

Unusual presentation of acute encephalopathy with biphasic seizures and late reduced diffusion in Miller–Dieker syndrome

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Case report

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Abstract

Background: Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is a unique subtype of acute encephalopathy that occurs in children. To date, there is no description of a patient with concurrent Miller–Dieker syndrome (MDS) and AESD. **Case presentation:** We present a case of 2-year-old girl with MDS, who was admitted for status epilepticus with a high fever, was diagnosed with AESD. She exhibited seizure for more than 1 h, which disappeared after administration of intravenous diazepam and phenobarbital. Brain magnetic resonance imaging (MRI), performed on the third day post-admission because she had not regained consciousness after the seizure ceased, showed abnormally high intensities in subcortical white matter, predominantly in the frontal areas on diffusion-weighted images (DWI). Acute encephalitis/encephalopathy was diagnosed based on electroencephalography (EEG) findings of diffuse high-voltage delta waves without seizure activity. Six days post-admission, frequent apneic episodes were observed, with oxygen desaturation due to clustered seizures. Although seizures disappeared with continuous intravenous midazolam, subclinical seizures were present in amplitude-integrated EEG (aEEG); these were suppressed by increasing the midazolam dose. **Conclusion:** This is the first report of AESD in a patient with MDS. The disturbance of consciousness was difficult to recognize because of severe motor and intellectual disabilities due to MDS. EEG aids the evaluation of consciousness in the acute phase, and aEEG can be helpful for monitoring and controlling subclinical seizures in the biphasic phase of AESD, especially patients with underlying neurological disorders.

Background

Miller–Dieker syndrome (MDS) is a contiguous gene deletion syndrome of chromosome 17p13.3, characterized by classical type I lissencephaly, severe developmental delay, seizures, cardiac defects and dysmorphic facial features including bitemporal hollowing, prominent forehead, furrowed brow, short nose with anteverted nares, prominent upper lip, and small jaw [1-3]. Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is an established encephalopathy syndrome that is diagnosed based on its clinical manifestations and imaging findings [4, 5]. Acute encephalopathy/encephalitis, including AESD, has not been reported in patients with MDS, although central nervous system symptoms, including epilepsy, are common. Herein, we describe the neurophysiological and neuroimaging findings of a patient with MDS who developed AESD, which is a unique subtype of acute encephalopathy in children.

Case Presentation

A girl aged 2 years and 8 months was born at 37 weeks of pregnancy with a birth weight of 1844 g and was admitted to the neonatal intensive care unit due to low birth weight and respiratory distress. MDS was diagnosed by brain magnetic resonance imaging (MRI) (Additional file 1) and FISH after noting microcephaly, a narrow forehead, a small nose and chin, and cardiac malformations. Her family history was unremarkable.

At the age of 5 months, she presented with repeated afebrile seizures, which led to a diagnosis of epilepsy. Before the onset of acute encephalopathy, generalized seizures occurred a few times each week; these were treated with zonisamide and levetiracetam. An awake EEG showed the background theta activity (50-150 μ V) with superimposed 18-20Hz fast activity (Additional file 2). She could pursue objects and ingest food orally, but could not hold her head up and exhibited severe motor and intellectual disabilities.

At the age of 2 years and 8 months, she was admitted to the hospital in status epilepticus with a fever of 40°C. The seizure continued for more than 1 h until intravenous diazepam and phenobarbital were administered. Three days post-admission, MRI was performed because she had not opened her eyes and was minimally responsive to stimulation, despite the disappearance of the seizures. Her Glasgow Coma Scale (GCS) score was 5/15 (E1V1M4), indicating severe injury. Diffusion-weighted imaging (DWI) MRI revealed abnormally high intensities in subcortical white matter, predominantly in frontal areas, and an apparent diffusion coefficient (ADC) map indicated reduced ADC values for the lesion (Fig. 1A, B). Acute encephalitis/encephalopathy was diagnosed based on electroencephalography (EEG) findings of diffuse high-voltage delta waves without seizure activity (Fig. 2A). Her cerebrospinal fluid (CSF) contained 5 cells/mm³, 10 mg/dL protein, and 66 mg/dL glucose. She was treated with methylprednisolone pulse therapy (30 mg/kg per day for 3 days), immunoglobulin (1 g/kg, one dose), and acyclovir infusion. She opened her eyes slightly 3–4 days after admission, but remained minimally responsive to stimulation. Six days post-admission, frequent apnea episodes were observed, with oxygen desaturation for approximately 30 s, which were sometimes accompanying jerking of eyelid. Amplitude-integrated EEG (aEEG) monitoring indicated that the apnea episodes were caused by seizures (Fig. 2B), and AESD was diagnosed based on the clinical course. The apnea episodes were suppressed by continuous intravenous midazolam (0.18 mg/kg/h); then, subclinical seizures were detected via aEEG monitoring. These were controlled by increasing the dose of continuous intravenous midazolam (0.27 mg/kg/h) (Fig. 2B). DWI MRI revealed diffuse abnormally high intensities in subcortical white matter (Fig. 1C, D). Rapid antigen tests for influenza and respiratory syncytial virus were negative. Antibodies to herpes simplex virus and Epstein-Barr virus were negative. CSF and blood samples were negative for herpes simplex virus in polymerase chain reaction analyses. No apnea episodes were noted after continuous intravenous midazolam was discontinued, 11 days post-admission. Twenty-nine days post-admission, MRI revealed brain atrophy and abnormally high intensities in diffuse subcortical white matter. The patient was discharged from our hospital at 35 days post-admission. One year post-admission, she could no longer pursue objects and required tube feeding. She had generalized brief tonic seizures more than 10 times a day despite therapy with anticonvulsant agents.

