findings of this case are in accord with those described in previous reports. The clinical characteristics of the five reported cases, including ours, are summarized in Table 1. Among the five cases, four involved patients of Asian ethnicity, and all five patients underwent CBT. Thus, these factors may be associated with the development of HHV6-PALE. The patients developed epileptic encephalopathy at 5-18 months after HHV6-PALE (mean: 10.6 months). In this type of epileptic encephalopathy, generalized seizures including tonic and atonic seizures, as well as epi-

<table>
<thead>
<tr>
<th>Reference</th>
<th>Howell et al., 2012</th>
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<th>Raspal-Chaure et al., 2013</th>
<th>This case</th>
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<tr>
<td>Gender/ethnicity</td>
<td>Male / Japanese mother</td>
<td>Female / Vietnamese</td>
<td>Male / Vietnamese</td>
<td>Male / Caucasian</td>
<td>Male / Japanese</td>
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<tr>
<td>Age (years) at seizure at CBT/ at follow-up</td>
<td>9/14/21</td>
<td>0/8/15/9</td>
<td>2/2/8/5</td>
<td>n/a/3/6</td>
<td>2/7.7/12</td>
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<tr>
<td>Indication for CBT</td>
<td>AML (secondary malignancy)</td>
<td>Relapsed AML</td>
<td>Relapsed JMML</td>
<td>Congenital neutropenia</td>
<td>Relapsed ALL</td>
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<tr>
<td>Onset of PALE (PTD)</td>
<td>20-23</td>
<td>25</td>
<td>35</td>
<td>25</td>
<td>25</td>
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<tr>
<td>MRI findings at onset of PALE</td>
<td>Bilateral swelling and T2/FLAIR hyperintensity in the hippocampi, thalami and insula</td>
<td>No abnormalities</td>
<td>Left hippocampal swelling and T2/FLAIR hyperintensity</td>
<td>Right hippocampal DWI/FLAIR hyperintensity and atrophy</td>
<td>Bilateral swelling and DWI hyperintensity in the hippocampi and amygdalae</td>
</tr>
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Table 1. Clinical characteristics of four previously reported cases and the present case of epileptic encephalopathy after HHV6-PALE

Epileptic encephalopathy after PALE

<table>
<thead>
<tr>
<th>Seizure types</th>
<th>Tonic, atonic</th>
<th>Tonic, atonic, atypical absence, epileptic spasms</th>
<th>Myoclonic, tonic, tonic</th>
<th>Epileptic spasms, tonic, atypical absence</th>
<th>Epileptic spasms, tonic</th>
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<tr>
<td>EEG findings</td>
<td>Generalized slow spike-wave activity</td>
<td>Generalized slow spike-wave activity</td>
<td>Generalized slow spike-wave activity</td>
<td>Generalized and bilateral frontotemporal slow waves</td>
<td>Generalized slow spike-wave activity</td>
</tr>
<tr>
<td>MRI findings</td>
<td>Bil hippocampal sclerosis</td>
<td>Bil hippocampal atrophy and 2 years after PALE, and bil hippocampal abnormalities at 6 years after PALE</td>
<td>Bil hippocampal atrophy</td>
<td>Bil hippocampal sclerosis</td>
<td>Bil hippocampal atrophy</td>
</tr>
<tr>
<td>Effective treatment</td>
<td>N/A</td>
<td>IVIG: Mildly increased alertness and mobility</td>
<td>N/A</td>
<td>Steroid pulse therapy: Slight improvements in alertness and language</td>
<td>ACTH therapy: Transient cessation of epileptic spasms, and moderate improvements in behavior and cognitive functions</td>
</tr>
</tbody>
</table>

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leptic spasms are the main seizure types. In all the reported cases, interictal EEG showed generalized slow spike-wave complexes. The electro-clinical characteristics of these patients at epilepsy onset were reminiscent of cryptogenic late-onset epileptic spasms, an age-dependent type of epileptic encephalopathy that is considered to reflect dysmaturation of the temporal lobe [5-7]. In four of the five cases, bilateral hippocampal involvement was seen on MRI at onset or during the follow-up period. Several authors have speculated that bilateral hippocampal injuries may play a critical role in the pathogenesis of secondary generalized epilepsy networks, leading to the development of symptomatic generalized epilepsy [8, 9]. However, in Case 4, the transient hyperintensities seen during the course of the patient’s PALE were confined to the right medial temporal lobe, and follow-up MRI scans performed at two years after the onset of epilepsy showed unilateral right hippocampal sclerosis. These findings indicate that this syndrome can arise in children with unilateral hippocampal lesions.

The outcomes of this type of epileptic encephalopathy in terms of seizures and neuropsychiatric development are poor. The mechanisms responsible for the development of epileptic encephalopathy after HHV6-PALE are not fully understood. Several possible mechanisms have been suggested, including (1) a chronic progressive inflammatory process that occurs after an acute infection; (2) secondary immune activation after a latent period lasting several months; and (3) epileptic activity due to an epileptogenic insult acquired as a sequela of limbic encephalitis [3, 4]. In our case, CSF examinations and an MRI scan obtained during epileptic encephalopathy showed no evidence of a chronic progressive inflammatory process or secondary immune activation. Previous studies speculated that HHV6-PALE might trigger an immune-mediated process because immunothrombocytopenia occurred in one patient (Case 4), and oligoclonal bands were detected in the CSF of two patients (Cases 2 and 4) during the epileptic activation period. However, several immunomodulatory therapies including steroid pulse therapy, IVIG, and immunosuppressive agents have been shown to be ineffective against this type of epileptic activity. The prognosis of the patients’ seizures and neuropsychiatric development was extremely poor in all cases.

In our case, ACTH therapy briefly suppressed both generalized seizures and generalized high-voltage epileptic discharges seen on interictal EEG for several months. However, focal abnormal discharges remained in bilateral central and temporal regions after the ACTH therapy, and recurrent secondary generalized epilepsy also occurred. These findings suggest that rather than having an immunological effect on epileptic foci, ACTH suppresses a secondary generalized network produced by hippocampal injuries. Oguni et al. [10] reported that ES can be produced by epileptic foci and speculated that ACTH therapy might suppress the development of generalized epilepsy networks, leaving only the most resistant foci intact.

In conclusion, we consider that ACTH therapy may be useful for treating epileptic encephalopathy after HHV6-PALE, for which there is currently no effective treatment. Considering that the prognosis of this type of epileptic encephalopathy is devastating, elucidation of the mechanisms responsi-
ble for the development of epileptic encephalopathy and development of a new strategy for its management are urgently needed.

Conflict of interest
The authors have no financial or personal relationships that could pose a conflict of interest.

References