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Case Report

Fulminant acute disseminated encephalomyelitis in children

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Abstract

Acute disseminated encephalomyelitis (ADEM) is a typically monophasic inflammatory demyelinating disease of the central nervous system with a favorable outcome. However, 2% of ADEM involves acute hemorrhagic leukoencephalitis (AHLE), which is a fulminant and hyperacute variant of ADEM with a poor outcome and high mortality. There are limited case reports of fulminant ADEM including AHLE in children. Herein, we report two pediatric cases of fulminant ADEM. Both cases had a rapid deterioration of consciousness, repetitive seizures, and brain edema on neuroimaging, in addition to atypical neuroradiological findings on magnetic resonance imaging (MRI), a reversible splenial lesion in case 1, and bilateral frontal and occipital cortical lesions in case 2. Both cases were treated with early high-dose methyl-prednisolone and immunoglobulin, while therapeutic hypothermia was also initiated in case 2 after the patient exhibited a decerebrate posture and irregular breathing pattern. Both cases had a favorable outcome. Further case reports on pediatric fulminant ADEM are required to clarify the various clinical types, and to examine the efficacy of various treatment modalities for fulminant ADEM and AHLE in children.

Keywords: Acute disseminated encephalomyelitis (ADEM); Fulminant ADEM; Acute hemorrhagic leukoencephalitis (AHLE); High-dose methylprednisolone (mPSL); Therapeutic hypothermia

1. Introduction

Acute disseminated encephalomyelitis (ADEM) is a typically monophasic inflammatory demyelinating disease of the central nervous system with a good prognosis. However, 11% of pediatric patients with ADEM have neurological sequelae, including acute hemorrhagic leukoencephalitis (AHLE) in 2% of cases [1]. AHLE is considered to be a fulminant and hyperacute variant of ADEM, with a poor outcome and high mortality [1]. It remains unclear whether AHLE is part of a spectrum of ADEM diseases or a different clinical entity, largely because of the paucity of case reports of fulminant ADEM in children [2,3].

High-dose intravenous glucocorticoids are widely used for ADEM, although without evidence from large prospective randomized clinical trials. Intravenous methylprednisolone (mPSL) was also used successfully in some AHLE cases [2]. Furthermore, other add-on treatment modalities for AHLE patients, including intravenous immunoglobulin (IVIG), cyclophosphamide, plasma exchange, therapeutic hypothermia, and craniotomy were reported to be effective in a handful of case reports [3,4]. Furthermore, there are only two reported pediatric cases of fulminant ADEM treated

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with therapeutic hypothermia [5,6]. Herein, we report two pediatric cases of fulminant ADEM in our institution with atypical neuroradiological findings, one of which was treated with therapeutic hypothermia. This study was approved by the institutional ethic committee at St. Mary's Hospital. There are no conflicts of interest to disclose.

2. Case report

Case 1 was a previously healthy 8-year-old boy admitted to our hospital with headache and intermittent altered mental status at 3 days after the onset of high fever, abdominal pain, and diarrhea. He was occasionally disoriented, with inappropriate use of words, and exhibited a Glasgow Coma Scale (GCS) of 14 (E4V4M6). His neurological examination was otherwise normal. Blood test showed 17.0×10^9 white blood cells/L (78% polymorphonuclear leukocytes) and elevated C reactive protein (16.8 mg/dL). Head computed tomography (CT) on admission revealed no abnormal findings. The patient was initially diagnosed with febrile delirium associated with appendicitis based on his peritoneal irritation signs and abdominal CT findings. On the 2nd hospital day, he had a decreased consciousness and generalized tonic-clonic seizures three times despite phenytoin administration, which ceased after intravenous diazepam, midazolam, and thiamylal administration, followed by continuous midazolam infusion. He underwent appendectomy and peritoneal lavage under general anesthesia, without respiratory and hemodynamic problems. Electroencephalography showed abnormal generalized slow waves and hemispherical spike-and-wave discharges. Fluid-attenuated inversion recovery (FLAIR) on brain magnetic resonance imaging (MRI) on the 3rd hospital day showed diffuse swelling of the cerebral parenchyma, narrowing of the lateral and third ventricles, and sulcal hyperintensity because of sulci narrowing (Fig. 1A–C). Hyperintense FLAIR lesions were also observed in the bilateral periventricular and subcortical white matter, thalamus, caudate nucleus, external capsule, midbrain, pons, dorsal lateral medulla oblongata, and cerebellar hemisphere (Fig. 1A–C). Diffusion-weighted imaging (DWI) showed hyperintense lesions in the corpus callosum (Fig. 1D) and subcortical white matter. Cerebrospinal fluid (CSF) examination showed increased cells (91/μL; with 41% lymphocytes), protein (230 mg/dL), and myelin basic protein (1270 pg/mL, normal range: 0–102 pg/ml). A presumptive diagnosis of ADEM was made, and intravenous mPSL (30 mg/kg/dose for 3 days) and IVIG (1 g/kg/dose) were started. Head CT on the 4th hospital day showed a low-density area and swelling of the brainstem and both cerebral hemispheres. Mannitol administration was initiated, and he was mechanically ventilated for 1 week. His level of consciousness gradually

