Post-COVID-19 febrile infection-related epilepsy syndrome in a child successfully treated with a multimodal approach

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SUMMARY

Post-infectious inflammatory syndrome following COVID-19 infection has been increasingly reported affecting multiple organs. Neurological presentations such as encephalopathy and seizures are common. Recently, during the surge of Omicron variant cases, we recorded a high prevalence of febrile seizure cases all over the country. Most febrile seizures are benign; however, a small proportion that progress into refractory epilepsy syndrome and require intensive care management. We report a 2-year-old child with refractory status epilepticus following COVID-19 infection, who was diagnosed and treated as febrile infection-related epilepsy syndrome (FIRES). A multimodal approach was adopted, using immunotherapy tocilizumab and ketogenic diet. The child currently has good seizure control but requires neurorehabilitation to improve ambulation, behaviour and cognition. This case highlights the importance of quick recognition of FIRES and its successful multimodal management that included tocilizumab.

INTRODUCTION

Neurological manifestations in relation to coronavirus disease 2019 (COVID-19) infections among the paediatric population have garnered much interest, with multinational studies reporting a prevalence of 22–44%.[1,2] Status epilepticus and encephalopathy were reported, but febrile infection-related epilepsy syndrome (FIRES) was rarely reported in adults and there was a single case report in a child with multisystem inflammatory syndrome in children (MIS-C).[3,4] FIRES is an epileptic encephalopathy of unknown aetiology affecting previously healthy children following a febrile illness. It has been defined under the subcategory of new-onset refractory status epilepticus (NORSE) and is similar to previous nomenclatures including acute encephalitis with refractory, repetitive partial seizures (AERRPS), or devastating epileptic encephalopathy in school-aged children (DESC).[5]

CASE PRESENTATION

A previously well and developmentally normal 2-year-old male initially tested positive by home self-test kit for COVID-19 and presented with fever and mild upper respiratory symptoms. He did not require hospital admission and was under home surveillance. On day 11 of illness, he presented with febrile seizures, requiring admission for 2 days and was discharged well, with no neurological deficits. Later on day 16 of illness, he presented again to a regional hospital with febrile status epilepticus lasting for 50 minutes. It was characterized by generalized tonic-clonic seizures with uprolling of eyeballs that were aborted with intravenous diazepam and phenytoin. He required intubation and ventilation for airway and cerebral protection for 72 hours and infusion of intravenous midazolam of 3 microgram/kg/minute. Following extubation, he remained encephalopathic with GCS 12-13/15. Unfortunately a few hours later, he developed recurrent refractory seizures that required multiple anti-seizure medications, including loading of phenytoin (30 mg/kg), phenobarbitone (40 mg/kg), levetiracetam (40 mg/kg) and infusion of midazolam 1 microgram/kg/minute. A regional hospital's first electroencephalogram (EEG) captured characteristic shifting ictal foci with an encephalopathic background seen in FIRES (Figure 1). He was transferred to our centre for further management on day 22 of COVID-19 infection.

Initial laboratory investigations during the presentation showed a total white cell count of 9.9×10^9/L, haemoglobin 13.6 g/dL, and platelet 184×10^9/L. The liver function test and renal profile were normal. Inflammatory markers such as C-reactive protein were normal (1 mg/L), and erythrocyte sedimentation rate was slightly elevated (18 mm/hr). His COVID-19 spike protein total antibody was positive 25.60 U/ml (normal <0.80 U/ml). His blood culture was negative. Cerebrospinal fluid findings did not suggest infection (no cells, glucose ratio 0.78%, total protein 0.2 g/L, and culture was negative). He did not fulfil the World Health Organization (WHO) case definition for MIS-C. His initial brain computed tomography and magnetic resonance imaging (MRI) were normal on days 16 and 20 of illness. The echocardiogram showed normal coronary arteries without any depression in ejection fraction.

In our centre, he was on continuous EEG monitoring which showed multiple episodes of a shifting pattern of focal electrographic and clinical seizures up to 30 times/hour (Figure 2). His clinical seizures were characterized by subtle blank stares, uprolling of eyeballs and twitching of upper limbs. He was given a single dose of intravenous tocilizumab (12 mg/kg) on day 22 of illness, as he was still febrile. He was readmitted to the paediatric intensive care unit (PICU) for cerebral protection on day 24 of illness and was commenced on therapeutic hypothermia to maintain a temperature

