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Case Report

Febrile Infection-related Epilepsy Syndrome: A Local Paediatric Case Report

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Abstract Febrile infection-related epilepsy syndrome (FIRES) is a very rare disease of unknown pathogenesis. With no established diagnostic criteria in place, diagnosis is made purely on clinical grounds. These children typically experience a prolonged course of refractory status epilepticus with poor response to antiepileptic drugs, hence disease management remains a formidable challenge. Outcomes for these patients are usually poor, with significant neurodevelopmental morbidity and even mortality. Here we report a 6-year-old Chinese girl who was diagnosed to have FIRES, treated aggressively and was able to recover with a relatively good neurological outcome.

Key words Febrile infection-related epilepsy syndrome; FIRES; Refractory status epilepticus

Case Presentation

Our case is a 6-year-old girl with good past health. She was admitted to our unit on 5th August 2018, presented with 2 episodes of focal motor seizures with impaired awareness prior to admission. The focal seizure started with jaw clenching and chewing-like movement, followed by a staring gaze, right upper limb clonic movement and loss of consciousness. The two episodes lasted for three and eight minutes respectively, followed by an hour of post-ictal drowsiness and todd's paralysis of right side. There was associated fever and coryzal symptoms for 4 days.

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On admission, the girl had full Glasgow coma scale (GCS) and was oriented to place and person. There was no focal neurological deficit. However, she subsequently developed sudden onset of expressive aphasia an hour later. It was soon followed by her third episode of focal seizure with impaired awareness - lip smacking, right facial twitching, staring gaze and desaturation with SpO2 down to 80%. One dose of intravenous lorazepam was given at 5 minutes and seizure was aborted. However, she did not regain full consciousness. She was transferred to Paediatric Intensive Care Unit (PICU) for close monitoring and further investigation.

Full septic workups were performed. Complete blood count and c-reactive protein were normal with negative urine and blood culture. Nasopharyngeal aspirate (NPA) was adenovirus positive. Cerebrospinal fluid (CSF) microscopy showed 6 white cells and <2000 red cells/mm^3. CSF glucose was 74% of serum glucose with no elevated protein. CSF bacterial and fungal culture and viral polymerase chain reaction (PCR) were negative, including adenovirus PCR. Electrolytes and glucose were normal and blood astrup showed no acidosis. CT brain and urgent MRI brain were also normal. Urine toxicology screening was negative. The girl was empirically covered with cefotaxime, oseltamivir, acyclovir and azithromycin for possible central nervous system infection. Her fever settled on day

6 of admission. Antibiotics were taken off when all the culture results came back negative.

After admission to PICU, despite the absence of motor manifestations, the girl never returned to full consciousness. Differential diagnoses of non-convulsive status epilepticus (NCSE) or encephalopathy were suspected. Continuous video electroencephalography (VEEG) monitoring was set up, which showed a diffusely 2-3Hz polymorphic delta rhythm in the entire background. In addition, very frequent spikes and spike-and-wave were seen predominantly over the right centro-temporal regions, which resembled periodic lateralized epileptiform discharges (PLEDs) (Figure 1). Diagnosis of herpes encephalitis was highly suspected. Lumbar puncture was therefore repeated to look for delayed viral infection picture. CSF was heavily blood stained with glucose 62% of serum glucose, bacterial culture and viral PCR were again negative.

Treatment for both herpes encephalitis and NCSE were continued simultaneously. The patient was covered with IV acyclovir until repeated CSF herpes virus PCR turned negative. Multiple conventional antiepileptic drugs (AEDs) were introduced (see Figure 2). Despite there were no clinical seizures, electrical seizures persisted. The initial centrotemporal spikes on EEG became generalised with high amplitude runs of spikes, sharps, spike-and-waves and polyspikes ictal discharges. The girl was thus electively intubated on day 5 and put on midazolam infusion, followed by general anaesthesia (GA) with thiopentone which achieved a burst suppression state. She was also put on high dose methylprednisolone for 5 days and intravenous immunoglobulin (IVIG) for 4 days to cover for possible autoimmune encephalitis and epilepsy.