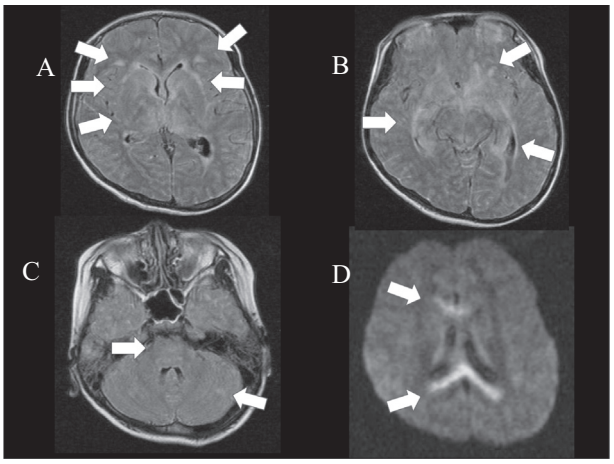

Fig. 1. Magnetic resonance imaging (MRI) on the third hospital day in case 1. (A–C) Fluid attenuated inversion recovery (FLAIR). (D) Diffusion-weighted imaging (DWI). FLAIR showed hyperintense lesions (arrow) in the bilateral periventricular and subcortical white matter, thalamus, caudate nucleus, external capsule (A, B), midbrain (B), pons (C), and cerebellar hemisphere (C), in addition to diffuse swelling of the cerebral parenchyma, narrowing of the lateral and third ventricles, and sulcal hyperintensity because of narrowing of sulci. DWI showed hyperintense lesions (arrow) in the corpus callosum (D).

improved after cessation of sedatives. Subsequent examination revealed right facial palsy, right abduction nerve paralysis, right hemiparesis, and bilateral increased deep tendon reflexes and Babinski signs. Microbiological study revealed no remarkable results. He was discharged home with no residual motor or sensory deficits on the 47th hospital day. T2-weighted MRI imaging (T2WI) at 2 months after onset revealed hypointensity lesions in the left thalamus and left pons, which were confirmed to be chronic hemorrhage by T2*WI at 2 years after

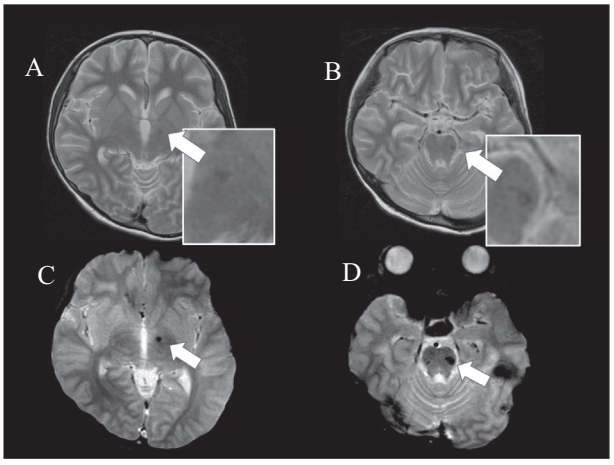

Fig. 2. MRI at 2 months and 2 years after disease onset in case 1. (A, B) T2-weighted MRI imaging (T2WI) at 2 months after onset. (C, D) T2*WI at 2 years after onset. T2WI at 2 months after onset revealed dilated ventricles and sulci, and low intensity lesions (arrow) in the left thalamus (A) and left pons (B). T2*WI at 2 years from onset revealed that these lesions were chronic hemorrhages (C, D, arrow).

onset, in addition to the dilated ventricles and sulci (Fig. 2A–D). He scored 81 in the Wechsler Intelligence Scale for Children-III edition, with occasional aggressive behavior and socially inappropriate words at 3 years after disease onset.

