

Acute encephalopathy with biphasic seizures and late reduced diffusion associated with *Streptococcus sanguinis* sepsis

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Abstract

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) develops in association with systemic as well as central nervous system (CNS) viral or bacterial infections. AESD is most often noted with influenza or human herpesvirus 6 infection in previously healthy infants. However, AESD has also been reported in an infant with developmental retardation and in a mentally and motor-disabled adolescent. Here, we report the case of a 4-year-old female with significant development delay due to spinal muscular atrophy, who developed AESD during *Streptococcus sanguinis* sepsis with no apparent CNS infection. Although the patient had extremely high serum procalcitonin (45.84 ng/mL, reference; <0.4) on admission indicating a poor prognosis, she was successfully managed for sepsis and AESD.

Introduction

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is a rare encephalopathy that is mostly reported in Japan.¹ AESD was originally described as the presentation of clinical biphasic seizures on day 1 and days 4-6 accompanied by radiological findings showing no or mild acute abnormality on days 1-2, followed by magnetic resonance imaging (MRI) findings showing reduced diffusion in subcortical white matter on days 3-9.² AESD mainly occurs in previously healthy infants, and is associated with viral infections such as influenza² or human herpesvirus 6 (HHV-6),³ as well as bacterial infections.⁴⁻⁶ AESD has also been reported in an infant with developmental retardation⁴ and in a mentally and motor-disabled adolescent.⁷ Here, we report a case of AESD caused by bacterial infection (*Streptococcus*

sanguinis [*S. sanguinis*] sepsis, but not meningitis) in a 4-year-old female with significant developmental delay.

Case Report

The patient was born full term with a birth weight of 3,184 g, and was the second-born child of her family. She was suspected to have developmental delay at the age of 6 months and was diagnosed with spinal muscular atrophy (SMA)⁸ at the age of 1 year. It was not determined if she had acute infantile SMA (type I) or chronic infantile SMA (type II).⁹ She became bed-ridden, could not roll over, and had a weak cough reflex. She had been able to take food with help, but needed biphasic positive airway pressure (BiPAP) apparatus to overcome sleep apnea syndrome until at the age of 4 years and 3 months, when she developed infection-related hemophagocytic lymphohistiocytosis (HLH; for which she fulfilled 5/8 of the clinical diagnostic criteria)¹⁰ with significantly abnormal laboratory data (serum brain natriuretic peptide >2,000 pg/mL; aspartate aminotransferase >13,000 U/L; lactate dehydrogenase >10,000 U/L; and ferritin, 7590 ng/mL), and suffered from severe dilated cardiomyopathy (Ejection Fraction, 30%; Mitral Regurgitation grade III). Fortunately, the patient survived this episode with methylprednisolone pulse therapy and hemodynamic and respiratory support. Eventually, tracheotomy and gastrostomy were performed and she was able to receive home care after discharge.

At the age of 4 years and 10 months, she was transferred to the emergency clinic with loss of consciousness associated with severe hypoglycemia (blood glucose, 10 mg/dL). On day 1 of admission, her physical condition was estimated as Japan Coma Scale (JCS) III-200 with blood pressure, 110/62 mmHg; heart rate, 106/min; respiration rate, 30/min; and SpO₂, 90% (room air). Along with persistent disturbed consciousness, the patient showed prolonged episodes of facial spasms and one-point stare-type seizures, associated with abnormal electroencephalogram (EEG), which revealed diffuse high-voltage slow wave pattern. No generalized seizures were noted. Her laboratory data were as follows: white blood cell count, 30,000/ μ L (neutrophils, 89%); Hb, 14.0 g/dL; platelet count, 421 K/ μ L; serum alanine aminotransferase, 19 U/L; lactate dehydrogenase, 360 U/L; BUN, 33 mg/dL; creatinine 0.16 mg/dL; blood glucose, 10 mg/dL; C-reactive protein (CRP), 0.13 mg/dL; procalcitonin, 45.84 (reference <0.4) ng/mL; and

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Key words: Acute encephalopathy with biphasic seizures and reduced diffusion, AESD, spinal muscular atrophy, *Streptococcus sanguinis*, sepsis.

