Kawasaki disease presented with status epilepticus and diffusion MRI abnormalities in the subcortical white matter

Dai Keino, Yuki Koto, Chisato Inuo

Department of Pediatrics, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan.

ABSTRACT

Background. Kawasaki disease (KD) is an acute, self-limited vasculitis of unknown etiology that occurs predominantly in infants and young children. Encephalitis/encephalopathy is an extremely rare complication of KD.

Case. A previously healthy 8-month-old Japanese boy had a prolonged seizure after febrile illness for one day. On the fourth day, he had bilateral nonexudative conjunctivitis, changes in the extremities, rash and induration at the Bacillus Calmette-Guerin inoculation site. He was diagnosed with incomplete KD and treated with immunoglobulin. On the fifth day, he had cluster seizures. Brain magnetic resonance imaging (MRI) showed restricted diffusion in the left subcortical white matter, which was consistent with acute encephalopathy with biphasic seizures and late reduced diffusion (AESD). He was treated with controlled normothermia, pulsed-dose methylprednisolone, continuous infusion of midazolam, and edaravone. On the tenth day, he had a recurrent fever and was treated with a second course of immunoglobulin. Subsequently, he had defervescence, and the abnormal signal detected in the MRI disappeared. At the age of 11 months, he had normal growth and development for his age by the Denver Developmental Screening Test.

Conclusion. It is necessary to consider AESD as the differential diagnosis of prolonged seizure in infants with KD. Brain MRI led to early diagnosis and intervention in our patient. The neurological prognosis of our patient was relatively good, but the prognosis of KD with AESD is unknown. To clarify this, further case accumulation is warranted.

Key words: incomplete, Kawasaki disease, encephalopathy, acute encephalopathy with biphasic seizures and late reduced diffusion.

Kawasaki disease (KD) is an acute, self-limiting febrile illness of unknown etiology that predominantly affects children younger than five years of age. KD is classically diagnosed on the basis of the presence of fever for more than five days and five principal clinical features (bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy). Patients who do not fulfill these criteria are diagnosed with incomplete KD.\(^1\)

\(^1\) The most important complication of KD is coronary arterial aneurysm, which may cause ischemic heart disease and sudden death.\(^1\) Complications such as febrile seizures and acute encephalopathy are extremely rare.\(^2,3\) Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) occurs in children with infection. It is characterized by prolonged febrile seizures in the first phase and a cluster of seizures, deterioration of consciousness, and white matter lesions with reduced diffusion in the second phase.\(^4\) Here, we report the clinical course of a pediatric case with incomplete KD, who presented with status epilepticus and characteristic brain MRI abnormalities. We explained the purpose of the report to the parents and obtained their informed consent.
Case Report

A previously healthy 8-month-old Japanese boy was admitted to our hospital, having experienced a prolonged generalized seizure on the first day of febrile illness. He was treated with three doses of midazolam (0.2 mg/kg), and the seizure lasted for approximately 50 minutes.

The blood count revealed no abnormalities. Hepatic enzyme, C-reactive protein, and procalcitonin levels were significantly elevated (Table I). The cerebrospinal fluid (CSF) examination revealed no abnormalities. The polymerase chain reactions for serum and CSF samples were negative for the influenza virus and the human herpes viruses (HHV) 6 and 7. Brain magnetic resonance imaging (MRI) revealed no abnormalities (Fig. 1, left column).

Thereafter, he was conscious with continued, mild lethargy. The laterality of deep tendon reflex response, muscle tonus, and motor function were normal. Paralysis was not observed. On the third day, he developed anterior uveitis and an induration at the Bacillus Calmette-Guerin inoculation site. By the fourth day, he developed bilateral nonexudative conjunctivitis, swelling in the extremities, and trunk rash. Blood biochemical findings revealed a progression of hypoalbuminemia and hyponatremia. Abdominal ultrasonography revealed gallbladder wall thickening. Therefore, he was diagnosed with incomplete KD and treated with immunoglobulin (2 g/kg) and aspirin (30 mg/kg).

On the fifth day, he had cluster seizures without laterality, and was somnolent during the intermittent phases. A brain MRI indicated hemicerebral lesions in the left subcortical white matter, which were most conspicuous in diffusion-weighted imaging (DWI; Fig. 1, middle column). An electroencephalography