Case 2 was a previously healthy 15-month-old girl, who exhibited status epilepticus on the 5th day of fever and was brought to a referring hospital. Brain MRI showed white matter lesions, with increased apparent diffusion coefficient signal and FLAIR, but normal DWI signals, in the bilateral frontal, temporal, and occipital regions (Fig. 3A and B). She was transferred to our hospital that day, and neurological examination revealed lethargic state with a GCS of 9 (E2V2M5), increased deep tendon reflexes in four extremities, and positive bilateral Babinski signs. She had had an influenza vaccination 1 month prior. She had no hypertensive episodes or renal diseases before admission. Blood test showed 8.6×10^9 white blood cells/L (with 47.5% polymorphonuclear leukocytes) and elevated C reactive protein (0.7 mg/dL). CSF examination revealed increased cells (14/μL; with 100% lymphocytes), normal protein (24 mg/dL), and normal myelin basic protein (50.9 pg/mL, normal range: 0–102 pg/ml). Electroencephalography showed generalized high-voltage continuous delta waves. She was diagnosed with ADEM, and intravenous mPSL (30 mg/kg/dose for 3 days) and IVIG (1 g/kg/dose) administration was initiated on the 1st hospital day. However, her conscious level deteriorated (GCS5; E1V2M2). She had three seizure episodes despite fosphenytoin administration, and each seizure ceased after diazepam intravenous administration. She started to exhibit a decerebrate posture and irregular breathing pattern on the 2nd hospital day, and brain CT on that day (Supplementary Fig. S1A) revealed global cerebral edema and low intensity areas in the white matter in both hemispheres, including the lesions previously confirmed by MRI taken at a previous hospital (Fig. 3A). Mannitol administration and therapeutic hypothermia (34 °C) for 72 h were initiated. She had no hypertensive episodes throughout the disease course, and brain CT on the 5th hospital day showed improved cerebral edema (Supplementary Fig. 1B). However, although brain MRI on the 9th hospital day showed no change in the demyelinating areas seen on previous MRI, DWI revealed a hyperintensity in the cortical and subcortical regions in the bilateral occipital (Fig. 3C), and the cortical rigions in the frontal lobes (Fig. 3D). Apparent diffusion coefficient map on the same day showed cortical hypointensity, and hyperintensity in the adjacent subcortical white matter in the bilateral occipital lobes (Fig. 3E). FLAIR also showed a hyperintensity in the cortical and subcortical regions in the bilateral occipital lobes (Supplementary Fig. 2A). Her consciousness disturbance improved, and she was discharged home on the 27th hospital day with mild muscle weakness of both legs, which later improved completely. At 40 days after onset of neurological symptoms, MRI showed no abnormal findings including MR angiography, except for the small demyelinating lesions in the left frontal lobe, which completely disappeared at three months after the onset. Her overall developmental quotient was 88 (Postural-Motor, 124; Cognitive-Adaptive, 86; Language-Social, 76) in the Kyoto Scale of Psychological Development 2001 at 6 months after disease onset.

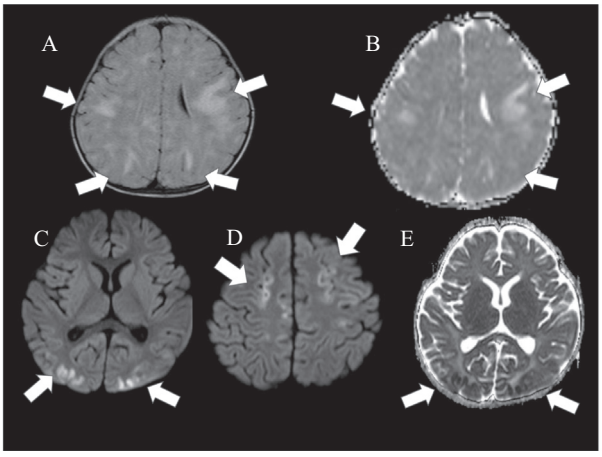

Fig. 3. Serial MRI taken at a previous hospital at the onset of the neurological symptoms and on the 9th hospital day in case 2. (A) FLAIR and (B) Apparent diffusion coefficient (ADC) at the same level taken at a previous hospital at the onset of the neurological symptoms. (C, D) DWI and (E) ADC map at the same level as (C) on the 9th hospital day. FLAIR and ADC map taken at a previous hospital showed hyperintense white matter lesions in the bilateral frontal, temporal, and occipital regions (A, B, arrow). DWI on the 9th hospital day showed hyperintensity in the cortical regions in the bilateral occipital (C, arrow) and frontal lobes (D, arrow), as well as hyperintensity in the subcortical regions in the bilateral occipital lobes (C, arrow), which were considered as 'T2-shine through'. ADC map on the same day showed hypointensity in the cortices, and hyperintensity in the adjacent subcortical white matter in the bilateral occipital lobes (E, arrow).

