Recovery without Neurological Sequelae in Fulminant Cerebral Edema in Pediatric Encephalitis with Human Herpesvirus Type 6

Viral encephalitis can lead to serious neurological sequelae and death among younger children. It is also known that the mortality rate in encephalitis with cerebral edema or transtentorial brain herniation is higher. A 4-year-old boy visited our emergency department exhibiting mental change. The patient had a high fever for four and a whole-body rash for three days prior to his visit. He had displayed irritable symptoms and been vomiting for six hours before his visit, accompanied by seizure. After 13 hours of admission, the patient’s right pupil became fixed and fully dilated, and the left pupil also became fixed and fully dilated within 30 minutes. Brain computed tomography (CT) was performed immediately, and severe brain swelling with transtentorial brain herniation was found. The mannitol dose was increased and dexamethasone was also added. Hyperventilation was performed through intubation to reach PaCO$_2$ levels of 25 to 30 mmHg. Fifteen hours later, pupillary reflex was observed and the cerebral edema and transtentorial brain herniation was found to be improving in follow-up brain CT. He was transferred to a general ward after 11 days and discharged on the thirteenth hospital day without any neurological sequelae. Human herpesvirus type 6 (HHV-6) was detected in the serological polymerase chain reaction (PCR) examination.

Key Words: Brain edema, Encephalitis, Herpesvirus 6, Human

Introduction

Encephalitis is an inflammation of the brain parenchyma which can lead to serious neurological sequelae and even death among younger children$^{1,2}$. Incidence rates of specifically viral encephalitis have been reported as between 3 and 30 per 100,000 children, with higher incidence in younger children$^{1,3,4}$. The mortality rate from acute encephalitis has been as low as 5%; however, neurological sequelae such as seizure or cognitive disorders occur in large numbers of between 6.7% and 67% of cases$^{1-6}$. It is also known that the mortality rate of encephalitis with cerebral edema or transtentorial brain herniation is higher$^7$. We report a case of encephalitis in a 4-year-old with fulminating...
cerebral edema and transtentorial brain herniation with human herpesvirus type 6 who recovered without any neurological sequelae.

**Case Report**

A previously healthy 4-year-old boy visited our emergency department with a mental change. He had presented fever for the last 4 days and a skin rash that appeared three days previously had now spread across his whole body. He was irritable and had been vomiting for six hours before arrival, suffering a generalised tonic-clonic seizure three minutes before arrival. At the emergency department, the convulsions stopped after administration of lorazepam 2 mg. There was no specificity in the patient’s past medical history or familial history. He appeared drowsy, and his vital signs were as follows: blood pressure of 105/70 mmHg; heart rate of 112 bpm; respiratory rate of 24 breaths per min; and 37°C of body temperature. In laboratory studies, the patient’s hemoglobin level was 13.9 g/dL and white blood cell count was 4,690 per mm³ with 83.4% neutrophil cells. C-reactive protein was at 1.19 mg/dL; serum sodium and potassium, and blood glucose, were all normal. Serum immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin M (IgM) levels were normal for the patient’s age.

Brain magnetic resonance imaging (MRI) was performed to produce a diffusion-weighted image with high signal intensity and an apparent diffusion coefficient (ADC) image with iso signal intensity in the cortex of both cerebral hemispheres and diffuse cortical swelling (Fig. 1). Two hours after visiting the emergency room, he started a generalised tonic-clonic seizure seizure with right eyeball deviation again. After administration of lorazepam 2 mg, phenytoin was administered at an initial loading dose of 20 mg/kg/dose. Phenytoin was administered at a dose of 5 mg/g/day every 12 hours thereafter. The patient was admitted to the pediatric intensive care unit and empirical therapies using acyclovir, ceftriaxone, vancomycin and mannitol were initiated. After admission, there was no seizure but the patient progressed to stupor. After 13 hours of admission, the patient’s right pupil became fixed and fully dilated, and the left pupil also became fixed and fully dilated within 30 minutes.

