A Case of Japanese Encephalitis Presenting with Fever and Seizure in a 7-month old Infant

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Introduction

Japanese encephalitis (JE) is one of the most prevalent types of endemic encephalitis in the world, especially in eastern and southeastern Asia. Up to 50,000 cases and 15,000 deaths annually are due to JE, especially in the rural areas. Most of the Japanese encephalitis virus (JEV) infections do not result in apparent illness, and the ratio of asymptomatic to symptomatic infection varies between 25:1 and 1000:1. The clinical presentation varies from a nonspecific febrile illness to severe encephalitis. However, 20-40% of symptomatic encephalitis patients die during the acute stage and
nearly half of the survivors have permanent neurological sequelae[4]. Korea had been one of the major endemic areas of JE, however, the number of cases has dropped sharply since the introduction of vaccination and vector control. The annual incidence of the disease had been less than 10 cases from 1984 to 2009, after the last outbreak in 1982. Especially, there were no case reports under the age of 9 years during the last ten-year period. Here, we report a 7-month-old boy with Japanese encephalitis whose initial presentations were fever and seizure.

Case Report

A 7-month-old boy was admitted to Seoul National University Bundang Hospital due to fever and a seizure. He was born via normal vaginal delivery without any perinatal problems and showed a normal pattern of development. Fever developed 2 days prior to admission without any other symptoms or signs of infection. On the day of admission, he vomited once and had a generalized tonic clonic seizure for two minutes. He lives in Bundang, Gyeonggido and has visited rural areas (such as Sockcho, Jechoen, and Jeonju) during the last 2 months. His vaccinations were up-to-date for BCG, hepatitis B, DTaP, polio, hemophilus influenza type b, pneumococcus, and rotavirus.

His initial vital signs at the emergency department were all within normal limits except for a body temperature of 40.0°C. He was alert and his physical examinations were unremarkable except for a pharyngeal injection and tonsillar hypertrophy. Neurologic examinations were not remarkable which showed normal light reflex, normal deep tendon reflex, normal muscle tone, equally symmetric muscle power of grade V and no Babinski sign or neck stiffness. Initial laboratory findings showed: hemoglobin 13.9 g/dL, WBC 13,900/uL (segmented neutrophil 66.1%, lymphocyte 23.5%, monocyte 9.9%, eosinophil 0.1%), platelet 341,000/uL, and C-reactive protein (CRP) 7.7 mg/dL (upper normal limit: 0.5 mg/dL). He received antimicrobial treatment for acute pharyngotonsillitis.

On the third day of admission, he became

![Fig. 1. Initial and follow-up brain MRI of the patient. (A) Initial axial T2-weighted image showing increased signal intensity in both thalami (asterisk). (B) Initial axial diffusion tensor imaging showing diffusion restriction in both thalami (asterisk). (C) Two-month follow-up axial T2-weighted image showing diffuse cerebromalacic change and atrophy.](image-url)
drowsy and showed a slightly tonic posture with intermittent leftward eyeball deviation with sustained fever and frequent vomiting. A neurologic examination revealed tense fontanel, slightly increased deep tendon reflex, and equivocal ankle clonus. His pupil sizes were both 1 mm, and his light reflex was prompt and isocoric. Cerebrospinal fluid (CSF) analyses showed: white blood cell 370/mL with 74% segmented neutrophils, protein 137 mg/dL, and glucose 86 mg/dL (serum glucose 87 mg/dL). The serum C-reactive protein was elevated to 20.65 mg/dL. The brain magnetic resonance imaging (MRI) showed increased signal and diffusion restriction in both thalami (Fig. 1A, 1B). An electroencephalography revealed diffuse slow and excessively suppressed background activities. Intravenous vancomycin, cefotaxime and acyclovir were initiated for the diagnosis of encephalitis.

On the fourth day of admission, he had another generalized tonic clonic seizure. His consciousness worsened to stuporous mentality on the Glasgow coma scale with an 8 (E2M4V2). Because of decreased self respiratory effort, a mechanical ventilator support was provided. During intensive care unit admission, the patient showed marked hemodynamic instability. Bradycardia (heart rate of 45–60), premature ventricular contractions (PVCs), and severe hypotension were controlled with intensive intravascular volume replacement, vasopressors and anti-arrhythmic agents.

Intravenous immunoglobulin (IVIG) (500 mg/kg/day, from the hospital days 4 to 7) and methylprednisolone pulse therapy (30 mg/kg/dose, from the hospital days 11 to 13) was administered to control inflammation of the central nervous system. On the 14th day of admission, the fever subsided and the patient showed spontaneous eye opening. On hospital day 17, the capture enzyme–linked immunosorbent assay showed positive for CSF Japanese Encephalitis B (JEB) IgM and serum JEB IgM, whereas all other tested bacterial or viral agents showed negative results. The follow-up serum JEB IgM absorption titer increased five times and IgG titer increased from less than 1:16 to 1:128.