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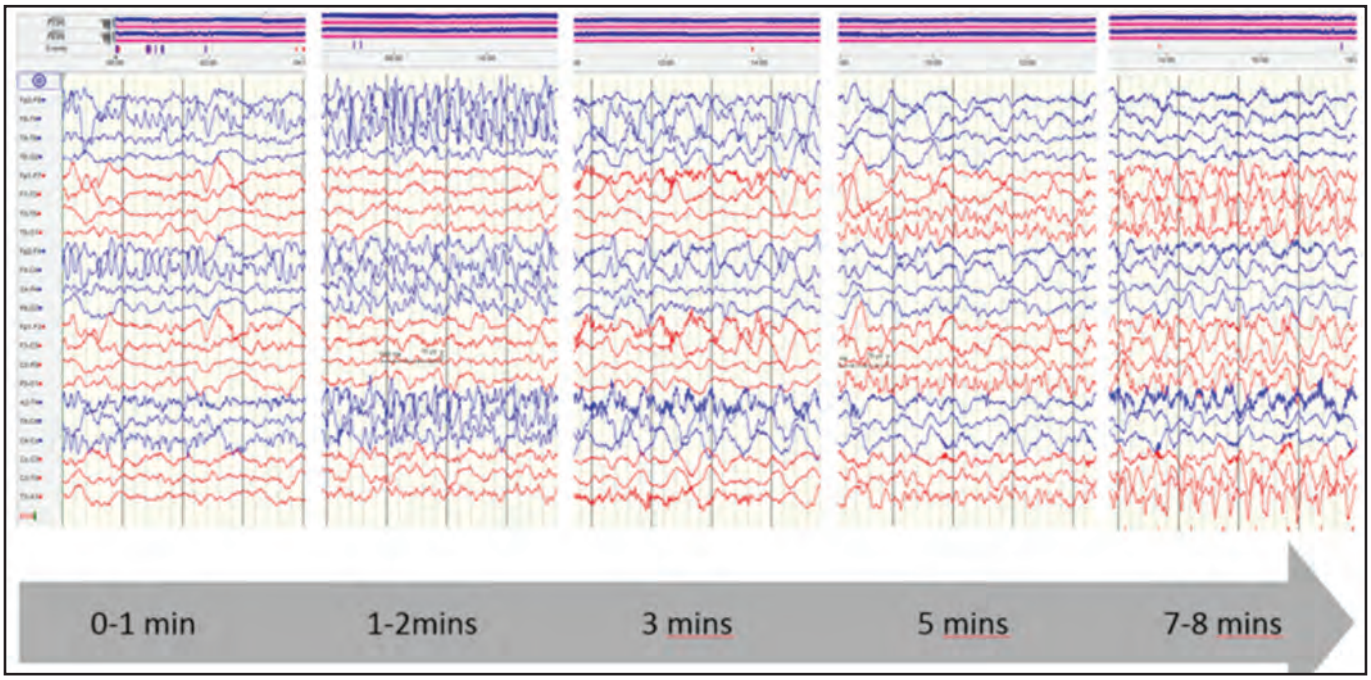

Fig. 1: A snapshots of first EEG captured a shifting pattern of electrographic seizures from right hemisphere to the left that lasted just over 8 minutes which is typically seen in a patient with FIRES

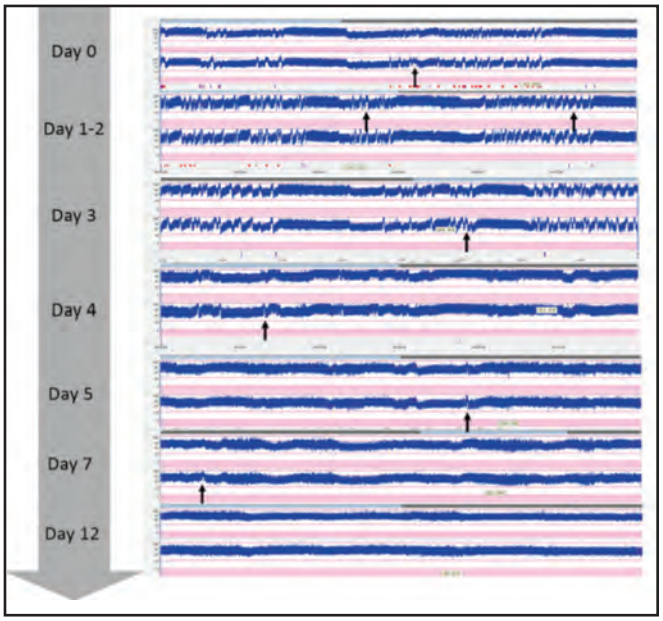

Fig. 2: A series of prolonged amplitude-integrated EEG (aEEG) monitoring in our centre. Cappings (arrows) on the aEEG represent electrographic seizures. As the days progressed, the number of capping had reduced notably from day 3 post tocilizumab and no further electrographic seizures seen by day 12 post tocilizumab

