

Acute encephalopathy with callosal, subcortical and thalamic lesions

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Abstract

Acute encephalopathy is classified into multiple syndromes, such as acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) and acute necrotizing encephalopathy (ANE), characterized radiologically by lesions in the cerebral subcortical white matter, splenium of the corpus callosum and bilateral thalami, respectively. We described a previously healthy 8-year-old boy who had febrile and biphasic seizures, and encephalopathy. MRI showed abnormal signal intensity in the corpus callosum on day 2 and cerebral subcortical white matter and bilateral thalamic lesions on day 8. This is the first case of acute encephalopathy in which callosal, subcortical and thalamic lesions co-existed. The clinical course of this case was typical for AESD, atypical for MERS, and different from that of ANE.

INTRODUCTION

Acute encephalopathy is classified into many syndromes, based on clinical and MRI findings. Among these syndromes, acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is the most common in Japan, followed by clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) and acute necrotizing encephalopathy (ANE).¹ Each of these syndromes shows distinct clinical and radiological features (Table 1). However, MRI findings are variable among cases. For example, a severe case of AESD showed cerebral swelling on day 1, which is atypical for AESD.² Another case of acute encephalopathy had bilateral thalamic lesions on day 3 and cerebral subcortical white matter lesions on day 10, findings characteristic of ANE and AESD, respectively.³ Here, we report on a child with AESD whose MRI findings had features overlapping those of MERS and ANE.

CASE REPORT

The patient was an 8-year-old Japanese boy born to non-consanguineous parents. There was no past or family history of neurological disorders. He was transferred to our hospital for the treatment

of static epilepticus.

Following a high fever and acute tonsillitis, he developed repeated tonic convulsions with intermittent decerebrate posturing and altered consciousness, with a Glasgow Coma Scale (GCS) score of E1V1M1. Status epilepticus lasted for approximately 1 hour, was refractory to intravenous diazepam (0.5 mg/kg/dose), and necessitated intravenous midazolam (0.2 mg/kg/dose) and tracheal intubation.

Body temperature was 40.4°C. On neurological examination, he presented with decerebrate posturing. There was no nuchal rigidity. The pupils were equal, round, and reactive to light. The face was symmetric. He had a gag reflex, and the tongue was positioned along the midline. Reflexes were hyperactive, but plantar flexor responses were observed bilaterally. Laboratory results were as follows: white blood cell count (WBC), 16,200/ μ L (neutrophils, 13,300/ μ L); C-reactive protein (CRP), 8.79 mg/dL; Na, 132 mEq/L; K, 2.9 mEq/L; Cl, 99 mEq/L; Ca, 8.2 mg/dL; BS, 156 mg/dL; BUN, 20 mg/dL; Cr, 0.51 mg/dL; T-Bil, 0.51 mg/dL; AST, 36 IU/L; ALT, 19 IU/L; LDH, 368 IU/L; CK, 443 IU/L; lactate, 2.5 mg/dL; and NH₃, 26 mmol/L. In the cerebrospinal fluid (CSF), pressure was 27 cmH₂O, cell count

1/mm³, protein 21 mg/dL, glucose 109 mg/dL, and Cl 119 mEq/L. Throat, blood, urine and CSF cultures were negative, as were herpes simplex virus DNA in CSF (PCR), influenza A/B antigen in the nasopharynx, and rotavirus antigen in stool (immunoassay).

After admission, treatment with intravenous 20% D-mannitol (20 ml/kg/day), three courses of steroid pulse therapy (intravenous methylprednisolone, 30 mg/kg/day for 3 days), and intravenous immunoglobulin (400 mg/kg/d for 2 days) were started. Ceftriaxone (120 mg/kg/day) was also administered to treat infection. On day 2 from onset, his consciousness slightly improved from E1V1M1 to E1V1M4 on the GCS. Cranial MRI showed a high signal lesion of the splenium of the corpus callosum (SCC) on diffusion-weighted images (DWI) (Figure 1). Ictal EEG showed 1-5 Hz slow waves bilaterally at the parietal and occipital dominant.

On day 3, there were four transient clusters of clonic convulsions of the bilateral extremities, each lasting for approximately 2 minutes. In addition, the consciousness deteriorated again to E1V1M1 on the GCS. The biochemical abnormalities also worsened: WBC, 12,100/ μ L; CRP, 21.5 mg/dL; Na, 145 mEq/L; AST, 118 IU/L; ALT, 68 IU/L; CK, 3545 IU/L; LDH 550 IU/L; serum interleukin-6 (IL-6), 615.32 pg/mL (<19.9); IFN- γ 15 pg/mL (<42.9); TNF- α 15 pg/mL (<11.1); and IL-10 193 pg/mL (<14.2). MRI on 8 day showed high-signal lesions bilaterally in the thalami and in the frontal and occipital white matter. The corpus callosum lesion had disappeared (Figure 2). From day 13, consciousness gradually improved. MRI on 21 day showed cerebral atrophy (Figure 3). Two

years later, he was able to eat with support, but had severe mental and motor deficits.

