Journal of Paediatrics and Child Health

Check for updates

doi:10.1111/jpc.15981

CASE REPORT

Acute encephalopathy with biphasic seizures and restricted diffusion

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Case Report

A 21-month-old Korean-Australian boy presented to the Emergency Department with altered conscious state, hypotonia and vomiting in the context of a 48-h febrile illness. He was up to date with his routine childhood immunisations, with an unremarkable perinatal and past medical history apart from speech delay. He was febrile to 41°C and tachycardic, with no withdrawal to pain, bilateral upper arm hypertonia with intermittent myoclonic jerking, representing clinical seizure. He was given two doses of midazolam (0.3 mg/kg) and intravenous loading of levetiracetam (40 mg/kg), intubated and commenced on broad-spectrum antibiotics (cefotaxime, vancomycin and acyclovir).

Key Points

1 Acute encephalopathy with biphasic seizures and late diffusion restriction (AESD) is an infection triggered encephalopathy syndrome.
2 The clinical syndrome of AESD is characterised by a prolonged febrile seizure, temporary improvement and a secondary phase of further seizures between day 4 and 6 in association with characteristic subcortical white matter diffusion restriction on magnetic resonance imaging.
3 AESD should be suspected in any patient following a prolonged febrile seizure with a protracted postictal drowsiness or irritability, as well as liver dysfunction.
4 Aggressive seizure control and hypothermia are currently suggested measures in unwell children with AESD.
5 There is a plausible role for anti-inflammatory therapies such as corticosteroids and IV immunoglobulin and potentially tocilizumab.

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Conflict of interest: None declared.

Accepted for publication 30 March 2022.

Initial blood tests demonstrated mild neutropenia 3.3 × 10^9/L (4.7–15.2), INR 2.4 (<1.2), APTT 43.8 s (24.0–39.2), creatinine kinase 1200 U/L (<180), CRP 52 mg/L (<10), PCT 62 μg/L (<0.5) as well as transaminitis that peaked on day 2 of admission (AST 5430 U/L (<66) and ALT 2910 U/L (<36)) and then progressively improved. Nasopharyngeal swab showed positive PCR for *adenovirus* and *bocavirus*.

When extubated after 24 h of admission he was irritable and had enlarged firm liver and cervical lymphadenopathy. An interictal electroencephalography (EEG) (on day 1) showed generalised slowing but no epileptiform activity. Fever abated after the first 24 h however, he remained lethargic with diarrhoea, reluctant to weight bear and had photophobia with intermittent back arching without loss of responsiveness. Magnetic resonance imaging (MRI) of the brain and cerebrospinal fluid (CSF) microscopy, culture and viral PCR performed on day 3 of admission were unremarkable. Over the first 5 days of admission, he became increasingly responsive with improving communication and ability to sit up without support and assisted standing.

On day 6 of admission, he had a bilateral tonic–clonic seizure, which terminated following intranasal midazolam. A repeat EEG was undertaken following this event, which demonstrated regular polyspike and wave discharges in bilateral occipital regions. A 90 s seizure was captured during EEG where he went 'floppy' with eyes rolled up. At this time, CSF neopterin results became available showing elevation – 142.15 nmol/L (6.0–30.0). In view of this secondary decline and the suspicion of a post-infectious inflammatory condition, IV methylprednisolone (30 mg/kg) was commenced. A repeat MRI on day 7 (Fig. 1) demonstrated bilateral frontal subcortical 'bright tree' restricted diffusion consistent with acute encephalopathy with biphasic seizures and late restricted diffusion (AESD). The patient was given one dose of tocilizumab (120 mg) and cotrimoxazole prophylaxis for 2 months. After 3 days, IV methylprednisolone was changed to oral prednisolone (1 mg/kg/day for 1 week followed by tapering over 1 month). The patient was also given a 3-day course of IV immunoglobulin, along with a metabolic cocktail of thiamine, ascorbic acid, biotin, vitamin E, ubidecarenone and levocarnitine for 1 month.