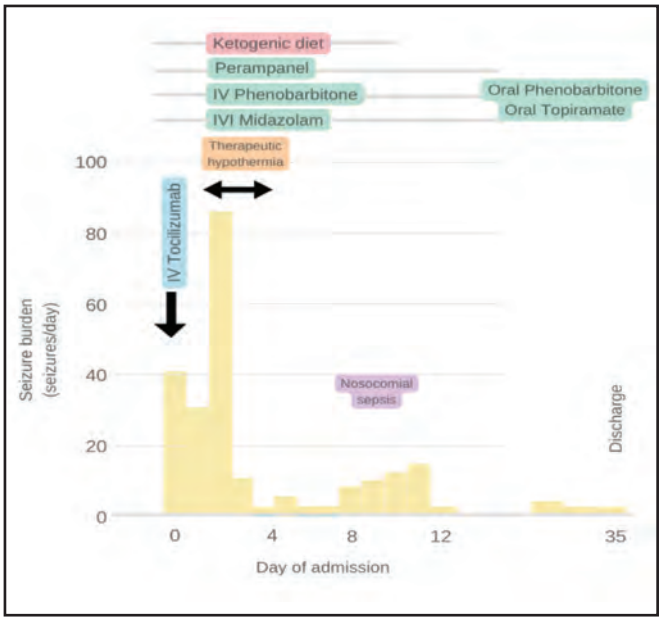

Fig. 3: The course of his illness during the hospital admission showing seizure burden following various treatments using a multi-modal approach

between 32 and 34°C for 72 hours. At this time, he was also started on ketogenic diet orally which subsequently had to be stopped due to feeding intolerance and diarrhoea (Figure 3). He required multiple antiseizure medications, namely midazolam infusion (titrated up to 3 µg/kg/min), a supratherapeutic dose of intravenous phenobarbitone (drug level: 223.10–401.34 umol/L range), and oral perampanel (loading dose 8 mg and maintenance dose 2 mg daily). His PICU stay of 2 weeks was complicated with nosocomial sepsis (Delftia acidovorans bacteremia), bicytopenia and acute kidney injury, which resolved over time. However, he became seizure free for 4 days on day 12 post-tocilizumab

administration. Following that, antiseizure medications, namely oral phenobarbitone and topiramate, were adjusted prior to discharge, when he only had brief daily seizures. His modified Rankin scale was 3; he was able to walk with assistance and had some fine facial and upper limb dyskinesia. During the outpatient clinic review at 3 weeks, 2 months and 4 months after discharge, he still has short brief seizures and remains nonverbal, had some aggressive behaviour and sleep disturbance. Repeat EEG showed mild background slowing, with no epileptiform discharges.

DISCUSSION

Our case highlights a rare and difficult-to-manage FIRES following COVID-19 infection. The pathogenesis of FIRES is currently unknown, while neurological manifestations in COVID-19 infections that can develop during acute COVID-19 infection or after its recovery or arise in the course of a MIS-C are largely hypotheses.[6] It has been postulated that the relationship between febrile illness and status epilepticus suggests deleterious effects of inflammation and autoimmunity on the onset and progression of seizures.[5] In our case, the biphasic clinical course suggests the possibility of post-infectious inflammation induced by COVID-19 triggering an autoimmune phenomena. Previous literature reported no specific biomarker, but selective upregulation of CSF proinflammatory cytokines particularly IL-6, macrophage migration inhibitory factor (MIF) and chemokines such as CXCL10, IL-8 are the hallmark of FIRES, providing strong evidence for the involvement of innate inflammation in the pathogenesis.[5] Unfortunately, we could not perform these CSF biomarkers in this patient due to limited resources. His other investigations, including neuroimaging and metabolic studies, were normal, as commonly described in previously reported cases of FIRES.[7]

As the postulation of innate immune system dysfunction is the contributing aetiology, the role of immunotherapy blocking proinflammatory cytokines, such as interleukin-1b and interleukin-6, has been explored. A previous case report had shown that the combination of tocilizumab and ketogenic diet was temporally associated with resolution of uncontrolled seizures in anakinra-refractory FIRES.[8] Similarly, in another cohort, refractory status epilepticus was terminated after 1–2 doses of tocilizumab in six adult patients with a median interval of three days from the initiation. However, two patients experienced severe adverse events related to infection during the tocilizumab therapy.[9] Ketogenic diet also has been reported to be helpful in FIRES. A large multicentre case series reported cessation of seizures within 2 days of starting the ketogenic diet in one of the patients.[7] Peng et al. observed seven patients who achieved cessation of status epilepticus within an average of 5 days after a ketogenic diet initiation.[10] Despite reported success with immunotherapy and ketogenic diet in controlling refractory seizures, the outcome of FIRES is universally poor, with most survivors developing learning disabilities, cognitive impairment and chronic refractory epilepsy.[7]

CONCLUSION

Any presentation of new-onset refractory status epilepticus following COVID-19 infection in otherwise previously healthy children should prompt the diagnosis of FIRES and necessary investigations, including ideally checking for pre treatment CSF biomarkers if possible. A multimodal approach, including tocilizumab administration and commencement of ketogenic diet, could lead to early seizure cessation and hopefully better long-term neurological outcomes.

ETHICS STATEMENT

Written consent has been obtained from the parent for publication purposes. This case report has obtained an exemption for ethical approval from the Medical Research & Ethics Committee (MREC), Ministry of Health Malaysia (NMRR ID-22-01335-BYT (IIR) dated 28th June 2022).

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CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

MAA and HM drafted the manuscript with inputs from all other authors. SM, ARM and TBK reviewed the manuscript and finalized the submitted version.

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