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SHORT REPORT

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Acute cerebellitis in primary human herpesvirus-6 infection

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Acute cerebellitis has been described in infections caused by many kinds of pathogens, but as yet has not been described in human herpesvirus-6 (HHV-6) infection [11]. We report here a case of acute cerebellitis during primary HHV-6 infection.

A 2.5-year-old girl was admitted to a local hospital because of a 3-day history of high fever and generalised tonic convulsions which occurred four times on the 3rd day. Physical examination showed a normally developed alert infant with truncal ataxia. A cranial CT scan was normal. Her CSF showed normal concentrations of protein and glucose and no pleocytosis. In the evening of the day of admission, she had five episodes of generalised tonic convulsions with high fever and became irritable, but was well oriented. Skin erythema on the face, trunk, and extremities clearly appeared the next morning and she became drowsy; she was then transferred to our hospital.

On admission, she was unconscious and showed a withdrawal movement, crying briefly in response to pain (Glasgow coma scale E3V2M4). Both pupils were equal in size and prompt in light reflex and her tendon reflexes were normal. There was no optic oedema. There was a rubella-like erythema on her face, trunk, and extremities without vesicles or petechiae. Laboratory data, including levels of ammonia, lactate and pyruvate, were normal except that of serum CK (1711 IU/l). Analysis of CSF showed 402 leukocytes/mm^3 (segmented 322, mononuclear 80), a glucose level of 68 mg/dl and a protein level of 79 mg/dl. No oligoclonal IgG bands or myelin basic protein were observed. Neuron specific enolase (NSE) in CSF was elevated (130 ng/ml; control mean 13.1 ng/ml).

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Her EEG showed normal findings. MRI on the 5th day of illness demonstrated a diffuse hyperintensity in the cerebellum based on the diffusion-weighted sequence but not obvious on the T1- or T2-weighted images (Fig. 1a). Brain single photon emission CT (SPECT) by ECD on the same day showed a marked hyperperfusion in the bilateral hemispheres of the cerebellum (Fig. 1b,c). With the diagnosis of acute encephalitis, predominantly in the cerebellum, she was treated with mannitol, dexamethasone, and phenobarbital. Acyclovir (10 mg/kg per dose) was used every 8 h for 2 weeks. She did not experience any convulsions after the therapy had started and she recovered her full consciousness within 1 week. After this significant recovery, severe cerebellar dysfunctions such as ataxia and dysmetria were more obvious, but excellent improvement was achieved within 1 month without any sequelae. The hyperintensity on MRI and hyperperfusion on SPECT in the cerebellum disappeared with clinical improvement (Fig. 1d,e,f). In addition to these radiological findings, MRI on admission demonstrated abnormal high intensities at the splenium of the corpus callosum on T2- and diffusion-weighted images, which disappeared 72 h after the first MRI [6].

Titres of serum immunoglobulins for HHV-6 (fluorescent antibody method) were significantly elevated during the illness (on the 6th day of illness: IgG $<1:10$, IgM 1:10; on the 25th day of illness: IgG 1:320, IgM 1:20), while those in CSF were not (on the 6th day of illness: IgG $<1:10$, IgM $<1:10$; on the 25th day of illness: IgG $<1:10$, IgM $<1:10$). The titres against the many other pathogens which can cause erythema or encephalitis including HHV-7, herpes simplex, Epstein-Barr virus, varicella zoster virus, rubella virus, measles virus, parbovirus, enterovirus 71, influenza virus, and *Mycoplasma pneumoniae* were not significantly elevated. Cultures of CSF did not reveal any viral pathogen. PCR analysis of CSF with specific primers for the U31 gene of HHV-6 (forward primer: 5'-TGCACCACCTCTCTGC-TTATAAC-3', reverse primer: 5'-CTAATTGCCG-TAGCGTGAGAAC-3') and the sequencing of the