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serum ferritin, 85 ng/mL. Blood gas showed a base excess of -8.2 mmol/L. After glucose infusion, cerebrospinal fluid (CSF) was examined, which showed cell counts of 1/ μ L; protein, 14 mg/dL; and glucose, 60 mg/dL. Tests for viral infections such as influenza A/B and HHV-6 were negative. Blood culture revealed the presence of *S. sanguinis*, thus, the patient was diagnosed as having *S. sanguinis* sepsis; however, clear CSF findings meant that she had no CNS bacterial infections. She was immediately treated with ceftriaxone, midazolam, and fosphenytoin sodium hydrate, and, from days 2 to 5, methylprednisolone pulse therapy. The above measures were effective to control sepsis, to obtain spasmodic and consciousness recovery. However, the patient lost consciousness again on day 5 in association with similar episodes of facial spasms and one-point stare seizures. This time, intravenous immunoglobulin (2 g) together with midazolam and diazepam was administered. Dextromethorphan was also given considering its efficacy for encephalopathy.¹¹ The first brain MRI (diffusion weighted imaging, DWI) taken on day 2 of admission showed mild localized

high signal intensities in the right temporal lobe and left parietal lobe (Figure 1A). However, DWI on day 5 showed bright-tree like features of bilateral generalized high signal intensities in the cerebral hemispheres, which was suggestive of severe acute encephalitis/encephalopathy in a biphasic pattern (Figure 1B). These clinical and radiological findings were compatible with the diagnosis of AESD. Although follow-up brain DWI on day 16 still showed high signal intensities bilaterally in the cerebral hemispheres, the patient gradually recovered with normal EEG findings and discharged.

Discussion

We report the case of AESD in a disabled child with SMA, which is a motor neuron disease caused by *SMN1* gene mutation. Infants with type 1 SMA, the most severe form, usually die within months or a few years due to respiratory insufficiency and bulbar paralysis.⁸ Our patient, who had respiratory problems, has survived beyond the age of 4 years old; however, during her infancy, she developed severe dilated cardiomyopathy at the time of HLH episode. Since no clear correlation has been confirmed between SMA and cardiac involvement,⁹ her cardiomyopathy could indicate one of HLH-related organ failures.¹² AESD developed in this SMA patient, 7 months after the episode of HLH.

Patients with AESD initially show a prolonged febrile seizure, which is followed by subsequent seizure occurring after several days of interval. Although the initial neu-

rologic symptoms are typically generalized seizures, but other symptoms such as non-convulsive status epilepticus,⁶ or involuntary movements are also described.¹³ It remains unknown if the partial seizures such as facial spasms/one-point stare in our case were related to SMA, in which myoclonic seizures have been reported.¹⁴ On MRI, she showed only mild DWI changes at day 2, and at day 5 typical bright-tree like characteristic DWI images. Thus, her clinical course of AESD was typical as described previously.^{1,2} In an analysis of 62 cases of AESD,¹ Tada *et al.* proposed an AESD prediction score system based on initial symptoms/laboratory data differentiating AESD from prolonged febrile seizures (mean scores 5.9 vs. 1.8 out of 9). In fact, our patient had score 4 out of 8, because mechanical ventilation was already placed for SMA.

S. sanguinis is a Gram-positive coccus and a member of the Viridans Streptococcus group. Although *S. sanguinis* is a normal inhabitant of the mouth in healthy humans, it may cause subacute bacterial endocarditis in patients even without structurally abnormal heart valves.¹⁵ In pediatrics, viridans streptococcus (including *S. sanguinis*) sepsis was mostly described in patients with cancer receiving chemotherapy.¹⁶ Our patient was not immuno-compromised, was not at risk of implantable venous port-associated bloodstream infections, and had not received specific procedures of recent dental cleaning or surgery. It is possible that her SMA-related respiratory dysfunction and HLH-induced cardiac disease became risk factors for *S. sanguinis*-induced sepsis.