DISCUSSION

We here in reported an 8-year-old boy with acute encephalopathy. He had impairment of consciousness of acute onset in the early stage of a febrile infection. There was neither pleocytosis nor increased protein in CSF. Based on the laboratory and imaging findings, we excluded intracranial inflammatory disorders, such as meningitis, viral encephalitis and acute disseminated encephalomyelitis.

After admission, the patient had biphasic seizures. MRI showed SCC lesions on day 2 and cerebral subcortical and bilateral thalamic lesions on day 8. To the best of our knowledge, this is the first case of acute encephalopathy in which callosal, subcortical and thalamic lesions co-existed.

As shown in Table 1, MERS has a mild clinical course, and most patients recover completely without sequelae. SCC lesions revealed by MRI are reversible. Laboratory findings are typically normal, with the exception of hyponatremia.⁴ AESD is characterized by an initial prolonged febrile seizure followed by a cluster of partial seizures several days later. While no acute abnormalities are visible on MRI during the first two days, MRI findings show a high intensity of subcortical white matter appearing around the time of the later seizures. Organ failure does not typically develop in AESD.⁵ ANE typically shows diffuse edema and multiple focal lesions of edematous necrosis which are symmetrically distributed in the bilateral thalami and other brain

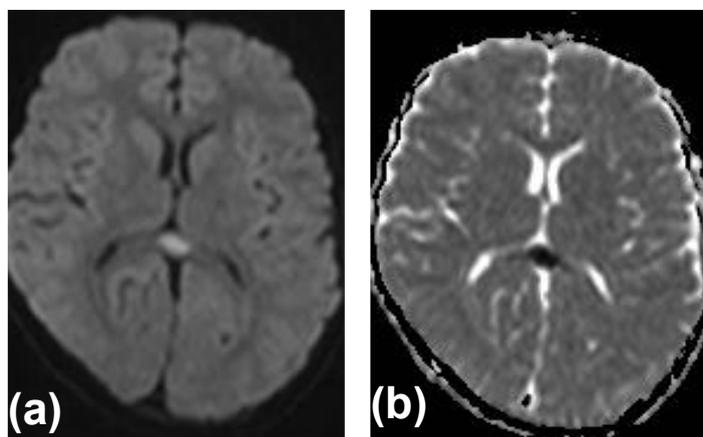


Figure 1 MRI on day 2. (a) Diffusion-weighted imaging (DWI) showed a lesion of restricted diffusion in the midline of the splenium of corpus callosum. (b) The lesion showed a reduction of apparent diffusion coefficient (ADC).

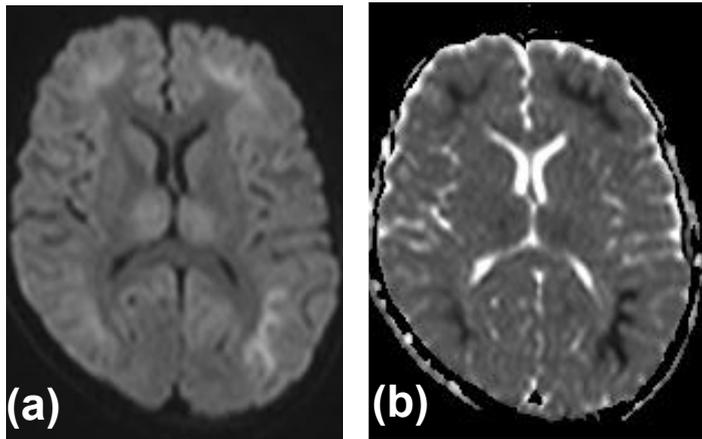


Figure 2 MRI on day 8. (a) DWI showed lesions of restricted diffusion in the bilateral thalami and subcortical white matter of the frontal and occipital lobes. The corpus callosum lesion had disappeared. (b) The lesions showed reduction of ADC, mild in the thalamus and moderate in the subcortical white matter.

regions. Petechial hemorrhage occurs at the central thalamic region at the onset of encephalopathy. The clinical course of ANE is monophasic and fulminant, with a rapid onset of convulsions and impaired consciousness. Multiple organ failure often develops in ANE, as evidenced by elevated AST and LDH, thrombocytopenia and DIC.⁶ According to these clinical data, several reports have implicated cytokine storm in the pathogenesis of ANE. Ichiyama *et al.* reported that the serum IL-6 level exceeds 1,000 pg/ml in ANE⁷, but not in AESD.⁸

