HK J Paediatr (new series) 2026;**31**:233-236

Case Report

Acute Encephalopathy with Biphasic Seizures and Restricted Diffusion in a Paediatric Patient: A Case Report

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Abstract We report a case of acute encephalopathy with biphasic seizures and restricted diffusion (AESD) in a two-year-old Chinese girl, who presented with biphasic seizures and characteristic imaging findings. She was started on anti-seizure medications and subsequently discharged with full neurological recovery. AESD is a rare clinico-radiological disease entity that should be considered in patients presenting with biphasic seizures; early imaging could guide the diagnosis.

Key words Acute febrile encephalopathy; Febrile seizures

Case Presentation

The patient is a two-year-old Chinese girl. She has a normal birth history, with a single episode of atypical febrile convulsion at 13 months old, and a strong family history of febrile convulsions (FC).

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Received October 30, 2025

At 24 months, she was admitted to Alice Ho Miu Ling Nethersole Hospital on 23rd September 2024, presenting with flaccid limb tone, eye-staring, and cyanosis lasting 3 minutes, followed by postictal drowsiness for one-hour. It was preceded by one day of fever up to 38.5°C. Rectal diazepam was given for seizure management. Her Glasgow Coma Scale (GCS) was 3/15 (E1V1M1) on the ambulance, improving to 13/15 (E4V4M5) in the emergency department. On exam, GCS was normal, with no meningism or focal neurological deficits. Right pincer grasp worsened from day 3, while the rest of the neurological examination and sensorium were unremarkable. Nasopharyngeal swab (NPS) revealed enterovirus/rhinovirus and Human Metapneumovirus. Complete blood count, liver and renal function tests, and ammonia were unremarkable. Creatine kinase (191, N: 2-134 IU/L) and lactate dehydrogenase (LDH) (303, N: 159-266 IU/L) were mildly raised, but subsequently normalised.

On day 5, she experienced two further seizures starting with right lower facial twitching and loss of consciousness for 30 seconds. It was followed by a generalised tonic-clonic seizure an hour later, lasting five minutes, aborted with a dose of intravenous lorazepam (0.1 mg/kg). Afterwards, she demonstrated reduced right upper limb movement with increased tone over right upper and lower limbs. Computed Tomography (CT) showed cerebral oedema in the left fronto-parietal region. Magnetic Resonance Imaging (MRI) on day 6 revealed characteristic

acute encephalopathy with biphasic seizures and restricted diffusion (AESD) changes, including 'bright tree appearance' (BTA) in bilateral asymmetric regions on diffusion-weighed imaging (Figure 1), and extensive T2 hyperintense lesions involving left frontal/parietal and mesial/lateral temporal lobes, with signal changes in the left caudate head and internal capsule (Figure 2).

Cerebrospinal fluid (CSF) after the second convulsion was acellular, with negative bacterial cultures and viral polymerase chain reaction; glucose, protein and lactate were normal. Autoimmune encephalitis antibodies (anti-CASPR2, anti-AMPA 1/2, anti-LGI1, anti-DPPX, anti-GABAR B1/B2 and anti-NMDA-R) were negative. CSF IgG level was <2.0 mg/dL. Anti-ganglioside, anti-MOG and anti-aquaporin 4 antibodies were also negative. Metabolic workup was unremarkable. Electroencephalogram (EEG) on Day 10 revealed focal cerebral dysfunction over the left hemisphere without epileptiform discharges.

The patient received antibiotics and antivirals, along with intravenous levetiracetam (20 mg/kg/day). Fever subsided on day 7, and her right-hand function improved with physiotherapy and occupational therapy. She was eventually switched to oral levetiracetam and experienced no further seizures, achieving full neurological recovery by the time of discharge after two weeks.

