

Case report

Sepsis associated encephalopathy in an infant with biliary atresia

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Abstract

We describe a girl with sepsis-associated encephalopathy complicating biliary atresia. At 4 months of age, decreased consciousness and repetitive seizures of the left upper and lower extremities occurred in association with fever. *Pseudomonas aeruginosa* was cultured from blood, while bacterial culture was negative and cell counts were normal in cerebrospinal fluid. The interleukin-6 level in the cerebrospinal fluid was markedly elevated. MRI revealed unilateral subcortical white matter lesions in the right hemisphere. She was diagnosed as having sepsis-associated encephalopathy and was treated with dexamethasone and midazolam. She achieved normal psychomotor development until the last follow-up at 19 months of age, whereas mild atrophic changes were observed in the right hemisphere.

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1. Introduction

Sepsis-associated encephalopathy (SAE) is defined as a brain dysfunction induced by the systemic response to an infection without a direct infectious involvement of the brain [1]. Early symptoms of SAE usually include an altered mental status preceding other organ manifestations. Although various causes, including bacterial toxins, inflammatory mediators, metabolic alterations, and abnormalities of cerebral circulation, are believed to be involved with the development of SAE, its pathogenesis remains poorly understood. Neuroradiological findings typically have been unremarkable in patients with SAE [1], although several studies have reported various neuroradiological abnormalities in patients with SAE [2–4].

We describe the clinical course and neuroimaging in an infant with SAE complicating biliary atresia. MRI revealed subcortical white matter lesions in the patient.

2. Patient report

A 2-month old girl was referred to our hospital because of a white stool. She had icterus and hepatosplenomegaly. Laboratory examination showed elevated hepatic function tests and bilirubin levels. She was diagnosed as having biliary atresia on the basis of ultrasonography and cholangiography. Portoenterostomy was performed at 2.5 months of age. Phenobarbital was administered for cholanerisis and predonisolone for prevention of cholangitis after surgery. However, elevated liver function tests (AST 100–160 IU/L, ALT 70–160 IU/L, LDH 250–370 IU/L), bilirubin (6.7–8.8 mg/dL), and biliary acid (170–280 μM/L) levels persisted.

Her general condition had been stable until 4 months of age, when she had pyrexia of 40.0 °C, vomiting, and

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lethargy. Septic workup, including bacterial cultures from blood, stool, urine, and cerebrospinal fluid, was performed. Ceftazidime and isepamicin were started. Later, *Pseudomonas aeruginosa* was isolated from her blood, while no pathogen was found in the stool, urine, or cerebrospinal fluid. Laboratory data showed an increased white blood cell count (36,000/ μL) and elevated C-reactive protein (25.9 mg/dL), lactate dehydrogenase (1025 IU/L), and creatinine kinase (2729 IU/L). Although AST and ALT were also elevated (735 IU/L and 314 IU/L, respectively), the platelet counts ($187 \times 10^3/\mu\text{L}$), ammonia level (67 $\mu\text{g}/\text{dL}$) and coagulation tests were within normal ranges. Blood gas analyses, glucose level, and electrolytes were within normal range. Cerebrospinal fluid analysis showed 1 cell/ μL , protein of 18 mg/dL, and glucose of 91 mg/dL.

On the same day, decreased consciousness and seizures with left eye deviation and clonic convulsions of the left upper extremity were observed. Although diazepam suppositories were administered, the seizures were not controlled. An anterior fontanel was mildly distended and mild hyperreflexia was present in the left upper and lower extremities. Meningeal signs, such as neck stiffness and Kernig's sign, were not observed. CT revealed low density areas in the right cerebral hemisphere (Fig. 1).

She was diagnosed as having SAE and treated with glycerol, intravenous dexamethasone, and a continuous infusion of midazolam. Seizures subsided at 2 days after the onset of SAE and her consciousness became alert at 4 days after the onset. Laboratory data returned to the level before the onset of fever within 4 days. During the first week, mild left hemiplegia was recognized. However, asymmetry of gross and fine movement became less clear within a month. Her general condition had been stable and no evidence of multiorgan failure was observed during the clinical course.

