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Original Research Article

Paediatric Encephalopathy and Complex Febrile Seizures

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Abstract

Objective: The most prevalent neurologic condition in children is febrile seizures. Medical professionals need to be knowledgeable about how to diagnose and treat this prevalent illness.

Method: A case study consisting of 2 children admitted in Patna Medical College and Hospital, Patna was carried out from November 2021 to October 2022.

Results: According to the findings, both of the children exhibited febrile status epilepticus related to acute encephalopathy, which was characterised by biphasic seizures and delayed diffusion restriction (AESD).

Conclusion: Children of any descent who exhibit febrile seizures followed by a protracted period before awakening coupled with transaminitis and an irregular EEG should be suspected of having AESD.

Keywords: Encephalopathy, Febrile Seizures, and Delayed Diffusion Restriction.

Introduction

In general, febrile seizures are described as seizures that happen in children between the ages of 6 months and 5 years who have a fever of more than 38°C (100.4°F), are not showing signs of an intracranial cause (such as an infection, head injury, or epilepsy), another definable cause of seizure (such as electrolyte imbalance, hypoglycaemia, drug use, or drug withdrawal), or have previously experienced an afebrile seizure [1]. Due to its high prevalence in young children and propensity to recur, febrile seizures pose a significant issue in paediatric practise [FIGURE 1].

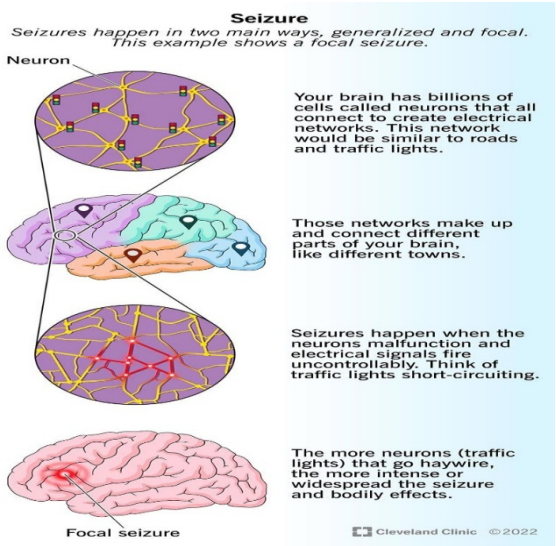

Figure 1: Prognosis of Seizure in children

The potential side effects of febrile seizures and how to treat them have come into more focus in recent years. The American Academy of Paediatrics (AAP) and the Japanese Society of Child Neurology, respectively, released updated guidelines

for the assessment and treatment of febrile seizures in 2011 and 2015 [2.3].

In this case study, the prevalence of febrile seizures in children with paediatric encephalopathy was reported.

Method:

In this study, an uncommon encephalopathy that affected two paediatric patients who had febrile seizures is discussed. The relatives of the patients gave their assent voluntarily for the IRB-approved data gathering and case publication.

Case Report:

Case 1:

On the third day of a respiratory infection, a developmentally normal 21-month-old girl who had previously experienced one febrile seizure came with a lengthy (11–21 minute) seizure.

At the time of presentation, the C-reactive protein (CRP) and peripheral white blood cell count were high, but the encephalitis panel and head computed tomographic (CT) and cerebrospinal fluid (CSF) tests were normal. On day 3, she developed an increased alanine transaminase (ALT) level (>1100 U/L), although her INR and ammonia levels were within normal range. Her sputum tested positive for enterovirus, but other tests for infectious diseases came back negative.

While brain magnetic resonance imaging (MRI) was normal, electroencephalography (EEG) revealed diffuse generalised slowness, intermittent rhythmic delta activity, occasional multifocal sharp waves, and a lack of typical sleep features consistent with diffuse cerebral dysfunction.

She experienced a seizure without a temperature but a significant rise in liver enzymes on day 4. Repeat brain imaging on day 5 revealed diffusion limitation with a bright tree appearance (BTA) sparing the peri-rolandic regions of the supratentorial cortices.