Discussion And Conclusions

AESD is an established encephalopathy syndrome that is diagnosed based on its clinical manifestations and imaging findings. The initial presentation includes a prolonged febrile seizure, followed by a cluster of subsequent seizures several days later (biphasic seizures). When consciousness deteriorates 3 to 7

days after the onset of AESD, MRI shows restricted diffusion that most frequently involves frontal or frontoparietal subcortical white matter, while sparing the perirolandic cortex (so-called bright tree appearance) [4, 5]. In the present case, a cluster of subsequent seizures and high DWI signals in subcortical white matter were recognized 5 days after she had presented with status epilepticus with a high fever. This clinical course was consistent with a diagnosis of AESD. The imaging findings, which were unique due to lissencephaly in MDS, were considered to be equivalent to bright tree appearance.

Patients with underlying neurological disorders were present in 14/55 acute encephalopathy cases (25.4%), would have a propensity for augmented neuronal hyperexcitability in acute encephalopathy, such as AESD and hemiconvulsion-hemiplegia syndrome [6]. In our case, the disturbance of consciousness was not discovered until 3 days post-admission because of the patient's severe motor and intellectual disabilities due to MDS. Although consciousness can be evaluated easily in normally developing patients, it may be difficult to evaluate deterioration of consciousness in patients who exhibit extremely severe developmental delay. EEG might be effective for the diagnosis of acute encephalopathy when episodes involve suspected deterioration of consciousness (e.g., when reduced responsiveness after status epilepticus is recognized in a patient with severe motor and intellectual disabilities).

In the patient in the present case, the cause of apnea episodes was not determined until aEEG monitoring revealed that the episodes were related to the seizures. A previous report described a cluster of seizures that presented with apnea, accompanied by staring and bradycardia, in a patient with compatible clinical signs of biphasic seizures and who was equivocally diagnosed with AESD [7]. Komatsu reported that aEEG was useful for monitoring children with AESD; moreover, it might reveal subsequent clusters of seizures and facilitate objective evaluation of the efficacy of antiepileptic drugs [8]. In the patient in the present case, aEEG monitoring was also useful for determining appropriate treatment for seizures, as subclinical seizures remained after continuous intravenous midazolam had eliminated the apnea episodes. Furthermore, aEEG monitoring was useful for recognizing frequent apnea as a symptom of partial seizures.

In conclusion, we have described a patient with MDS who developed AESD. There have been no reports of concurrent MDS and AESD. Because disturbances of consciousness might be difficult to recognize in patients with severe motor and intellectual disabilities (e.g., MDS), EEG may be useful for evaluating consciousness. Furthermore, aEEG could enable continuous monitoring of patients with AESD, thereby aiding the appropriate evaluation of treatment efficacy.

Abbreviations

MDS: Miller–Dieker syndrome; AESD: Acute encephalopathy with biphasic seizures and late reduced diffusion; MRI: Magnetic resonance imaging; GCS: Glasgow Coma Scale; DWI: Diffusion-weighted imaging; ADC: apparent diffusion coefficient; EEG: electroencephalography; aEEG: Amplitude-integrated electroencephalography.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent

Written informed consent was obtained from the patient's parents for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Availability of data and materials

All data related to this case report are contained within the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Acquisition of data: SK, MK, AT. Drafting of the manuscript: SK, MK. Critical revision of the manuscript for important intellectual content: KY, SS. All authors read and approved the final manuscript.

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Additional File Legend

Additional file 1: MRI images at 28 days after birth: T1-weighted imaging (A) and T2-weighted imaging showed lissencephaly.

Additional file 2: An awake EEG at the age of 1 year and 7 months: EEG showed the background theta activity (50-150 μ V) with superimposed 18-20Hz fast activity.

