An Adult Case of Relapsing Human Herpesvirus-6 Encephalitis

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Abstract

Human herpesvirus-6 (HHV-6) is the main etiologic agent of exanthema subitum in young children. Central nervous system (CNS) infections in children due to HHV-6 have been described on many occasions. HHV-6 is also a common cause of infections in immunocompromised individuals. However, little is known concerning the impact of HHV-6 on the CNS in immunocompetent adults. We report the first case of relapsing HHV-6 encephalitis in a healthy 73-year-old female.

Key words: human herpesvirus-6 (HHV-6), relapse, encephalitis, immunocompetent

(Introduction)

Human herpes virus-6 (HHV-6) was first isolated in 1986 from patients with lymphoproliferative disorders or HIV infection, and it has been identified as the causal agent of exanthem subitum in young children (1, 2). Central nervous system (CNS) disorders such as febrile seizures, meningoencephalitis, and encephalopathy may complicate the course of HHV-6 primary infection in children (3, 4). HHV-6 is also a common cause of infections in immunocompromised individuals (4). However, CNS infection induced by HHV-6 is very rare in immunocompetent adults, and the pathogenesis of these cases remains unclear (5-14).

Here, we report the first case of relapsing HHV-6 encephalitis in an immunocompetent 73-year-old female.

Case Report

A 70-year-old healthy female was admitted to our hospital with disorientation after tonic-clonic seizures in June 2002. She had been well until one month earlier, when she began to feel general fatigue. She had no anamnesis and had never gone abroad. Neurological examinations revealed disturbance of consciousness, right Chaddock sign, and frontal sign. Blood cell counts were normal and blood serum and chemistry showed mild liver dysfunction and elevation of C reactive protein (CRP). Analysis of cerebrospinal fluid (CSF) showed a protein increase (85 mg/dl) with a normal leukocyte count (3 cells/mm³). Magnetic resonance imaging (MRI) performed in early July revealed high intensity lesions at the bilateral basal ganglia on a T2-weighted image and a fluid attenuated inversion recovery image (Fig. 1A). Oral antiepileptic drugs (phenytoin: 30 mg and phenobarbital: 100 mg per day respectively) were started after admission. But drug-induced skin eruptions appeared on her hip the next day, and the rashes extended to her trunk, limbs and face with high fever on the following day. Therefore the treatment of phenytoin and phenobarbital was discontinued, and oral prednisolone (30 mg per day) was administered from the same day. Improvement of the skin rashes and fever were seen from mid-July, and the eruption was disappeared by the end of July. Her consciousness improved gradually, and she left the hospital two months after admission with mild cognitive impairment. HHV-6 IgG antibody titer of the serum which was collected three days after admission, was elevated to 80 -fold (reference value is less than 10 -fold), and decreased to 10 -fold early in July, while the serum IgM antibody was not elevated. The abnormalities on MR images disappeared by April 2003.

In January 2005, she complained of general fatigue. She became disoriented with a slight fever of 37.8°C in early February and was readmitted to our hospital. Neurological examinations revealed disturbance of consciousness and bi-
lateral patellar hyperreflexia. Signs of meningeal irritation were not observed. Her blood cell count was normal, and blood serum and chemical studies showed neither liver nor renal dysfunction. CRP was not elevated. CSF analysis performed on the admission day revealed increase in leukocytes (32 monocytes/mm$^3$) and protein (102 mg/dl) with a normal glucose level. Bacterial, fungal, and mycobacterial cultures of the CSF were all negative. Human herpesvirus simplex (HSV) PCR was negative, and cytology showed no malignant cells. Electroencephalography showed a diffuse slowing, but no seizure discharge. Brain computed tomography performed in early February revealed no abnormal lesion. Because viral encephalitis was suspected from the clinical findings and CSF analysis, aciclovir (ACV) was started immediately, but her consciousness disturbance did not improve. Skin rashes appeared three days after admission, and corticosteroids were administered. She could speak after a few days, and skin eruptions disappeared. After three weeks, she could walk with support. Brain MRI findings at the end of February revealed no abnormal lesion apart from mild atrophy of bilateral frontal lobe (Fig. 1B). HHV-6 IgG antibody titer of the serum which had collected in mid-February was significantly elevated (maximum value: 320-fold), and decreased to 20-fold with improvement of consciousness by mid-March, while serum IgM antibody was not elevated. Neither anti-HHV-6 IgG nor IgM antibodies were detected. Furthermore, neither IgG nor IgM antibodies to other herpesvirus (including HSV-1, varicella-zoster virus, cytomegarovirus, and Epstein-Barr virus) and Japanese encephalitis virus were abnormally elevated. From these results, we assumed that this relapsing encephalitis might be caused by HHV-6. Finally, she was discharged without any sequelae fifty-one days after hospitalization.