Case 2:

On day 2 of a respiratory infection, a developmentally normal, 3-year-old girl who had previously been healthy presented to the hospital with one brief (31-second) generalised seizure. She also had a fever. Her initial head CT revealed no abnormalities, but her liver enzymes (ALT > 20000 U/L, aspartate transaminase [AST] 2500 U/L, and international normalised ratio [INR] 4.3) were markedly increased. Ammonia and bilirubin levels were normal, the CSF was normal, and an infection screen came back clean.

The EEG displayed high-voltage rhythmic activity, diffuse generalised slowing, and no signs of sleep. On day 4, the brain MRI was normal. On day 7, however, the repeat brain MRI revealed reduced diffusion over the entire cortex along with the distinctive BTA.

Final Diagnosis:

Biphasic seizures and delayed diffusion constriction are features of febrile status epilepticus due to acute encephalopathy (AESD).

Health Course

Table 1 displays pertinent investigations and patient demographics.

Table 1: Baseline characteristics of the patients

Parameter	Case 1	Case 2
Age	21 months	3 years old
Past medical history	Simple febrile seizure at 14 months	Healthy
Virus	Enterovirus (sputum)	None isolated

Liver enzymes/function	ALT >1w00 U/L INR normal Ammonia normal	ALT > 20000 U/L INR 4.3 Ammonia normal
EEG	symptoms of general slowness and lack of sleep	symptoms of general slowness and lack of sleep
MRI	Day 5: BTA-induced diffusion restriction with peri-rolandic regions spared	Day 7: Diffusion limitation with a BTA in the entire cortex and both cerebral hemispheres.
Treatment	Steroids Vitamin B6 Temperature regulation	Carnitine
Outcomes	Death	Significant motor and cognitive delays
ALT = alanine transaminase; INR = international normalised ratio; EEG = electroencephalography; BTA = bright tree appearance; MRI = magnetic resonance imaging; PEE = post-encephalopathic epilepsy		

Case 1: Although aggressive neuroprotective measures were started, the patient eventually experienced increasing cerebral edoema and autonomic instability. The use of vitamin B6 and pulsed steroids was tested. A brain biopsy revealed anoxic-ischemic necrosis and damage. On day 11, comfort care was started because the patient's coma persisted and his cerebral edoema advanced. The cerebellar cortex, brainstem, and spinal cord were spared, and autopsy revealed acute/subacute anoxicischemic alterations bilaterally within the neocortex, hippocampus, and basal ganglia.

Case 2: Carnitine was tried since the patient's cerebral edoema required severe neuroprotective therapy. On day 15, a second MRI revealed a marginal improvement in diffusion limitation. She was released with significant cognitive and motor damage.

Discussion*:*

A dangerous illness, paediatric encephalopathy has a 5% overall death rate [4]. In Asian nations, the AESD is well-described [2]. It accounts for 5% to 30% of cases of encephalopathy and is the most prevalent paediatric encephalopathy syndrome documented in Japan [3]. With a female predominance, the median age at presentation is 15 to 19 months, and the mortality rate is often low but the morbidity rate is significant [5]. Although there are just a few case reports worldwide, there has only been one reported case in the United States [6] and none in Canada. These cases indicate that AESD can happen outside of Japan and in children of different races, while it is still unclear if the illness is underrecognized or actually uncommon in North America.

Early diagnosis and consideration of the diagnosis are essential because the best prognostic indicator is fast treatment. Biphasic seizures and a distinctive BTA on diffusion-weighted imaging (DWI)-MRI are two characteristics that help to distinguish the AESD from other encephalopathies [5]. Patients initially experience protracted febrile seizures and a delayed time to awakening, followed by a brief improvement in consciousness for 3 to 7 days. Thereafter, awareness deteriorates and clusters of afebrile seizures form [7].

As the illness worsens, transaminitis and cerebral edoema are frequently observed [7]. Early brain imaging is frequently normal, but 3 to 14 days after onset, DWI-MRI reveals limited diffusion in the bilateral subcortical white matter, which is characterised as a BTA pattern and typically spares the occipital region [5,7]. Although comparable patterns can be detected in other disorders, the BTA pattern seems to be a sensitive diagnostic for AESD. The majority of patients recover

from the acute episode, but neurological aftereffects can be severe [8].

