Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Case Report

Successful treatment of acute encephalitis and hepatitis in a child with COVID-19 infection

Chiao-Yu Cheng a, Cheng-Hsien Tsai b,*, Hsin-Pei Wang b, Wei-Tse Chiu b, Hsi-Chuan Hung b, Chun-Yi Chi c, I-Jung Tsai a

a Department of Pediatrics, National Taiwan University Children's Hospital, Taipei, Taiwan
b Department of Pediatrics, National Taiwan University Hospital Yunlin Branch, Douliou, Yunlin County, Taiwan
c Department of Medical Nephrology, National Taiwan University Hospital Yunlin Branch, Douliou, Yunlin County, Taiwan

Received 19 August 2022; received in revised form 25 October 2022; accepted 20 November 2022

KEYWORDS
Critical care; COVID-19; Encephalitis; Continuous renal replacement therapy; Plasma exchange

Abstract We present the case of a 6-year-old Taiwanese boy with a fulminant course of COVID-19 manifesting as high fever, acute consciousness changes, and status epilepticus. Brain MRI showed restricted diffusion in the bilateral hemisphere. Electroencephalogram showed diffuse slow waves with few spikes. CSF study was clear without evidence of common pathogens. He received treatment with antiviral agents, corticosteroids, intravenous immunoglobulins, and anti-IL-6 monoclonal antibodies. However, progressive fulminant hepatitis, hyperammonaemia, and disseminated intravascular coagulopathy developed. Rescue therapy with hybrid continuous renal replacement therapy and plasma exchange were performed in the first 11 days. The patient improved and was extubated on the 11th day. After physical therapy, his neurological function improved significantly. The patient was discharged under rehabilitation after 1 month of hospitalization. Viral sequencing confirmed infection with the Omicron BA.2.3 variant, one of the dominant strains in Taiwan and Hong Kong. Whole-exome sequencing revealed heterozygous uncertain significance variants in <I>TICAM-1</I>, <I>RNF 31</I>, and mitochondrial <I>MT-RNR1</I>, which provide additional support for the fulminant course. To the best of our knowledge, this is the first reported case of COVID-19 in a child with a fulminant course of acute encephalitis and hepatitis who successfully recovered by hybrid continuous renal replacement therapy and plasma exchange.

Copyright © 2023, Formosan Medical Association. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

* Corresponding author. Department of Pediatrics, National Taiwan University Hospital Yunlin Branch, No. 579, Sec. 2, Yunlin Rd., Douliou City, Yunlin County 640203, Taiwan.
E-mail addresses: chtao60@ntu.edu.tw, r11452002@ntu.edu.tw (C.-H. Tsai).

https://doi.org/10.1016/j.jfma.2022.11.014
0929-6646/2023, Formosan Medical Association. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Introduction

SARS-CoV-2 infection was reported in high proportions in asymptomatic and mildly symptomatic children. In epidemiological data from the United States, headache was the most common neurological sign. However, fatal paediatric cases of COVID-19 and encephalitis have been reported. In Taiwan, endemic COVID-19 was deferred due to strict border quarantine until April 2022, and several fatal paediatric cases of COVID-19 occurred. According to the information from the Central Epidemic Command Center (CECC), 159 children were reported to have severe COVID-19, and 27 died between April 1 and August 11, 2022, due to acute encephalitis (10), pneumonia and croup (6), sepsis (2), myocarditis (1) and other causes (8).

The Taiwan CECC published the Preliminary Guideline for Treatment of Children with COVID-19 Infection and Acute Encephalitis on May 21, 2022. The current possible management of critically ill patients includes mechanical ventilation, antiviral agents, corticosteroids, and anti-interleukin-6 (IL-6) receptor monoclonal antibodies. IL-6 is one of the elevated cytokine markers in COVID-19 patients and is associated with their outcomes.

We present the case of a 6-year-old boy with acute severe encephalitis and fulminant hepatitis due to COVID-19. He recovered with the hybrid treatment of therapeutic plasma exchange (TPE) and continuous venovenous haemodiafiltration (CVVHDF) support.