3. Discussion

We report two cases of fulminant ADEM in children, both of whom had a rapid deterioration of consciousness, repetitive seizures, and brain edema on neuroimaging, in addition to atypical neuroradiological findings. Case 1 had a reversible splenial lesion, while case 2 had bilateral frontal and occipital cortical lesions, as revealed by MRI. Therapeutic hypothermia was initiated in case 2, in addition to high-dose mPSL and IVIG administration, as her decerebrate posture and irregular breathing pattern suggested a raised intracranial pressure. Both cases had only mild neurological deficits as a long-term outcome.

In case 1, impaired consciousness, increased cells in the CSF, and MRI abnormalities in white matter, deep

gray matter, cerebellum, and brainstem were indicative of ADEM. The hypointense lesions in the left thalamus and left pons on T2WI and T2*WI at follow up (Fig. 2A–D) were considered to reflect chronic hemorrhage, which was suggestive of AHLE. Clinical and paraclinical features to discriminate between patients with AHLE or ADEM include a rapid deterioration of consciousness (a few days), cerebral edema or hemorrhage of brain imaging, and pathological findings with perivascular hemorrhagic demyelinating lesions and neutrophilic inflammatory infiltrates [7]. However, MRI findings do not always distinguish AHLE from ADEM, as no evidence of hemorrhage on MRI was previously reported in some cases of proven AHLE at autopsy [7]. Restricted diffusion in the corpus callosum and subcortical white matter are characteristics of mild encephalitis/encephalopathy with a reversible splenial lesion, which has a mild clinical presentation and favorable outcome without neurological deficits. However, MRI findings for case 1 differed, with presence of basal ganglia and brain stem lesions (Fig. 1A–D).

Case 2 was diagnosed with ADEM based on the updated ADEM criteria by the International Pediatric Multiple Sclerosis Study Group in 2013, which included a first polyfocal clinical central nerve system event with presumed inflammatory demyelinating cause, encephalopathy, brain MRI abnormalities consistent with demyelination during the acute phase, and no new clinical or MRI findings 3 months or more after the onset. She had altered mental status, signs of pyramidal tract involvement, mild increased cells in the CSF, and diffuse bilateral and vaguely marginated polyfocal white matter lesions, mainly affecting the juxtacortical and deep white matter, in both cerebral hemispheres on MRI in the acute phase, part of which remained at 40 days after onset, without new clinical or MRI findings 3 months or more after onset. The cortical lesions with restricted diffusion on the 9th hospital day (Fig. 3C and D) were considered encephalitis accompanied by ADEM. Encephalitis with bilateral cortical lesions was reported in several cases of myelin oligodendrocyte glycoprotein (MOG) antibody associated demyelination [8]. Children with ADEM with MOG antibody were also reported to have almost similar clinical presentation to children with ADEM without MOG antibody except for MRI characteristics of large, hazy and bilateral lesions with an increase frequency of longitudinal extensive transverse myelitis, lower CSF cell count, less often emotional or behavioural problems at initial presentation, and favorable clinical outcome [9]. We did not examine by a spinal MRI or serum CSF MOG antibodies in case 2 because of no presence of spinal symptoms except for signs of pyramidal tract involvement, although serum anti-aquaporin 4 antibody by enzyme-linked immunosorbent assay at admission was negative. It is also important to differentiate these lesions from posterior reversible leukoencephalopathy syndrome (PRES), as high-dose mPSL, which was started on the 1st hospital day in this case, and hypertension, are commonly associated with this disease. PRES is a reversible condition related to vasogenic edema in the parieto-occipital regions, with a clinical presentation of headache, alterations in consciousness, visual disturbances, and seizures. Patients with extreme PRES may also exhibit coma and areas of signal abnormality consistent with ischemia on neuroimaging, which progress to true infarction [10]. However, we excluded the diagnosis of stroke associated with extreme PRES for these lesions, as the hyperintense areas on DWI were only confined to the cortices, there were no abnormal findings on following MR angiography, and there was complete disappearance of the cortical lesions, but prolonged white matter lesions, in the left frontal lobe, which remained on MRI at 40 days after onset.

Recently, pathological evidence of primary astrocyte damage with secondary demyelination was reported in an AHLE patient [11], suggesting that therapeutic hypothermia may be useful for AHLE patients by suppressing the glial excessive activation [12]. Therapeutic hypothermia may also be an option for neuroprotection, as well as for decreasing raised intracranial pressure, in fulminant ADEM. Although therapeutic hypothermia has several side effects, including hypotension, suppression of the immune and digestive systems, and mild coagulopathy, the majority are easily controlled in a pediatric intensive care unit. In case 2, the patient had no serious side effects during therapeutic hypothermia, and exhibited milder long-term neurological deficits than initially expected from her symptoms. However, further pediatric fulminant ADEM cases are required to understand the clinical and radiological features, and develop evidenced-based treatments for fulminant ADEM in children.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2018.11.007.

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