At follow-up assessments one-month later, EEG

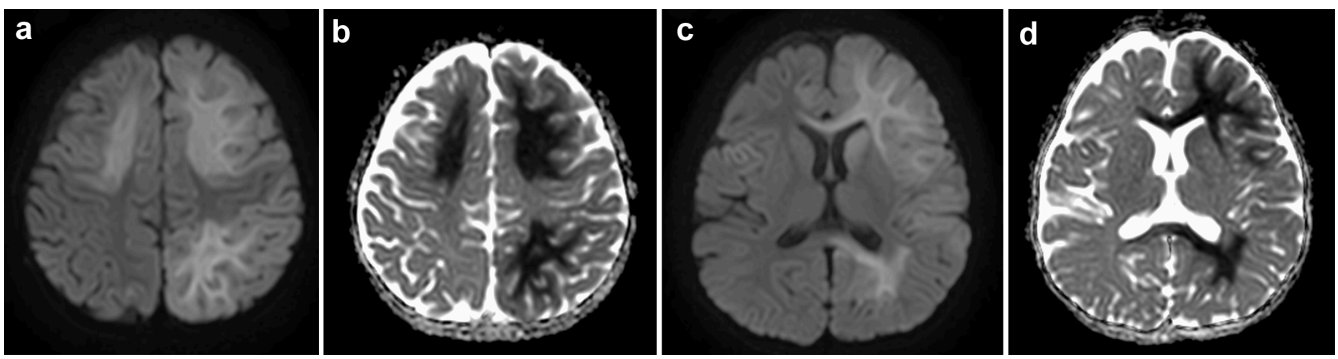

Figure 1 (a) Areas of high diffusion-weighed imaging signal predominantly involving the white matter of bilateral frontal and left parietal lobes, resembling bright tree appearance, with sparing of the perirolandic regions; (b) corresponding low signal on ADC map, in keeping with restricted diffusion; (c) confluent high diffusion-weighed imaging signal is seen extending to the genu and splenium of corpus callosum; (d) corresponding low signal on ADC map, in keeping with restricted diffusion.

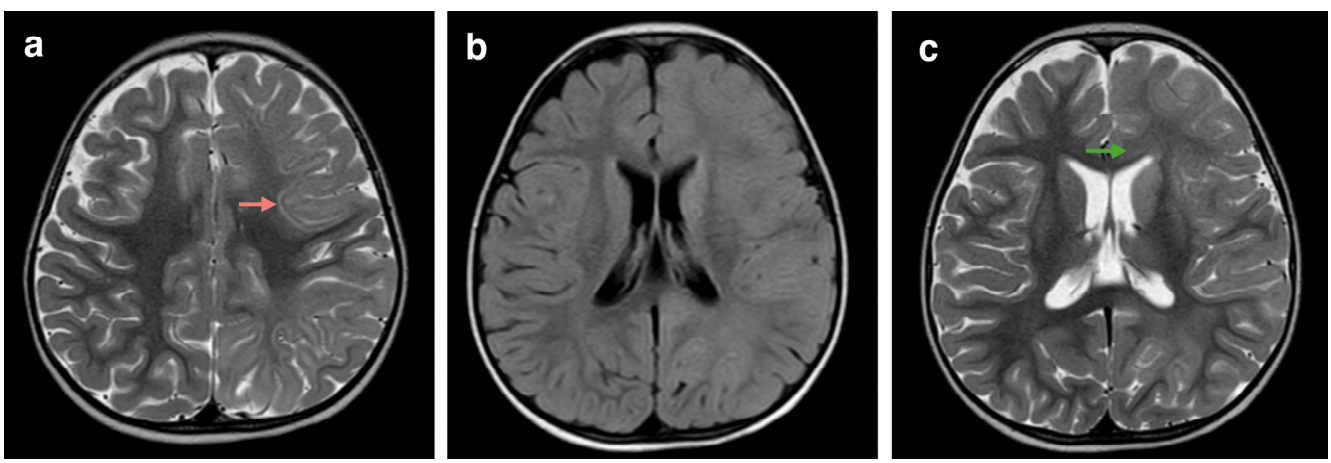

Figure 2 (a) & (c) Abnormal mildly T2 hyperintense signal involving the left frontal and parietal white matter with extension to the corpus callosum; (b) corresponding areas of abnormality appear mildly hyperintense on FLAIR sequence.

indicated mild left-sided attenuation, suggesting persistent dysfunction. Repeat MRI showed resolution of the BTA lesions, with residual white matter signals over the left basal ganglia and cerebral atrophy. Whole Exome Sequencing (WES) for the proband and her parents revealed no monogenic epilepsy-related mutations. She regained full right-hand function and attained normal developmental milestones without regression.

In the previous episode of atypical FC at 13 months of age, the patient required Pediatric Intensive Care Unit admission in Princess Margaret Hospital. She exhibited left upper limb twitching, cyanosis, and right-sided eye deviation lasting 43 minutes. It was preceded by a high-grade fever of 40°C with coryzal symptoms. NPS confirmed Influenza B; CT brain was normal and EEG revealed no epileptiform discharges or encephalopathy. She was treated with oseltamivir and fully recovered without further seizures. Development at 17 and 21 months was normal.

Notably, there is a strong family history of FC. Her mother experienced three episodes requiring hospitalisation before the age of two and required anti-seizure monotherapy until age six. The mother's twin sister had an episode of FC at age six; both the maternal grandmother's younger brother and her paternal aunt's son had recurrent FC before age five. Her parents are both Chinese and non-consanguineous.