Case presentation

A 6-year-old boy without any hospitalization or family history of neurological disease had sudden-onset seizure 6 h after fever on May 21, 2022 (Day 0). His mother and 2 sisters tested positive for COVID-19 on the same day.

The boy’s COVID-19 rapid antigen test was positive at 6:00 PM. He had fever and chills, followed by altered mental status, nonbilious vomiting, and generalized tonic–clonic seizures at 11:00 PM. He was sent to the nearby emergency department (ED). An extremely high fever of 42.7 °C and hypotension were recorded, and he had a positive nasopharyngeal COVID-19 PCR test, with a cycle threshold (Ct) value of 14. He was transferred to our hospital. At our ED, the initial Glasgow coma scale (GCS) was E1V1M4 with critical vital signs, including blood pressure (BP) of 65/30 mmHg, pulse rate (PR) of 180, and SpO2 of 100% under an O2 mask. Mechanical ventilation, fluid resuscitation and inotropes, including dopamine and norepinephrine, were administered. Empiric antibiotics were prescribed for septic shock. Neurological examination showed trace light reflex, absent doll’s eye reflex, a cough and gag reflex, and positive Babinski sign. Laboratory data revealed leukopenia (WBC 2.7 K/μL), impaired renal function (creatinine level 1.2 mg/dL), and elevated lactate (5.1 mmol/L) and troponin-T levels (103.68 ng/L). CT scan revealed tight ventricles without mass lesions and a left lower lung consolidation patch (Fig. 1). Under the impression of COVID-19 encephalitis and

![Fig. 1](image_url)

*Footnotes: ADC: apparent diffusion coefficient; CT: computed tomography; DWI: diffusion-weighted imaging; MRA: magnetic resonance imaging of angiography; MRI: magnetic resonance imaging.*
pneumonia, remdesivir (5 mg/kg on Day 1, 2.5 mg/kg from Day 2 to Day 5), tocilizumab (12 mg/kg/dose), levetiracetam (30 mg/kg/day), betamethasone (0.15 mg/kg/day), mannitol, 3% hypertonic saline, and intravenous immunoglobulins (IVIGs) (2 g/kg) were given following the guidelines. The patient was transferred to the ICU on Day 1.

Increased intracranial pressure (IICP) was noted with bradycardia (PR 77), hypertension (BP 133/68 mmHg) and the absence of the brainstem reflex. The optic nerve sheath diameter (ONSD) was more than 0.50 cm bilaterally (max ONSD 0.68 cm). Acute fulminant cerebral edema was substantial. However, repeated brain CT (2nd) showed no herniation or haemorrhage. On Day 3, decorticate posture was noted, and CT (3rd) showed progression. The ICP monitor was placed, and the initial ICP level was 18–22 mmHg.

Acute fulminant hepatitis was noted with a rapid increase in liver function and ammonia levels 16 h after admission (Fig. 2A). The disseminated intravascular coagulopathy (DIC) profile showed prolonged prothrombin time by international normalized ratio (INR), decreased fibrinogen level and high D-dimer level. Pathogen surveys, including hepatitis virus, CMV and EBV, were all negative. Continuous venovenous haemofiltration (CVVH) (50 mL/kg/hr) was given for hyperammonaemia with stage 3 acute kidney injury. On Day 2, due to a poor response to CVVH, hybrid approach of therapeutic plasma exchange (TPE) (1.5 x plasma volume for 2 h every 2–3 days) was used in combination with continuous venovenous haemodiafiltration (CVVHDF) (50–100 mL/kg/hr continuously, interrupted with TPE). Under treatment for 3 days, liver function recovered spontaneously, and we discontinued CVVHDF after Day 5 (Fig. 2B). As the serum IL-6 level was still high, TPE was given for a total of 5 sessions until Day 11, and the serum IL-6 level decreased dramatically (Fig. 2C).