![Fig. 1. Initial brain magnetic resonance imaging (MRI) showing (A, B) diffuse cortical swelling in both cerebral hemispheres and (C, D) diffusion-weighted image with high signal intensity and apparent diffusion coefficient (ADC) image with iso signal intensity in both cerebral hemispheres.](image1)

![Fig. 2. Brain computed tomography (CT) showing diffuse brain swelling and transtentorial herniation (A, B).](image2)

![Fig. 3. Follow-up brain computed tomography (CT) showing the improving state of cerebral edema and transtentorial herniation (A, B).](image3)
Brain computed tomography (CT) was performed immediately, and severe brain swelling with transtentorial brain herniation was found (Fig. 2). The mannitol dose was increased and dexamethasone was also added. Endotracheal intubation was performed for hyperventilation treatment to reach PaCO2 levels of 25 to 30 mmHg. Fifteen hours later, pupillary reflex was observed and the cerebral edema and transtentorial brain herniation were found to be improving in follow-up brain CT (Fig. 3). His fever subsided on the second hospital day. There was no seizure for 48 hours, so administration of phenytoin stopped. Hyperventilation therapy was stopped on the six hospital day. On the seventh day of admission, he was alert but irritable. In a follow-up brain MRI on the seventh day of admission, we observed a diffusion-weighted image with multifocal high signal intensity and an ADC image with iso signal intensity in the right posterior parahippocampal gyrus and left thalamus, and in the cortex of the uncus, the gyrus rectus and the orbital gyrus, in addition to markedly decreased edema (Fig. 4). An electroencephalogram (EEG) performed on the third hospital day had diffuse high amplitude 1–1.5 Hz delta activity in the background, and results improved on fifth day of admission.

Human herpesvirus type 6 deoxyribonucleic acid (DNA) was detected through performing polymerase chain reaction (PCR) on the patient’s serum; PCR results for Epstein–Barr viruses, herpes simplex virus, and cytomegalovirus on the patient’s serum were negative. Respiratory virus PCR results for Influenza virus, respiratory syncytial virus, adenovirus, enterovirus and so on were negative.

The patient was transferred to general ward on the eleventh hospital day and discharged on the fourteenth without any neurological sequelae.

**Discussion**

Acute encephalitis can increase intracranial pressure and lead to brain herniation; mortality rates in these cases are higher. Glaser et al. report that 47 (3%) of 1,570 encephalitis cases presented rapid evolution to fulminant cerebral edema and that 34 (72.3%) of those patients died within seven days of hospitalization10). Relatedly, Lan et al. describe 25 (2.4%) of 1,038 children with encephalitis who presented with fulminant cerebral edema: 16 (64%) patients died because of severely increased intracranial pressure with profound shock or were discharged against medical advice, eight (32%) developed a vegetative status, and one (4%) developed severe neurological sequelae7).

Human herpesvirus type 6 is the cause of exanthema subitum which itself is characterized by high fever followed by rash. The disease is common in infancy and symptoms are usually mild, but encephalitis and other neurological complications have been reported. Primary human herpesvirus-6 infection can invade the central nervous system and cause severe neurologic symptoms, resulting in severe outcomes11,12). Although primary infection is rare in children older than 3 years of age, the case of a 14-month-old girl diagnosed with HHV-6 encephalitis who remained unconscious and ultimately died has been reported in Korea13).

HHV-6 diagnosis is made by positive identification of HHV-6 DNA using PCR analysis serum and cerebrospinal fluid, or by observing changes in the titers of IgG and IgM antibodies, HHV-6 can be present with inactive infection in an immunocompetent patient14). Diagnosing central nervous system infection is difficult, especially in cases of encephalitis. For example, normal cerebrospinal fluid does not preclude encephalitis14,15).

In our case, a spinal examination was not carried out due to the possibility of brain herniation suggested by the accompanying mental change and the diffuse cortical swelling observed via brain CT.

Despite the use of mannitol after admission, our patient’s...
cerebral edema developed rapidly, progressing to transtentorial brain herniation; we anticipated severe outcomes because of this. We had thought that hyperosmolar therapy and hyperventilation treatment without initial cerebrospinal fluid test might have affected the outcome. However, the treatment with mannitol and steroid, and hyperventilation procedure, were successful and the patient recovered to normal without neurological damage. A diffusion-weighted image shown in a follow-up brain MRI on the seventh day of admission was interpreted as sequelae of encephalitis or infarction, (Fig. 4). But so far, there is no sequelae to be seen by him. We will continue to monitor him in the future. We concluded that HHV-6 should be considered the potential cause of the patient’s encephalitis as evidenced by his symptoms, the brain MRI, and HHV-6 positive serum PCR results.

This concludes our case report of encephalitis in a 4-year-old boy with fulminant cerebral edema and transtentorial brain herniation with HHV-6 who recovered without any neurological sequelae.

References