Towards the end of the GA treatment period, while tailing down thiopentone, multi-focal epileptiform discharges reappeared. The inter-ictal discharges progressed to electrical seizures. AEDs were further stepped up aggressively (see Figure 2). Electrical seizures finally decreased in frequency and resolved completely on day 17. The patient regained her full motor response on day 18 and full consciousness on day 26.

More extensive investigations including autoimmune markers, serum copper, ceruloplasmin and lead levels, metabolic screening including urine and plasma amino acid,

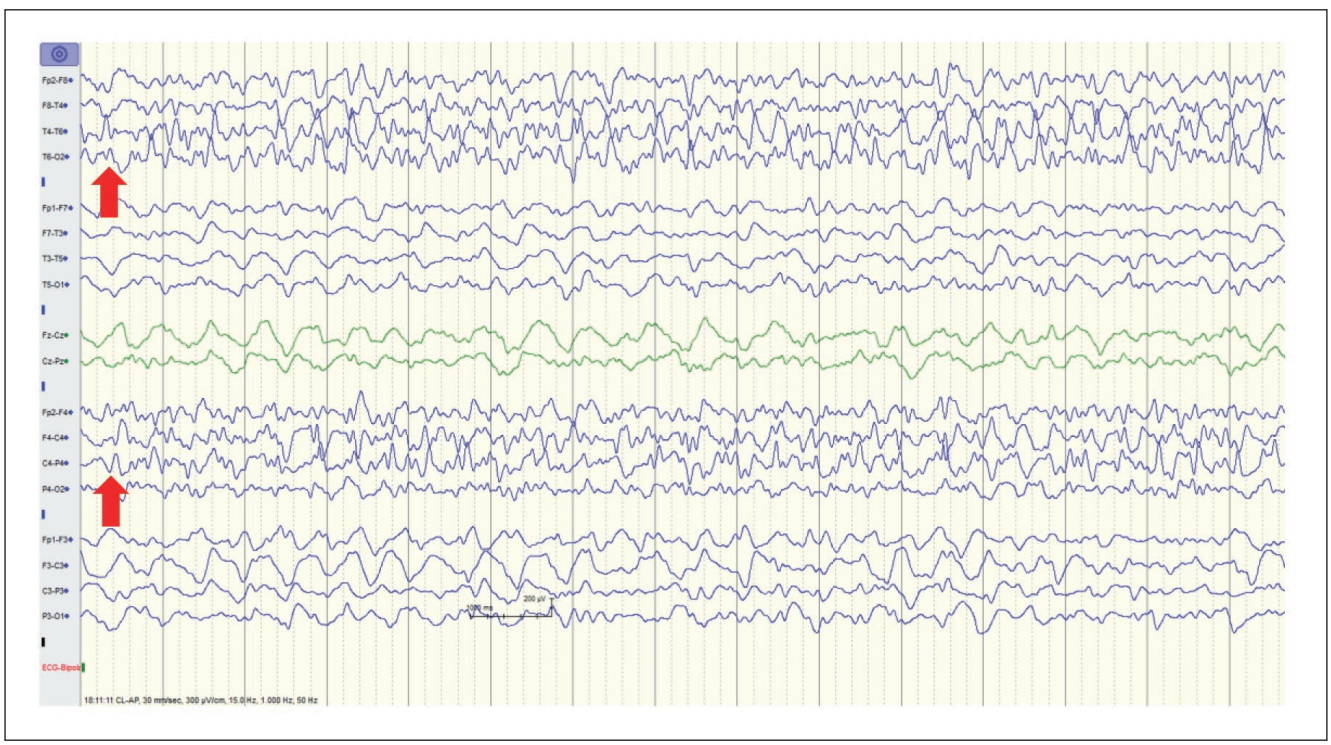

Figure 1 EEGs in bipolar montage. Very frequent spike waves, spike-and-slow waves were seen over the right centro-temporal regions resembling PLEDs (arrows).

urine organic acid, very long chain fatty acid, dried blood spot test and porphyrin screening were all normal. Screening for rare infections including anti-HIV antibody, VDRL, borrelia burgdorferi and bartonella antibodies were normal. Serum and CSF anti-NMDA receptor antibodies were negative. In addition, serum and CSF were sent overseas for autoimmune encephalitis anti-neuronal antibodies panel test. Anti-Caspr 2, anti-LGI1, anti-AMPA, anti-GABA-B and anti-GAD antibodies came back all negative.