| Table I. Laboratory finding at admission. |
|------------------------------------------|
| Peripheral Blood                        | Cerebrospinal Fluid                     |
| WBC 7100 /µL                            | glucose 133 mg/dl                      |
| RBC 363 ×10⁴/µL                         | glucose 133 mg/dl                      |
| Hb 10.0 g/dl                            | NH3 82 µg/dl                           |
| Hct 31.2 %                              | pH 7.22                                |
| Plt 27.5 ×10⁴/µL                        | pCO2 42.2 mmHg                         |
| PT 42 %                                 | HCO3 16.5 mmol/L                       |
| PT-INR 1.60                             | BE -10 mmol/L                         |
| APTTT 56.6 sec                          | cell count 1 /µL                      |
| D-dimer 1.8 µg/ml                       | polynuclear 0 %                       |
| WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Hct: hematocrit, Plt: platelet, PT: prothrombin time, APTTT: activated partial thromboplastin time, TP: total protein, Alb: albumin, T-Bil: total bilirubins, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, γ-GTP: gamma-glutamyl transpeptidase, CPK: creatine phosphokinase, Cr: creatinine, BUN: blood urea nitrogen, UA: uric acid, CRP: C-reactive protein, PCT: procalcitonin, BE base excess.
(EEG) performed during sleep demonstrated a left-right difference in the spindle waves and reduced activity in the left hemisphere (Fig. 2). He was diagnosed with AESD and treated with controlled normothermia for four days, high-dose methylprednisolone pulse therapy (30 mg/kg/day for three consecutive days), continuous midazolam infusion (0.5 mg/kg/h) alongside a 24-hour EEG for five days, and edaravone (1.0 mg/kg/dose twice for four days). On the tenth day, he had recurrent fever and was treated with a second course of immunoglobulin (2 g/kg). Subsequently, he had defervescence and periungual desquamation, and we confirmed the recovery of his consciousness. On the twelfth day, the abnormal signal on DWI had disappeared, and an MRI revealed mild left cerebral atrophy (Fig. 1. right column) and right

**Fig. 1.** Magnetic resonance images of the brain. Left column: On the first day of febrile illness. Results of brain MRI were normal. Middle column: On the fifth day. Brain MRI indicated left subcortical white matter of hemicerebrum lesions, which were most conspicuous with diffusion-weighted imaging (DWI). Right column: On the twelfth day, the abnormal signal detected using the examination of brain MRI disappeared, and the MRI revealed mild left cerebral atrophy.
paresis. The EEG abnormality had improved. Echocardiography revealed a fusiform dilation (measuring 3.0 mm in diameter) of the right coronary artery. Thus, aspirin (3 mg/kg) was administered as an antiplatelet treatment for three months. At the third month, the fusiform dilation and right paresis improved. At the age of 11 months, although the mild left cerebral atrophy persisted, he could sit up on his own, pull himself up, and take his first steps, all of which are normal for his age according to the Denver Developmental Screening Test.

Discussion

Neurological involvements in KD have been infrequently reported. Transient unilateral facial nerve palsy, irritability, and lethargy are sometimes observed; however, encephalitis/encephalopathy is an extremely rare complication of KD. Although clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) has been reported as a neurological complication, there has been only one report of KD-related AESD. Our patient had a typical clinical course, and MRI confirmed AESD, for which KD was the only likely etiology.

There have been several reports on the diffusion MRI abnormalities following status epilepticus. Among them, there is an infantile subgroup that is characterized by a stereotypical clinical course and spatial distribution of the MRI lesions, designated as AESD. AESD is usually associated with infection, most often with that of the influenza virus, HHV 6, or HHV 7, and its incidence is high during infancy. Rarely, AESD may occur even in cases of non-infectious illnesses, such as in traumatic brain injury. The neurological outcomes of AESD vary from normal to mild or severe sequelae, including mental retardation, paralysis, and epilepsy. Previously reported KD-related AESD involved severe neurological sequelae.

The poor prognosis associated with the neurological outcomes of AESD is largely unknown, and an effective treatment for AESD has not been established. The effects of controlled normothermia, high-dose methylprednisolone pulse therapy, high-dose immunoglobulin therapy, continuous midazolam infusion alongside a 24-hour EEG, and edaravone administration were unclear in our patient. High-dose methylprednisolone pulse therapy is provided in acute encephalitis/

Fig. 2. Electroencephalography finding.
EEG during sleep demonstrates a left-right difference in the spindle waves and lazy activity in the left hemisphere.
encephalopathy (associated with influenza virus infection) and as the second line of treatment for KD. Controlled normothermia, continuous midazolam infusion alongside a 24-hour EEG, and edaravone administration are provided in acute encephalitis/encephalopathy (such as that associated with the influenza virus infection).\textsuperscript{11} Edaravone is a free radical scavenger that interacts biochemically with a wide range of free radicals.\textsuperscript{12} CSF-8-OHdG levels decreased after edaravone treatment, and this treatment is expected to be partially effective for AESD associated with HHV-6.\textsuperscript{13} Since an established treatment for AESD is unavailable, we speculated that the above mentioned treatments may be effective for our patient.

The good neurological prognosis of our patient, as compared to that previously reported, was thought to be due to the unilateral nature of the lesion in the brain MRI. We must document more cases of KD-related AESD. We hope to develop a strategy for treatment and the analysis of neurological prognosis in such cases.

In conclusion, it is important that pediatricians acknowledge that encephalitis/encephalopathy, such as AESD and MERS, can occur in patients with KD, an acute febrile systemic vasculitis not directly associated with a pathogen. Further clinical, radiological, and immunological studies are necessary to clarify the frequency, mechanism, and prognosis of AESD-complicated KD.

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