Sequential EEGs showed improvement of bilateral posterior slowing to a normal recording on day 15 after presentation. At discharge, he had normal ambulation, responsiveness and communication. His EEG remains normal and he has no neurological

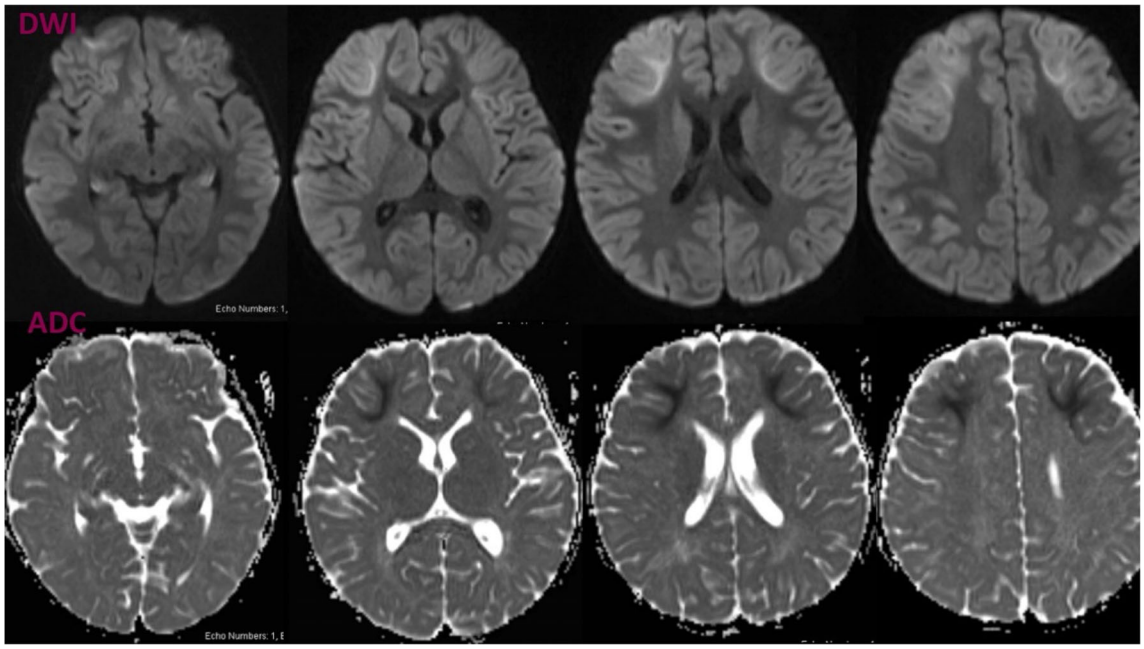

Fig. 1 Magnetic resonance imaging (MRI) brain with diffusion-weighted imaging (DWI) sequences on the top and apparent diffusion coefficient (ADC) map on the bottom. Images show bilateral frontal subcortical restricted diffusion mainly involving the middle frontalgyri with 'Bright tree' appearance suggestive of cytotoxic oedema of acute encephalopathy with biphasic seizures and late diffusion restriction.

morbidity when assessed at his 6-month follow-up. His cognition and speech, though awaiting formal assessment, have not changed and show age-appropriate progression.

Written consent was obtained for anonymised reporting of this case from the patient's parents. The consent form and intention to submit the case report was approved by the SCHN Ethics committee.