Figures

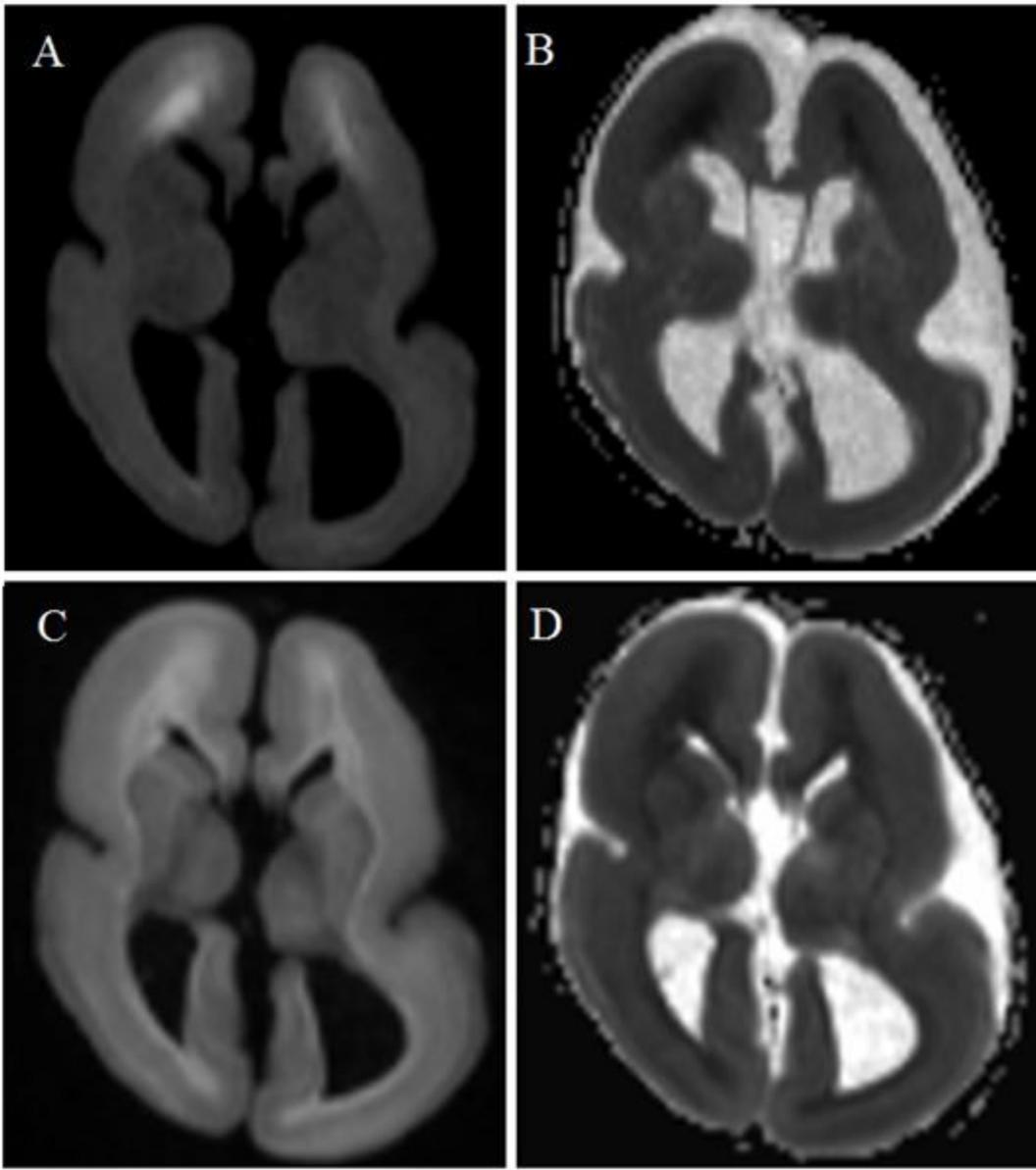


Figure 1

MRI images: On the third day post-admission, diffusion-weighted imaging (DWI) (repetition time, [TR]/echo time [TE] 2800/88, b value = 1000) (A) and the apparent diffusion coefficient (ADC) map (B) showed abnormally high intensities in subcortical white matter, predominantly in frontal areas. On the sixth day post-admission, DWI (TR/TE 2800/88, b value = 1000) (C) and the ADC map (D) showed abnormally high intensities in subcortical white matter, predominantly in frontal areas.



Figure 2

A) On the third day post-admission, electroencephalography showed diffuse high-voltage delta waves with no seizure activity. (B) On the sixth day post-admission, amplitude-integrated electroencephalography showed a “saw-tooth” (arrows) pattern, indicating seizures. The seizures were suppressed by treatment with intravenous midazolam.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CAREchecklist20190503MDSwithAESD.pdf](#)
- [AdditionalFile1.doc](#)
- [StudyTimeline.docx](#)