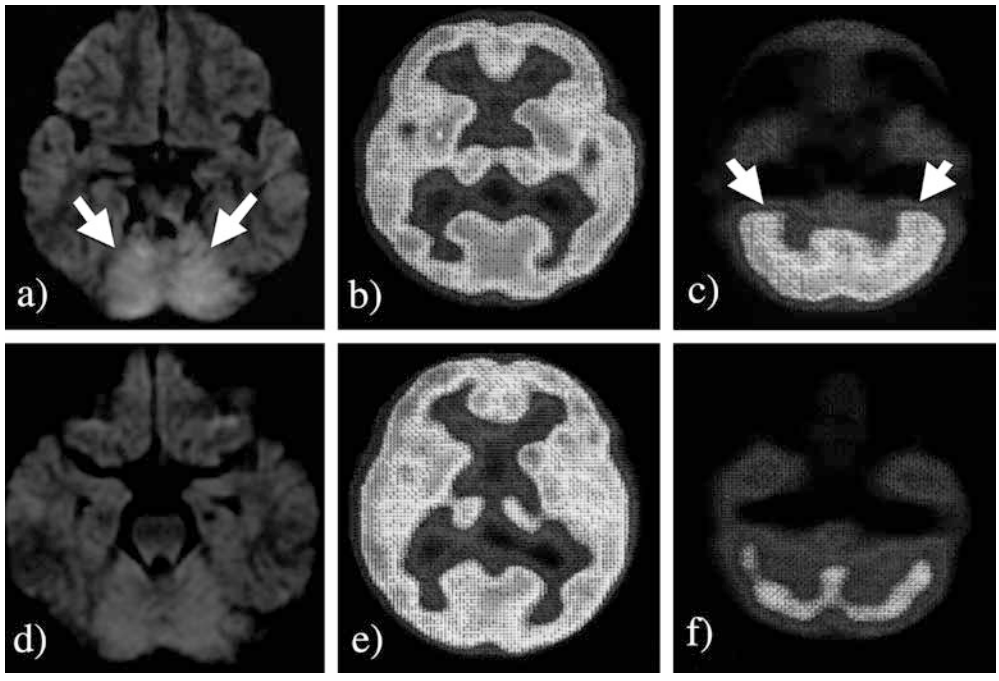

Fig. 1 MRI and SPECT on admission showing a diffuse hyperintensity and hyperperfusion of the cerebellum. **a,d** MRI: axial sections of the cerebellum on diffusion-weighted (TR/TE;3000/98.9, b value = 1000 s/mm^2) sequence on the 5th and 33rd day of illness. *Arrows* indicate regions with abnormal intensity. **b**, **c** , **e** , **f** SPECT: axial sections of cerebrum and cerebellum on the 5th and 38th day of illness respectively. *Arrows* indicate the regions with abnormal intensity or perfusion

amplified fragment confirmed the HHV-6 genome sequence [3]. These analyses proved the primary infection and invasion of the central nervous system by HHV-6 during her illness.

HHV-6 is the pathogen initially found in association with immunocompromised hosts and later proved to be a cause of roseola infantum [10,11]. Roseola infantum is itself a benign disease but sometimes cause convulsions, which is closely associated with invasion of HHV-6 into the central nervous system [11]. Encephalitis or encephalopathy during primary HHV-6 infection has been described, but cerebellitis has not been reported to date [4,11]. The prognosis of cerebellitis is usually good and our patient recovered without any neurological sequelae, but carebellitis can cause severe neurological complications such as brain stem herniation [5].

Several mechanisms such as direct invasion or angiopathy have been postulated as the pathogenesis of neurological complications by HHV-6 [11]. In the previous reports, patients with HHV-6 encephalopathy associated with angiopathy did not have significant elevation of the cell count in CSF [7]. In contrast, our patient showed a marked increase in CSF cell count with the presence of viral genome and the significant elevation of NSE in CSF. These findings suggest an invasion of the HHV-6 stimulating the host immune responses in our patient.

At present, gancyclovir is the most potent drug for HHV-6 infection. However, we decided not to use gancyclovir because of possible severe adverse effects [1,8]. We empirically used acyclovir for our patient diagnosed with encephalitis caused by an unknown virus. HHV-6 does not possess thymidine kinase which changes acyclovir to its active form, but in vitro experiments showed that acyclovir can inhibit HHV-6 replication in peripheral blood mononuclear cells at an IC50 of 12—32 μM [9]. In our patient, the regimen of acyclovir was three times per day at 10 mg/kg per dose. The maximum serum concentration with this regimen should be about 80 μM in children. The concentration of acyclovir in CSF also should be above the IC50 according to the data of protein binding [2,9]. Acyclovir could have partial protective effects against virus replication or immune responses by reducing the HHV-6 antigen, but a rapid bedside diagnostic method and new antiviral compounds such as cidofovir should be administered as a more efficient therapeutic strategy [8,9].

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