Discussion

AESD is the most common subtype of infection associated with paediatric encephalopathy in Japan occurring in infants between 1 and 2 years. It is characterised by an initial febrile seizure that lasts longer than 30 min on day 1, with neuroimaging being normal when performed, followed by a secondary seizure or cluster of seizures on days 4–6.[1] A diagnosis of AESD is made when the patient has biphasic seizures, with MRI performed on or after day 3 showing subcortical white matter diffusion restriction described as a 'bright tree appearance', while MRI performed on day 1 or 2 is usually normal.[1]

The exact aetiopathogenesis of AESD is not known but various predisposing factors have been proposed. A number of viruses are thought to be potential triggers, including HHV-6/7, influenza and echoviruses. Importantly, the absence of a preceding or concurrent viral infection does not rule out the diagnosis of AESD.[1] In view of an East Asian population predilection, a genetic or HLA vulnerability is plausible though this is supported only from isolated descriptions of genetic variants in *ADORA2A*, *CPT2*, *SCN1A* or *SCN2A*.[1–3]

Though cytokine assays were not available in our clinical setting, In patients with acute encephalopathy following prolonged febrile seizures, CSF studies have shown significantly higher levels of IL-6 when compared to those without encephalopathy. Elevated IL-10 and TNFR-1 were also noted in those who did experience a second seizure.[4] Prominent elevations in Th1 cytokines including IL-6 are also reported in febrile infection-related epilepsy syndromes without prominent Th2, B-cell and IL-10 compared to patients with encephalitis. In these conditions, serial CSF studies have demonstrated a decline in IL-6, IL-8, TNF-a, CXCL9, CXCL10, CXCL1 following the acute phase of illness suggesting that there may be a time window to target these inflammatory molecules.[5] Proposed hypotheses also suggest a role of energy depletion from mitochondrial dysfunction.[6]

Important differentials for a child with prolonged febrile seizures are included in Table 1. Patients with AESD generally have significantly longer postictal drowsiness, respiratory acidosis hyperglycaemia, liver transaminitis and hyperammonaemia when compared to non-AESD patients with complex febrile seizures.[7]

A scoring model (Table 2) to predict the likelihood of AESD has been devised with a sensitivity and specificity of 95% and 91% respectively. A score of more than 3 is deemed high risk.[7] Our patient scored 4 due to deranged liver enzymes and prolonged time until waking.

EEG within the first 24–48 h post-seizure is non-contributory to the diagnosis of AESD as it demonstrates non-specific diffuse slowing and attenuation often seen post status epilepticus. In the second stage (days 3–4 onwards), the EEG demonstrates focal epileptiform activity as captured in our patient.

A glutamine/glutamate peak is reported on MR spectroscopy between day 1 and 4 in some cases, prior to the bright tree appearance on diffusion-weighted imaging and is proposed to be predictive of neurological sequelae by comparing N-acetylaspartate peaks over time.[8]

Reported outcomes of patients with AESD are variable. Whilst the mortality rate is low (5%), around 28–44% of patients have

Table 1 Differentials of acute encephalopathy with biphasic seizures and late diffusion restriction

Infection	Bacterial and viral meningoencephalitis Viral illness with provoked febrile status • Adenovirus • Bocavirus
Autoimmune	Acute disseminated encephalomyelitis (ADEM) Vasculitis
Infection triggered encephalopathy – associated with significant cytokine storm	Acute encephalopathy with biphasic seizures and late diffusion restriction (AESD) Acute necrotising encephalopathy of childhood (ANEC) Febrile infection related epilepsy syndrome (FIRES) Mild encephalopathy with reversible splenial lesion (MERS)

Table 2 AESD scoring model adapted from Yokochi *et al.*[7]

Variable	Score points
pH <7.014	1
ALT (IU/L) ≥28	2
Blood glucose (mg/dL) ≥228	2
Time until waking (h) ≥11.0	2
Creatinine (mg/dL) ≥0.3	1
Ammonia (μg/dL) ≥125	2

AESD, acute encephalopathy with biphasic seizures and late diffusion restriction. Our patient scored 4 due to deranged liver enzymes and prolonged time until waking (underlined).

full recovery, 41–51% have mild to moderate neurological morbidity and 2–25% have severe neurological morbidity such as severe cognitive deficits, paralysis and epilepsy.[1]