In the present case, the callosal and subcortical lesions on MRI had features commonly noted in MERS and AESD, respectively. With regards to clinical course, the present case had features typical of AESD such as febrile status epilepticus at onset and clusters of partial seizures 2 days

later. Our patient had refractory convulsions in the acute period and severe neurological deficits in convalescence, both of which are incompatible with the diagnosis of MERS. The clinical significance of callosal lesions in this case remains obscure. These lesions are most often associated with MERS, but are also observed in a variety of neurological conditions with or without status epilepticus. Previous studies have suspected the pathogenesis as intramyelinic edema, in association either with inflammatory infiltration, hyponatremia, acute cerebral edema and hypoxic cerebral damage.^{4,5}

AESD is characterized by the biphasic clinical course and neuroradiologic findings of cerebral cortical involvement. In typical cases, cranial CT/MRI is normal immediately after the initial seizure (on day 1-2), but shows cerebral cortical edema

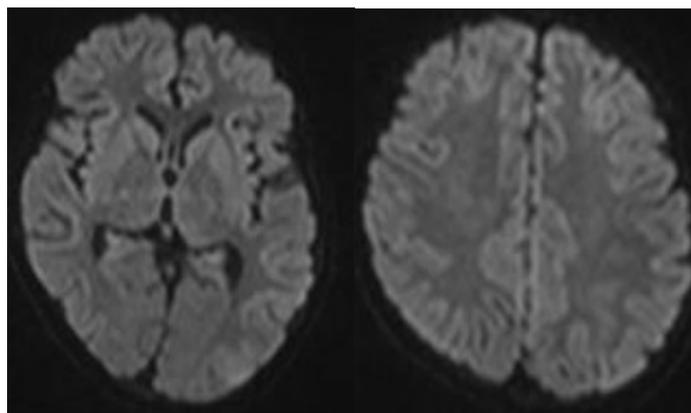


Figure 3 MRI on day 21. DWI showed atrophy of the bilateral cerebral hemispheres.

Table 1: Summary of clinical, cerebrospinal fluid (CSF) and MRI findings and outcome of acute encephalopathy

	Clinical findings	CSF findings	MRI findings	Outcome¹
AESD	Biphasic clinical course with early seizure (prolonged febrile seizure on day 1) and late seizure (cluster of partial seizures on day 3-9), each followed by coma.	No pleocytosis	Normal on initial imaging (after early seizure). Cerebral edema with restricted diffusion in the subcortical white matter on subsequent imaging (around late seizure).	Recovery in sequelae, such as intellectual deficit, motor paralysis and epilepsy, in 66% and death in 1%.
MERS	Transient alteration of consciousness, abnormal behavior and seizures. Recovery within ten days in most cases.	No pleocytosis	Transient restricted diffusion in SCC.	Recovery in 90%, sequelae in 7% and no death.
ANE	Rapid evolution of coma with seizures and signs of increased intracranial pressure and systemic organ damage.	No pleocytosis. Increase in protein.	Symmetric lesions in the bilateral thalami. Lesions also common in the cerebral periventricular white matter, internal capsule, putamen, upper brain stem tegmentum and cerebellar medulla.	Recovery in 13%, sequelae in 56% and death in 28%.
Our case	Onset with impaired consciousness and seizures with fever. Biphasic clinical course.	No pleocytosis.	SCC lesions on day 2, and cerebral subcortical and bilateral thalamic lesions on day 8.	Severe sequelae

AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; MERS, clinically mild encephalitis/encephalopathy with a reversible splenial lesion; ANE, acute necrotizing encephalopathy; SCC, splenium of the corpus callosum.

with restricted diffusion of the subcortical white matter (termed “bright tree appearance”) around the second cluster of seizures (on day 3-9).⁹ The most plausible explanation of this finding is excitotoxicity, as evidenced by the increase in glutamine/glutamate complex detected by MR spectroscopy.⁹ Severe cases of AESD have profound neurologic sequelae, such as intractable epilepsy and motor and intellectual deficits. MRI in such cases often shows widespread cortical lesions and/or basal ganglia/thalamic lesions, such as those noted in the present case (Figure 2).¹⁰

The thalamic lesions of this patient lacked many features characteristic of ANE, such as the early appearance of brain lesions within 48 hours after onset, marked swelling and/or central hemorrhage of the thalamic lesions and normal apparent diffusion coefficient.^{6,9} In addition, the biphasic clinical course, absence of systemic organ involvement and cytokine profiles were atypical of ANE. On the other hand, Takanashi *et al.* reported 4 out of 17 patients with AESD had thalamic lesions, in addition to the subcortical lesions.¹⁰ Therefore, the thalamic lesions in our current case may be associated with AESD, but not with ANE.

We described here the first case of acute encephalopathy with callosal, subcortical and thalamic lesions visualized by MRI. Clinical course, biochemical studies and CSF studies revealed characteristics of AESD, but not those of MERS or ANE.

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