It can be difficult to distinguish between AESD and FSE in the early clinical stages when the waking period is prolonged. Long-lasting seizures at the time of presentation, followed by a protracted period before awakening, are important AESD diagnostic indicators. Time to awakening was observed to be 11 hours in AESD patients as opposed to 4 hours in non-AESD patients by Yokochi et al. [4]. However, sedative drugs like antiepileptics make it difficult to interpret the longer time to awakening. Our patients' second afebrile biphasic seizures caused the diagnosis of AESD to be delayed, delaying the start of treatment. Elevated liver enzymes, lactate dehydrogenase, ammonia, creatinine, and respiratory acidosis have been documented to occur more frequently in AESD than in febrile seizures, as was the case with our patients [8,9]. In addition, diffusely slow EEG without sleep spindles within 48 hours of disease onset has also been proposed as a potential early biomarker of AESD, just like in our patients [7].

All of the cases in our series exhibited some combination of these prognostic characteristics, despite the fact that there is still no conclusive early biomarker for AESD. The influenza virus, HHV-6, enterovirus, and adenovirus are the most typical infectious pathogens found in patients with AESD [7,8]. Enterovirus was found in 2 of our patients, in fact.

Creating the best management plans is challenging due to the ambiguous pathophysiology of AESD. It has been suggested that glutamate and subsequent neuronal cell death are involved in the pathogenesis of the condition [10]. According to the theory, glutamate is released during the initial seizure and is then followed by a gradual rise in glutamine, which causes secondary deterioration and cytotoxic edoema [11]. This theory is further supported by investigations using magnetic resonance spectroscopy (MRS) on kids with AESD [10,11].

Patients with AESD have shown success in reducing glutamate release by cooling or hypothermia [10,12], and hypothermia has antiepileptic benefits [7]. While there is some evidence that early temperature regulation within 6 hours of the beginning of symptoms has a positive effect in AESD [10,12], treating patients before determining the cause of their symptoms may lead to many individuals being unnecessarily cooled. Therapeutic hypothermia was started by Yokochi and colleagues4 after the onset of the second seizure, and they came to the conclusion that because therapeutic hypothermia was linked to a positive outcome in 50% of patients, temperature regulation might still be effective even if started later in the disease course. Due to the fact that AESD is not a problem of cytokine release, the glutamate theory may also help to explain why immunomodulating therapies that reduce inflammatory cytokines, such as high-dose steroids and IVIg, have little to no effect on the condition.

An further pathogenetic pathway that has been put up links mitochondrial dysfunction to energy failure. Patients with AESD who showed a lactate peak on MRS, which indicates a shift towards anaerobic glycolysis and an imbalance in energy supply and demand, fared worse [10]. In line with this theory, early treatment with vitamins and co-enzymes, such as vitamin B1, B6, and l-carnitine, has been suggested and has been shown to improve outcomes in cases of suspected AESD [13,14].

Early detection is crucial because it has been demonstrated that delay has cellular and molecular repercussions. Tau protein, a CSF biomarker of axonal damage, is elevated in children with AESD within the first two days of illness, according to Shiihara and colleagues [15], suggesting that waiting to start treatment until biphasic seizures appear or until BTA changes are noticed may be too late to reverse pre-existing brain damage. [16]

Although Japan is said to have a low death rate for AESD (5%), a wide range of unfavourable neurodevelopmental outcomes have been recorded [3,5,8]. Overall, 40% to 50% of patients have minor deficits, 28% to 45% of patients make a good recovery, and 5% to 45% of patients have severe sequelae [3,5,8]. Refractory epilepsy and motor and/or cognitive impairment are examples of poor outcomes. The occurrence of PEE has been documented to take place 2 to 39 months following AESD and frequently involves numerous seizure types that are challenging to control [2,12].

Conclusion

Children of any origin who appear with febrile seizures, a lengthy period before awakening associated with transaminitis, and an irregular EEG should have the AESD suspected. More investigation is required to pinpoint specific biomarkers of AESD, which may include vitamin B1, vitamin B6, l-carnitine, and temperature control.

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