Our patient developed AESD in associ-

ation with *S. sanguinis* sepsis, but with no apparent CNS infection. Indeed, encephalopathic symptoms may occur in the course of a severe bacterial infection, even in the absence of apparent signs of intracranial purulent infection.¹⁷ As a possible mechanism for sepsis-related encephalopathy, toxin-infectious process is hypothesized. Encephalopathy can be caused either by direct action of bacterial toxins or through intracerebral activation of pro-inflammatory cytokines.¹⁷ In fact, chemokines and cytokines were shown to play a role in AESD.³ *S. sanguinis* can induce human peripheral blood monocytes to synthesize pro-inflammatory cytokines by producing active proteins that bind to the CD14/Toll-like receptor 4 complex.¹⁸ Thus, it is possible that *S. sanguinis* sepsis might have caused AESD with its inflammatory cytokines in our patient.

In the management of AESD, we think that our measures were successfully achieved. Both early and subsequent seizures were controlled well with midazolam and fosphenytoin. In addition, early introduction of methylprednisolone was thought to be beneficial for her good outcome. After diagnosis of AESD was made, we employed IVIG, which effectiveness as treatment for subsequent seizure control remains to be further determined in the process of seeking most appropriate management of AESD in future.

Another interesting finding in our patient was the significantly high serum procalcitonin level (45.84 ng/mL) on day 1, which was suggestive of septic shock and predicted a poor prognosis. It is well known that procalcitonin is a better marker of sepsis than CRP.¹⁹ In terms of diagnostic and prognostic value, serum procalcitonin on day 1 has been shown to be significantly higher in patients with than without septic shock [median, 14 (0.3-767) ng/mL vs. 1 (0.5-36) ng/mL, $P < 0.01$].²⁰ In addition, a cutoff value of 6 ng/mL on day 1 separated patients who died from those who survived with 87.5% sensitivity and 45% specificity.²⁰ Thus, in patients with sepsis or septic shock, procalcitonin becomes a prognostic marker.^{20,21} Fortunately, with intensive treatments, procalcitonin of our patient declined to 0.38 ng/mL at day 8, and she survived regardless of significantly high serum levels on admission.

Conclusions

This paper describes a unique case of AESD; the patient developed *S. sanguinis* sepsis-related AESD with underlying SMA,

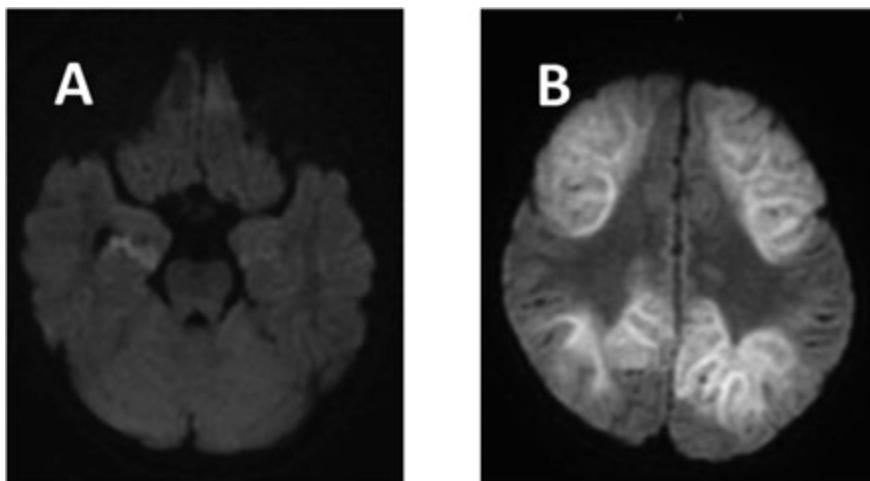


Figure 1. Magnetic resonance imaging diffusion weighted imaging on day 2 showed a localized high signal intensity in the right temporal lobe (a left parietal lobe lesion is not shown on this figure) (A) and, on day 5 showed generalized high signal intensities in the cerebral hemispheres bilaterally (B), indicating a biphasic pattern.

and fully recovered. However, since the eventual outcome of AESD is thought not to be bright,¹ we plan to carry out long-term follow-up of mental and physical development in this patient.

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