Discussion

HHV-6 is the main etiologic agent of exanthema subitum in young children, and has been implicated as a possible cause of encephalitis in pediatric patients (1-4). Epidemiologic studies have shown that most people are infected with HHV-6 at an early age. The virus remains latent state in lymphocytes, salivary glands, and brain tissue after primary infection, and has been reactivated in immunocompromised individuals, e.g., HIV-positive patients; recipients of bone marrow transplants, liver transplants, and renal transplants; and persons with lymphoproliferative disorders (1, 17, 18). However, there are few reports on the involvement of HHV-6 in the CNS in immunocompetent adults suffering from meningitis and/or encephalitis (5-14). Furthermore, there is no report of relapsing encephalitis due to HHV-6 in an immunocompetent adult. The present non-immunocompromised patient experienced a recurrence of HHV-6 encephalitis, which is very rare.

After primary infection, HHV-6 is characterized by lifelong latency in peripheral blood monocytes, salivary glands, and brain tissue (15, 16). HHV-6 seems to be a resident virus of human brain and is able to cause a restricted or minimally productive infection of brain cells, including microglial cells, astrocytes, and oligodendrocytes (16). There have been several reports that suggest the direct invasion of HHV-6 into the CNS. The frequency of detecting the HHV-6 genome by PCR in the brain tissue of immunocompetent adults was reportedly between 15% and 85% (19, 20). One group demonstrated HHV-6 DNA in 57% of brain tissues obtained from AIDS patients (21). Reactivation of infection occurs occasionally during pharmacological immunosuppres-
HHV-6 may be considered an important opportunistic pathogen. In contrast, immunocompetent adults very rarely have HHV-6-induced CNS infection (5-14). In the present case, the serum HHV-6 IgG antibody was elevated in the early stage and decreased afterward, while the serum IgM antibody against HHV-6 was not elevated. The considerable increase of IgG antibodies without a positive IgM antibody titer indicates reactivation of the virus (14), but its cause is unknown. One possibility is that the pathogenic mechanism involved in HHV-6 meningitis/encephalitis in immunocompetent adults may be related to the ability of HHV-6 to evade host immune responses through various mechanisms; induction of CD4 lymphocyte depletion via apoptosis, down-regulation of CD3 expression in T cell clones infected in vitro, a decrease of peripheral blood lymphocyte proliferation by HHV-6 via transcriptional down-regulation of IL-2, and decreased generation of reactive oxygen intermediates from monocytes that were infected with HHV-6 in vitro (22). Another undeniable possibility is that the patient had an immunocompromising disease that had not been diagnosed. In the present case, ACV was administered because the etiology was uncertain at first, but ganciclovir (GCV) and foscarnet were demonstrated to be more effective than ACV for some immunosuppressed patients with HHV-6-induced encephalitis (17, 18).

According to the past literature about immunocompetent patients with HHV-6-induced encephalitis, the majority (80%) of the patients presented with an altered level of consciousness; 60% had seizures, and 55% had focal neurological signs (9). Meningeal irritation, weakness of limbs, hyperreflexia, ataxia and visual disturbance were reported as the neurological findings. Analysis of CSF revealed mild-moderate increase of leukocytes (monocytes-dominant) and proteins in almost cases. In about half cases there were CT or/and MRI abnormal findings at CNS: including basal ganglia, thalamus, cerebral white matter, brain stem, and spinal cord, but there were no lesion at CNS in the other cases (5-14).

The first symptom of our patient was disturbance of consciousness and tonic-clonic seizures, but the only recurring symptom was disturbance of consciousness. The MRI findings in the first hospitalization revealed bilateral basal ganglia lesions, but there was no obvious lesion on MRI in the second hospitalization. The reason is unknown, but we assume that the degree of second HHV-6 reactivation was more subtle, and therefore the clinical features due to HHV-6 were different in the same individual. It is reported that basal ganglia lesion on MRI is often observed in encephalitis caused by some viruses such as Japanese encephalitis virus, Nipah virus, West Nile virus (23-25). Because serum antibody levels to Japanese encephalitis virus were not elevated in our case and the patient had never gone abroad, it was thought that these viruses were not the cause of encephalitis in this patient.

Drug-induced hypersensitivity syndrome (DIHS) is characterized by a severe, potentially fatal, multiorgan hypersensitivity reaction. DIHS usually occurs 3 weeks to 3 months after starting a limited number of drugs, including carbamazepine, phenytoin, phenobarbital, dapsone, mexiletine, salazosulfapyridine, allopuronil, and minocycline. The diagnosis of DIHS is confirmed by the presence of five of the following six criteria: 1) maculopapular rash developing >3 weeks after starting therapy with the above drugs, 2) lymphadenopathy, 3) fever, 4) leukocytosis, 5) hepatitis, 6) HHV-6 reactivation (26). HHV-6 encephalitis associated with DIHS was reported previously (27). In the present case, a skin rash with high fever appeared soon after the dosage of phenytoin and phenobarbital in the first hospitalization. Our case can not be said to satisfy this DIHS criteria, as it lacked the following criteria: lymphadenopathy, leukocytosis, and hepatitis. But the skin rash appeared in both the first and the second hospitalization, which may also be related to encephalitis by HHV-6.

It is particularly unusual for a person not in an immunocompromised state to suffer from relapsing encephalitis due to HHV-6. We should consider the possibility of HHV-6 in the differential diagnosis of encephalitis in immunocompetent adult patients when the viral etiology of meningoencephalitis is unknown.

References