![Fig. 2](image-url)  
(A) Laboratory data trends in the first 11 days after admission: The timeline from the point of admission through the 5 sessions of therapeutic plasma exchange (TPE) with trends of inflammatory markers (serum procalcitonin, ferritin), coagulopathy markers (platelet (PLT), D-dimer, fibrinogen, international normalized ratio (INR)), hepatic markers (alanine transaminase (ALT), total bilirubin, ammonia), renal parameters (creatinine (Cre), lactic acid) and a cardiac marker (Troponin-T).  
(B) Serum ammonia levels in the first 9 days after admission and related hybrid management. Asterisks * indicate the serum ammonia level just before therapeutic plasma exchange (TPE). CVVH: Continuous venovenous haemofiltration; CVVHDF: Continuous venovenous haemodiafiltration.  
(C) Serum and CSF IL-6 levels before and after therapeutic plasma exchange. CSF: cerebrospinal fluid; IL-6: interleukin-6 (normally less than 7 pg/mL).
His initial light and corneal reflex were negative. On Days 2–5, his consciousness score was E1M4Vt under sedatives. EEG showed diffuse slow waves without epileptiform discharge. Brain MRI on Day 5 (Fig. 1) revealed multiple high signal changes in the grey matter of both hemispheres on DWI and mild signal changes in the cerebral cortex and striatum on T2-weighted images. On Day 6, CSF study showed no WBCs with normal protein level, and the pathogen survey was negative. His consciousness score improved to E4M4Vt on Day 7. He could open his eyes spontaneously and respond to voices on Day 9. After completing five sessions of TPE on Day 11, the endotracheal tube was removed. The patient was transferred to the general ward after a 14-day stay in the ICU.

The SARS-CoV-2 PCR test was rechecked on Day 16 with a Ct value of 38.8. Rehabilitation assessment showed global developmental delay on Day 23, which improved gradually. He could stand, climb stairs, swallow, and follow simple orders such as clapping but was not able to express urine or defecate. Compared to motor recovery, his cognition and language function slowly improved. The patient was discharged after one month of hospitalization and is currently under rehabilitation.

Whole-exome sequencing identified heterozygous variants of uncertain significance (VUS) in TICAM-1 (c.1831G>T, p. Gly611Cys), RNF31 (c.58G>A, p. Ala20Thr), and the mitochondrial MT-RNR1 gene with the homoplasmic variant of mt1555A>G. Viral sequencing confirmed infection with Omicron BA.2.3 variant, one of the dominant strains in Taiwan and Hong Kong.

Discussion

To the best of our knowledge, this is the first reported case of COVID-19 in a child with a fulminant course of acute encephalitis and hepatitis who successfully recovered by hybrid treatment with TPE and CVVHDF.

In children with severe COVID-19, MODS involving the brain, kidney, liver, heart and gastrointestinal tract has been reported. Viral infection leads to proinflammatory cytokines, including TNF-alpha, IL-6, and GM-CSF, and induces cytokine storm syndrome (CSS). To treat CSS, supportive care treatment is crucial, including mechanical ventilation, adequate intravenous hydration, and empirical antiviral agents. The administration of IL-6 antagonists has been proven to be associated with lower mortality in critical COVID-19 cases. In our case, fulminant hepatitis, MODS, and elevated IL-6 levels developed under the above treatment.

TPE has been reported to improve critical COVID-19 in adult populations and in patients with encephalitis, but there is no report on the treatment of fulminant hepatitis and encephalitis in children. TPE is an immunomodulatory treatment for acute liver failure that provides detoxification and synthetic function as a bridge to liver transplantation or spontaneous recovery. In our case, spontaneous recovery developed after hybrid treatment with TPE and CVVHDF and the IL-6 level decreased after TPE. TPE offers a safe and effective approach as a rescue therapy.