Third, fourth and seventh cranial nerve palsy and flaccid paralysis of all extremities persisted. A follow-up brain MRI showed diffuse tissue loss of both thalamic area and cerebromalatic change of the cerebral cortex, brainstem and cerebellum. Maintenance methylprednisolone therapy had been continued, and the patient was transferred to the ward with a home ventilator at hospital day 33. A follow-up brain MRI that was performed 2 months after admission showed a large area of tissue loss in both thalami and diffuse cerebromalatic change with atrophy in both cerebral cortex, brainstem, and cerebellum (Fig. 1C). The patient is currently 12-months old and in a neurologically vegetative state with a home ventilator support through a tracheostomy tube. Although not persistent, there is intermittent self respiration and other vital signs are stable. He is being fed with a nasogastric tube and motor activity shows flaccid paralysis in all extremities.

Discussion

Viral encephalitis is an acute inflammatory process involving brain parenchyma. There are various causes of acute viral encephalitis, but the identification of a pathogenic organism
remains challenging. A virus culture is difficult, time consuming and is not readily available in many cases. A brain biopsy is invasive and is usually considered only for diagnostically challenging cases. Because of these limitations, the cause of viral encephalitis is not found in approximately half of all the viral encephalitis cases. So clinicians consider many factors such as the patient’s age, immunization state, and the incidence for the tentative diagnosis to initiate effective treatment as soon as possible. Common viral causes of sporadic encephalitis in Korea are herpes simplex virus, varicella zoster virus, and enterovirus. Japanese encephalitis, once a prevalent disease in Korea, has been on the decline since the 1980s. Actually, the annual incidence of disease had been less than 10 cases from 1984 to 2008, especially no case had been reported under the age of 9 years. So, it is possible that pediatricians may not consider JEV as a pathogenic organism of viral encephalitis in children. But as we can see in this case, we should consider the possibility of JEV infection in patients whose etiologic diagnosis is uncertain. Especially in patients who were not immunized for JEV.

Specific brain MRI findings may provide a clue to the diagnosis of an underlying etiologic organism. Although most of the pathogens reveal nonspecific changes, but in some cases specific findings in the brain MRI are noted. For example, inflammation of the temporal and frontal lobe suggests herpes simplex encephalitis; parietooccipital cortex and corpus callosal inflammation are seen in Ebstein Barr virus encephalitis; brainstem, basal ganglia and thalamus lesions are frequent in enteroviral encephalitis. In the brain MRI of JE cases, thalamic involvement can be seen in 84–94% of patients, with involvement of the brainstem, cerebellum, and cerebral cortex. In our case, the initial brain MRI showed an increased signal change of both thalamic areas, which is characteristic of JE and similar to that of an enteroviral infection. When lesions are present at the thalamus and brainstem in patients with encephalitis whose etiologic diagnosis is unidentified, laboratory tests to reveal enterovirus and Japanese B encephalitis should be performed. As we mentioned earlier, the diagnosis of JE should be suspected in patients who were not immunized, especially when there is no identifiable cause of the encephalitis and specific brain MRI findings are present involving both the thalamus and brainstem.

Although there are certain antiviral agents for specific pathogens such as acyclovir for herpes simplex encephalitis or a newly developing antiviral agent for enteroviral encephalitis, no specific antiviral therapy is available in most viral encephalitis including JE. Therefore, supportive and symptomatic care is the most important treatment until now. These conservative treatments include prompt application of intensive care to decrease mortality and morbidity, to control and treat the factors that cause secondary deterioration such as increased intracranial pressure, convulsion, electrolyte imbalance, respiratory failure and secondary bacterial infection. In addition to the intensive conservative treatment, there has been extensive research on immunomodulatory therapy including corticosteroid or intravenous immunoglobuline (IVIG). There was a study that showed a favorable outcome of using corticosteroid with acyclovir compared to using just acyclovir only in 45 adult patients with herpes simplex encephalitis. On the contrary,
the study of Hoke et al. in 1992, failed to show the beneficial effect of corticosteroids in JE\textsuperscript{(16)}. But case reports published recently, showed the effect of corticosteroid in JE as well as other viral encephalitis\textsuperscript{(17, 18)}. These studies also included patients with low GCS whereas the studies in the past did not. Moreover, there were some case reports of using IVIG, which suggested the effectiveness of treatment for the west Nile virus encephalitis\textsuperscript{(19)} and JE\textsuperscript{(20)}. Although there are no data with strong evidence that showed the effectiveness of immunomodulatory treatment, anecdotal reports suggest possible benefits of using corticosteroids and IVIg. Also considering that there is no etiology specific treatment of JE, we can consider these treatments when there are no contraindications for the treatment.

To the best of our knowledge, this is the first report of JE in an unimmunized infant proven by serologic testing. We should consider the diagnosis of JE in encephalitis patients with uncertain etiology and especially if they are not immunized to JEV. The specific findings of an MRI that show increased signal intensity in the thalamus and brainstem are a clue that can point to the diagnosis of JE. Prompt intensive management can decrease the mortality and morbidity of patients with JE. Although it is controversial, immunomodulatory treatment such as corticosteroids and IVIg may be administered as long as there are no contraindications.

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