There are currently no guidelines for the treatment of AESD and similar infection triggered excitotoxic syndromes.[9] Most studies emphasise aggressive seizure control and therapeutic hypothermia. The use of anti-inflammatory agents such as corticosteroids and intravenous immunoglobulin has been reported in AESD although the evidence for effect is lacking.[1] IL-6 blockade with tocilizumab has been used effectively and safely in similar excitotoxic syndromes such as acute necrotising encephalopathy of childhood.[9] We decided to use tocilizumab in our case given the high risk of neurological morbidity and the plausible role of similar cytokine dysfunction as acute necrotising encephalopathy of childhood. In addition, supplementation with various cofactors and vitamins such as vitamin B1, B6, C, E, biotin, coenzyme Q10 and L-carnitine have been used with the aim of reducing oxidative stress and preventing mitochondrial dysfunction.[6]

Given the potential for severe morbidity associated with AESD, we treated our patient with corticosteroids, tocilizumab, intravenous immunoglobulin and metabolic supplementation. To our knowledge, this is the first report of treatment with tocilizumab for AESD. We postulate that antagonising IL-6 may help to reduce excitotoxic brain injury and improve neurodisability given that AESD patients have demonstrated elevated levels of CSF IL-6.[4]

In conclusion, we have described the first patient with AESD treated with tocilizumab, with a normal 6-month outcome. This case highlights the need to be vigilant to the differential of AESD in children with long postictal drowsiness following prolonged febrile seizures. In the context of this suspicion and any hint of secondary worsening, a repeat MRI brain scan is essential to making a diagnosis despite a normal result in the first few days. Further studies to explore the effects of tocilizumab on the outcomes of AESD are warranted.

Acknowledgement

SS Mohammad acknowledges support from Cerebral Palsy Alliance, Australia for unrelated research. Open access publishing facilitated by The University of Sydney, as part of the Wiley - The University of Sydney agreement via the Council of Australian University Librarians.

References

1 Yamaguchi H, Nishiyama M, Tokumoto S *et al*. Detailed characteristics of acute encephalopathy with biphasic seizures and late reduced diffusion: 18-year data of a single-center consecutive cohort. *J. Neurol. Sci.* 2020; **411**: 116684.
2 Shinohara M, Saitoh M, Takanashi J-i *et al*. Carnitine palmitoyl transferase II polymorphism is associated with multiple syndromes of acute encephalopathy with various infectious diseases. *Brain Dev.* 2011; **33**: 512–7.
3 Shinohara M, Saitoh M, Nishizawa D *et al*. ADORA2A polymorphism predisposes children to encephalopathy with febrile status epilepticus. *Neurology* 2013; **80**: 1571–6.
4 Ichiyama T, Suenaga N, Kajimoto M *et al*. Serum and CSF levels of cytokines in acute encephalopathy following prolonged febrile seizures. *Brain Dev.* 2008; **30**: 47–52.
5 Kothur K, Bandodkar S, Wienholt L *et al*. Etiology is the key determinant of neuroinflammation in epilepsy: Elevation of cerebrospinal fluid cytokines and chemokines in febrile infection-related epilepsy syndrome and febrile status epilepticus. *Epilepsia* 2019; **60**: 1678–88.
6 Omata T, Fujii K, Takanashi JI *et al*. Drugs indicated for mitochondrial dysfunction as treatments for acute encephalopathy with onset of febrile convulsive status epilepticus. *J. Neurol. Sci.* 2016; **360**: 57–60.
7 Yokochi T, Takeuchi T, Mukai J *et al*. Prediction of acute encephalopathy with biphasic seizures and late reduced diffusion in patients with febrile status epilepticus. *Brain Dev.* 2016; **38**: 217–24.
8 Takanashi J, Tada H, Terada H, Barkovich AJ. Excitotoxicity in acute encephalopathy with biphasic seizures and late reduced diffusion. *Am. J. Neuroradiol.* 2009; **30**: 132–5.
9 Koh JC, Murugasu A, Krishnappa J, Thomas T. Favorable outcomes with early interleukin 6 receptor blockade in severe acute necrotizing encephalopathy of childhood. *Pediatr. Neurol.* 2019; **98**: 80–4.