In our case of acute encephalitis and hepatitis, it was difficult but feasible to treat the patient with acute kidney injury who required dialysis and therapeutic hypernatremia. Several methods are recommended to manage dysnatremias with CRRT. We administered 3% saline in a continuous infusion and achieved the targeted sodium level by adjusting the rate. The calculation and frequent laboratory monitoring are key points. We demonstrated controlled and predictable therapeutic hypernatremia when CRRT was performed with ultrahigh dose condition of CVVHDF.

Before the COVID-19 pandemic era, acute fulminant cerebral oedema (AFCE) and encephalitis were reported to have high mortality rates. In Taiwan, between 2000 and 2010, 25 children had encephalitis and AFCE, with a mortality rate of 64%, and all survivors had sequelae. The California Encephalitis Project (CEP) reported 30 children diagnosed with AFCE between 1998 and 2012, with a mortality rate of up to 80%. The majority of these children were Asian/Pacific Islander (44%), which implied a possible genetic factor. Regarding aetiologies, enterovirus, human herpes virus type 6, influenza, Epstein–Barr virus or mycoplasma were reported in these 2 studies, and this showed that the possible aetiologies of AFCE might be related to infection. Our report showed that fulminant SARS-CoV-2 infection may also trigger AFCE in children. COVID-19-associated encephalitis has also been reported in South Asia and Europe. Initial clinical manifestations of COVID-19-associated encephalitis include headache, fever, and a new-onset seizure. Other than infectious encephalitis, SARS-CoV-2 or other pathogen may not be detected in the CSF study which indicates possibility of peri-infectious inflammation and altered neurotransmission.

In 2022, a population-based cohort study in Hong Kong reported 1144 hospitalized children aged 0–11 years with COVID-19 Omicron infection. A total of 171 (15%) children had neurological complications, and 5 (0.4%) had COVID-associated encephalitis or encephalopathy. The 2 patients who died of neurological complications had encephalopathy and fulminant cerebral oedema. The study also revealed that Omicron BA.2 was more neuropathogenic than influenza and parainfluenza viruses. Patients infected with Omicron BA.2 showed more neurological complications than those infected with other viruses in the Asian population, and ethnicity may play important genetic roles in Omicron BA.2 fulminant cases.

In our case, heterozygous missense variants of TICAM-1, RNF31, and MT-RNR1 were noted. TICAM-1 was reported as a risk factor for inborn errors of type I IFN immunity, and the TLR3/TICAM-1 pathway is mandatory for the innate immune response to RNA virus infection to protect host cells. RNF31-mediated ubiquitination is one of the main pathogenic mechanisms of acute liver injury in inflammatory cytokine storms. These variants required further study with functional assays to prove the association between the genes and the clinical presentations.

Conclusion

This case report provides an experience of hybrid treatment with TPE and CVVHDF as an effective rescue therapy for children with critical COVID-19. The genetic study supported the hypothesis of SARS-CoV-2 as a trigger in vulnerable Asian children.
Declaration of competing interest
The authors have no conflicts of interest relevant to this article.

Funding/support
No funding was secured for this study.

Acknowledgement
We appreciate Prof. Wang-Tso Lee, the paediatric neurologist at National Taiwan University Children’s Hospital, for advising the diagnosis, management and supervision of the patient with encephalitis. We thank Prof. Hi-Chung Lee and the research group at the Department of Medical Genetics, National Taiwan University Hospital for performing whole exon sequencing and its interpretation. We thank Dr. Ming-Tsai Liu and Dr. Huai-Te Tsai, at the Taiwan Centers for Disease Control, for the viral sequencing and report. We also thank Dr. Jian-Te Lee, the paediatric infectious disease specialist at the National Taiwan University Hospital Yunlin Branch.