Discussion

We report a case of AESD with a strong maternal family history of seizures. AESD is a childhood seizure disorder presenting with febrile status epilepticus with a recovery period, followed by a second phase of focal seizures with impaired consciousness 3-9 days later. In half of the cases, the initial convulsion is prolonged, with a median duration of 53 minutes. In our case, the initial seizure was relatively brief and was followed by right-sided hemiparesis, making the diagnosis challenging. While the global incidence is unknown, the majority of cases occur in Japan with 100-200 cases documented annually.[1] Around one-third of patients presenting with AESD have a past medical history of febrile seizures. Viral infections such as Influenza, Human Herpesvirus and Hand-foot-mouth disease have been identified as triggers in up to one-third of cases. HMPV, as seen in our case, has only rarely been reported as a cause of encephalopathy, including AESD.[2] Fatalities are rare, but long-term neurologic sequelae including cognitive impairment, motor dysfunction and epilepsy occur in up to 60% of patients.[3] Our patient had a short seizure duration, responded well to anticonvulsants, and had relatively preserved function at follow-up.

Early biochemical abnormalities including elevated transaminases, increased serum LDH, severe acidosis, hyperglycemia, and raised serum creatinine, may be helpful for prognostication.[4] Cerebrospinal fluid analysis is also essential; AESD typically shows normal cell counts and negative infectious studies, differentiating it from CNS infections. In our case, however, biochemical findings were largely unremarkable, underscoring the importance of neuroimaging in establishing the diagnosis. Neuroimaging is recommended to distinguish AESD from other infection-triggered encephalopathy syndromes.[5,6] Diffusion weighted MRI is particularly useful for supporting the diagnosis and is most sensitive when performed in the subacute phase (3-9 days), typically after the second phase of seizures.[7] On T2-weighed or T2 FLAIR sequences, subcortical U-fiber hyperintensities may also be seen, representing cortical edema. Our case demonstrates radiological features of AESD, with bilateral asymmetric frontal BTA on MRI six days after the initial convulsion. Asymmetric lesions have been described in the literature but are uncommon.[7] Gene polymorphisms, including ADORA2A, STK39, and SCN1A/2A, have been associated with susceptibility to AESD, although causal relationships have not been established.[5] Given the strong family history of febrile convulsions, whole-exome sequencing (WES) was performed for our patient, but no significant gene mutations were identified. A limitation of WES is that it does not assess non-coding regions, copy number variants, or mitochondrial genes.

Treatment of AESD includes optimal seizure control and supportive care.[6,8] Targeted temperature management has been proposed based on results from multiple comparative studies to be administered within 12 hours of symptom onset to reduce neurological sequelae and AESD development.[9] Regarding immunomodulation, Japanese guidelines recommend early pulse methylprednisolone in 'cytokine-storm' type acute encephalopathies such as acute necrotising encephalopathy (ANE), which may be heralded by signs of systemic inflammatory response syndrome, hyperferritinaemia and elevated liver enzymes.[6] However, the same guideline classifies AESD as an excito-toxic type encephalopathy and thus does not recommend any specific immunomodulatory treatment based on efficacy. Diagnosing AESD in the early phase is also

clinically challenging, when imaging features have not yet emerged and it being difficult to distinguish from prolonged febrile seizures. Hence, the use of corticosteroids and immunoglobulin in AESD should be carefully considered on a case-by-case basis. Moreover, Tocilizumab, a monoclonal antibody against the IL-6 receptor, has been reported to improve early survival in ANE.[10] There have been select cases where tocilizumab has been tried in severe AESD with varying outcomes.[8] However, guidelines for its usage, timing of initiation and dosage in AESD have not been established. More experience with biologics such as tocilizumab is needed to elucidate their role in treating AESD.

Conclusion

AESD is a rare and challenging diagnosis that should be considered in cases with biphasic seizures, even with relatively mild initial presentations. Early neuroimaging is crucial in establishing the diagnosis. Treatment of AESD includes optimal seizure control and supportive care. Specific immunomodulatory treatment is generally not recommended and should be carefully considered on a case-by-case basis.

Declarations

The authors would like to wholeheartedly extend their gratitude to Dr CY Cheung (Department of Radiology, North District Hospital), Dr Maggie Lo Yee Yau (Department of Paediatrics & Adolescent Medicine, Prince of Wales Hospital), Dr KH Ma (Department of Paediatrics & Adolescent Medicine, Alice Ho Ming Liu Nethersole Hospital) and Dr KY Liu (Department of Paediatrics & Adolescent Medicine, Alice Ho Ming Liu Nethersole Hospital) for their valuable input during all phases of this case report without which it would not have been possible.

Conflicts of Interest

There are no conflicts of interest.

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