MRI on the third day demonstrated areas of abnormal intensity in the right cerebral hemisphere (Fig. 2). The lesions were primarily located in the subcortical

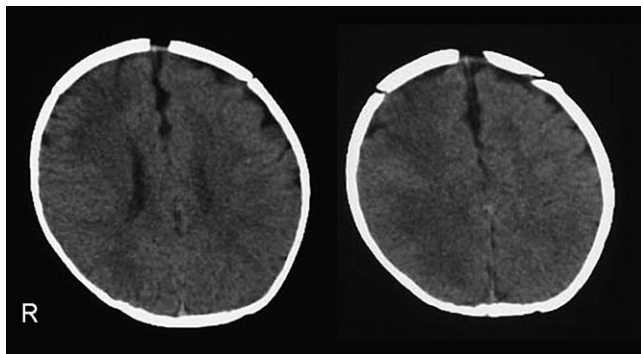


Fig. 1. Cranial CT on the day of the onset of sepsis associated encephalopathy. Low density areas were observed in the right frontal and occipital regions.

white matter in the frontal and occipital regions, and showed low intensities on T1-weighted images and high intensities on T2- and diffusion-weighted images. MR angiography did not demonstrate abnormal findings. MRI at 4 weeks after the onset of SAE revealed mild atrophic changes and abnormal high intensity areas on T2-weighted images in the same regions (Fig. 2). An electroencephalogram on the third day showed mild lazy activities in the right hemisphere. No slowing of background electroencephalographic activities was observed. The levels of interleukin-6, interleukin-4, and tumor necrosis factor- α in the cerebrospinal fluid at the onset of SAE were 151, 6.4, and 6 pg/mL, respectively.

Liver transplantation was successfully performed at 11 months of age in another hospital. Her neurological development was within normal range until the last follow-up at 19 months of age.

3. Discussion

The outstanding features of our patient were positive bacterial culture and clinico-radiologically confirmed encephalopathy, without evidence of direct infectious involvement in the central nervous system. The blood culture yielded *Pseudomonas aeruginosa*, and the girl's altered mental state, seizures, and hemiplegia indicated cerebral dysfunction. MRI revealed remarkable white matter involvement, although bacterial culture, cell counts, and protein level in the cerebrospinal fluid were within normal ranges. Elevated liver function tests and creatinine kinase were observed, but no other signs of liver failure or rhabdomyolysis was evident. Potential causes of encephalopathy, such as hypoxia, renal failure, electrolyte imbalance, and hypoglycemia, were excluded. On the basis of these clinical and laboratory findings, we believe that our patient satisfied the criteria for SAE.

The pathophysiology of SAE is still largely unknown, but many factors, including toxins from microorganisms, inflammatory mediators, metabolic derangement, and cerebral circulatory disorders, have been associated with the development of SAE [5,6]. Hotchkiss et al. reported that bacterial toxins can directly induce brain dysfunction [7], but bacterial toxins cannot pass the blood–brain barrier. Thus, inflammatory mediators are presumed to play an important role in the development of SAE [8,9]. In our patient, the interleukin-6 level in the cerebrospinal fluid was markedly elevated, despite negative bacterial culture and normal cell counts, protein and glucose levels in the cerebrospinal fluid. This suggests that cytokines induced by bacteremia participated in the pathogenesis of SAE in our patient.

Neuroradiological findings in patients with SAE are poorly understood. Vasogenic edema [1], basal ganglia-thalamic involvement [2], or cerebritis [4] have been reported as neuroradiological abnormalities of patients with SAE in the previous reports. Bartynski et al.