Patient was transferred back to general ward after 22 days of PICU stay. She was started on neurorehabilitation. Interval EEG showed normal sleep and awake background, with no epileptiform discharges. A total of three MRI brains with contrast over two months showed no abnormalities. The girl was finally discharged with three AEDs (sodium valproate, lacosamide and clobazam) after 6 weeks of hospitalisation. Assessment by clinical psychologist revealed cognitive impairment, with impaired execution function and increased impulsivity. Nevertheless, she managed to return school 4 weeks after discharge, slowly catching up with academic tasks.

Discussion

Febrile infection-related epilepsy syndrome (FIRES), an epileptic encephalopathy of unknown aetiology, affects

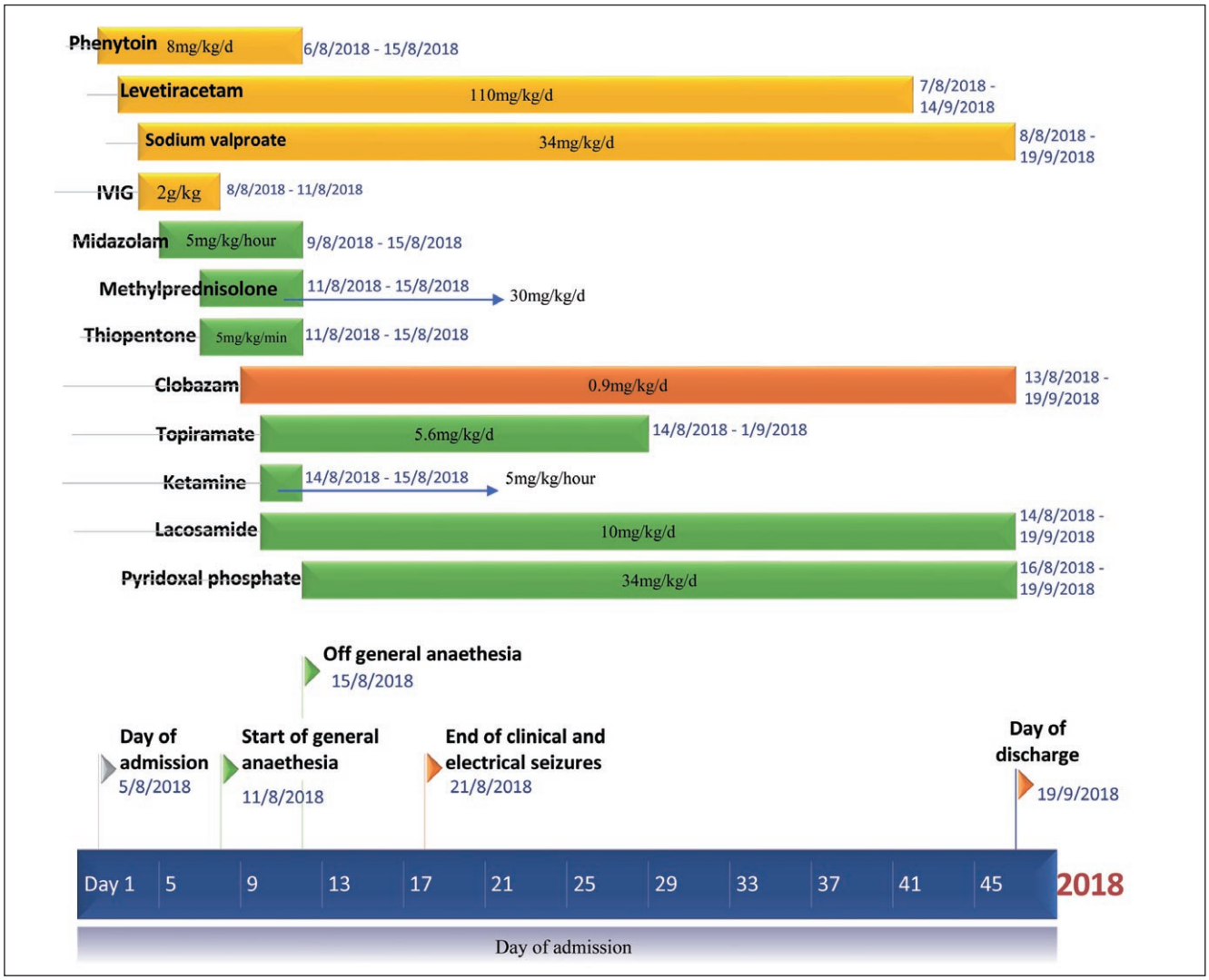

Figure 2 Timeline showing the initiation of AEDs, immunotherapy and GA, their maximum doses and duration of use.

children who are previously healthy following a febrile illness.[1,2] The prevalence is estimated to be around 1 in 1,000,000 children.[3] Exact cause is unknown, but high levels of proinflammatory cytokines and chemokines have been found in the serum and CSF of children with FIRES, which suggest the role of immune system in pathogenesis.[4] With the lack of biological markers, diagnosis has to be made on clinical grounds with the following features, after exclusion of other differential diagnoses:[5]

1. Status epilepticus or fulminant onset of bilateral focal or generalised seizures of different types for days or weeks despite treatment
2. Illness with fever or other clinical evidence suggestive of infection preceding seizures
3. Absence of previous neurological disease
4. Absence of evidence of infectious encephalitis and metabolic disorders
5. Absence of abnormal behaviour and movement disorders
6. Negative neuronal antibody test results
7. Drug resistant focal epilepsy and neuropsychological impairments immediately following the phase of high seizure frequency in nearly all patients
8. Age of onset is in childhood with a peak onset in school age