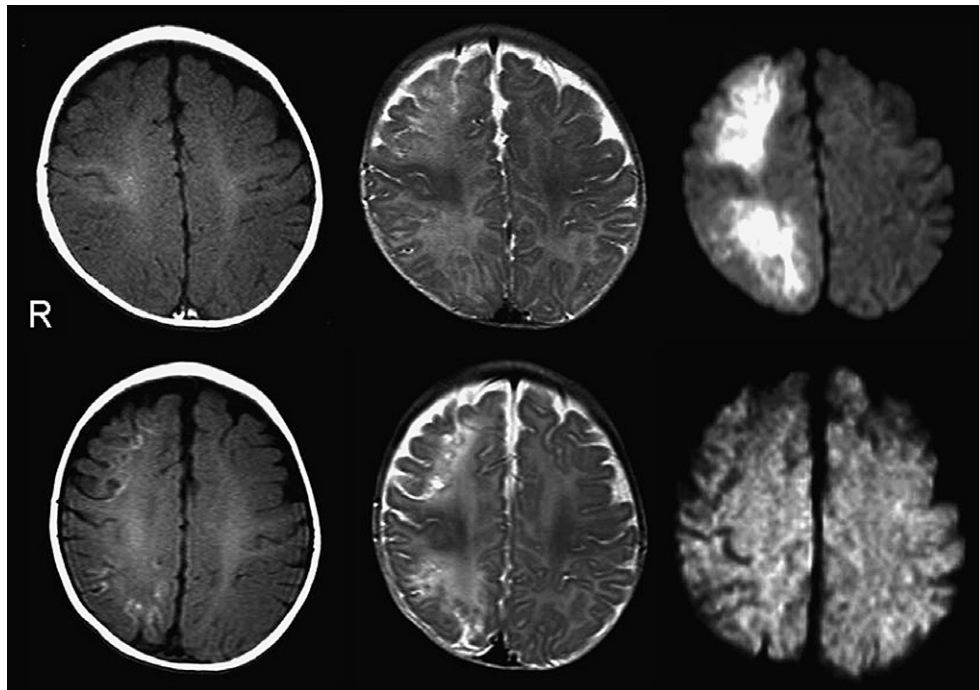


Fig. 2. Cranial MRI. Upper: MRI on the day after onset. Subcortical white matter in the right frontal and occipital regions showed abnormal low intensities on T1-weighted images (left). T2-weighted (middle) and diffusion-weighted (right) images revealed abnormal high intensities in the same regions. Lower: MRI at 4 weeks after onset. Mild atrophic changes with patchy high intensities at the depth of the gyri were seen on T1-weighted images (left). Subcortical white matter showed abnormal high intensities on T2-weighted images (middle). Abnormal high intensity areas were not recognized on diffusion-weighted images (right).

reported that posterior reversible encephalopathy syndrome can be observed in patients with isolated infection, sepsis, or shock [3]. However, no specific neuroradiological abnormalities have been described. In our patient, T2- and diffusion-weighted images revealed abnormal high intensity areas, located in the subcortical white matter in only the right hemisphere during the acute phase of SAE. These MRI findings of our patient suggest the presence of cytotoxic edema in the subcortical white matter, because increased intensities on diffusion-weighted images were more remarkable than that on T2-weighted images. Similar MRI abnormalities have been reported in hemiconvulsion-hemiplegia-epilepsy syndrome [10,11], and in acute encephalopathy due to human herpesvirus-6 [12] and -7 [13]. Interestingly, these encephalopathies were also possibly related to hypercytokinemia. This is consistent with the hypothesis that inflammatory mediators are closely related to the development of SAE.

The separated distribution of brain lesion is difficult to explain at present, although split focal lesions are not uncommon in several subtypes of acute encephalopathy [12,14,15]. Some authors suggest that excitotoxicity will play an important role in these types of brain lesions [16]. Focal production of proinflammatory cytokines following the disruption of the blood–brain barrier may also cause separated focal lesions. However, these hypotheses need to be further tested.

In summary, we describe an infant with SAE induced by *Pseudomonas aeruginosa* bacteremia. MRI revealed subcortical white matter lesions, and elevated interleukin-6 levels in the cerebrospinal fluid suggest a role for inflammatory mediators in the development of SAE.

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