In our patient, extensive investigations were performed to exclude infectious, metabolic, autoimmune, genetics and toxic causes. NPA was found adenovirus positive. However, there were no detectable infectious pathogens or biochemical markers in the CSF suggestive of infections, and brain imaging did not reveal any evidence of encephalitis. Hence, adenovirus infection itself could not be attributed to be the cause of her super-refractory status epilepticus. On the other hand, she did not have any abnormal behaviours, movements, or autonomic dysfunction. Her neuronal antibodies were negative and repeated brain imaging were normal. This made her unlikely to suffer from autoimmune encephalitis. Overall, her clinical picture fitted into the diagnosis of FIRES.

Treatment remains a significant challenge in FIRES. With its sporadic occurrence, best therapeutic options are unclear still. From available case series, there is no single superior AED, and seizures in FIRES typically do not respond to high doses of conventional AEDs. GABAergic therapy at high doses and early introduction of ketogenic diet have been proposed as more promising therapies.[3,5] Anakinra, a recombinant human interleukin-1 receptor antagonist, was also reported to be effective in these patients.[6] Prognosis is frequently poor. Up to 87% of patients exhibit residual and/or refractory epilepsy. 10% of cases result in death during the acute phase and 66% to 100% of survivors suffer from intellectual disability.[3,7,8]

Conclusion

Traditionally, monotherapy of AED with gradual dose increments is recommended in treatment of newly diagnosed epilepsy. However, with super-refractory status epilepticus like FIRES, we advocate proactive treatment, with rapid escalation of AEDs doses, use of combination of alternative AEDs and early initiation of unconventional treatment such as GA, lignocaine and ketogenic diet. It is also important to achieve not just clinical but EEG control of seizures. More multi-centre researches need to be carried out to study the pathogenesis of FIRES, and to derive a standardised treatment regime to improve the prognosis of these children.

Declaration of Interest

The authors declare that there is no conflict of interest.

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