References
1. Lu X, Zhang L, Du H, Li YY, Qiu J, Zhang W, et al. SARS-CoV-2 infection in children. N Engl J Med 2020;382(17):1663–5.
2. Chou SH-Y, Beghi E, Helbok R, Moro E, Sampson J, Altamirano V, et al. Global incidence of neurological manifestations among patients hospitalized with COVID-19—a report for the GCS-NeuroCOVID consortium and the ENERGY consortium. JAMA Netw Open 2021;4(5):e2112131. e2112131.
3. Conto-Palomino NM, Cabrera-Bueno ML, Vargas-Ponce KG, Rondón-Abuhadba EA, Atamari-Anahui N. Encephalitis associated with COVID-19 in a 13-year-old girl: a case report. Medwave 2020;20(7):e7984. e7984.
4. Kim MG, Stein AA, Overby P, Kleinman G, Nuoman R, Gulko E, et al. Fatal cerebral edema in a child with COVID-19. Pediatr Neurol 2021;114:77.
5. Ninan S, Thompson P, Gershon T, Mills W, Jewells V, et al. Fatal pediatric COVID-19 case with seizures and fulminating cerebral edema. Child Neurology Open 2021;8:2329048X211022532.
6. Rubin EJ, Longo DL, Baden LR. Interleukin-6 receptor inhibition in COVID-19—cooling the inflammatory soup. Mass Medical Soc; 2021. p. 1564–5.
7. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Shankar-Hari M, Vale CL, Godolphin PJ, Fisher D, Higgins JPT, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. JAMA 2021;326(6):499–518.
8. Adeli SH, Asghari A, Tabarraili R, Shajari R, Afshari S, Khalir N, et al. Using therapeutic plasma exchange as a rescue therapy in COVID-19 patients: a case series. Pol Arch Intern Med 2020;13:455–8.
9. Keith P, Day M, Perkins L, Moyer L, Hewitt K, Wells A. A novel treatment approach to the novel coronavirus: an argument for the use of therapeutic plasma exchange for fulminant COVID-19. BioMed Central; 2020. p. 1–3.
10. Cao A, Rohaut B, Le Guennec L, Saheb S, Marois C, Altmayer V, et al. Severe COVID-19-related encephalitis can respond to immunotherapy. Brain 2020;143(12):e102. e102.
11. Akdogan M, Camci C, Gurakar A, Gilcher R, Alamian S, Wright H, et al. The effect of total plasma exchange on fulminant hepatic failure. J Clin Apher 2006;21(2):96–9.
12. Beraud M, Al Hashami S, Lozano M, Bah A, Keith P. Role of therapeutic plasma exchange in the management of COVID-19-induced cytokine storm syndrome. Transfus Apher Sci 2022;103433.
13. Yessayan LT, Szamosfalvi B, Rosner MH. Management of dysnatremias with continuous renal replacement therapy. Wiley Online Library; 2021. p. 472–9.
14. Yee J, Mohuiddin N, Gradinariu T, Uduman J, Frinak S. Sodium-based osmotherapy in continuous renal replacement therapy: a mathematical approach. Kidney 2020;1(4):281.
15. Boer DP, Mourik SL, van den Hoogen MW, Langendonk JG, de Geus HR. Successful treatment of severe hyperammonaemia with ultra-high dose continuous veno-venous haemodiafiltration. Blood Purif 2019;48(3):283–5.
16. Lan SY, Lin JJ, Hsia SH, Wang HS, Chiu CH, Lin KL, Cheese Study Group. Analysis of fulminant cerebral edema in acute pediatric encephalitis. Pediatrics & Neonatology 2016;57(5):402–7.
17. Krishnan P, Glenn OA, Samuel MC, Sheriff H, Foster-Barber A, Sejvar JJ, et al. Acute fulminant cerebral edema: a newly recognized phenotype in children with suspected encephalitis. J Pediatric Infect Dis Soc 2021;10(3):289–94.
18. Piloatto A, Benussi A, Libri I, Masciocchi S, Poli L, Premi E, et al. COVID-19 impact on consecutive neurological patients admitted to the emergency department. Feb J Neurol Neurosurg Psychiatry 2021;92(2):218–20. https://doi.org/10.1136/jnnp-2020-323929.
19. Panda PK, Sharawat IK, Panda P, Natarajan V, Bhakat R, Dawman L. Neurological complications of SARS-CoV-2 infection in children: a systematic review and meta-analysis. J Trap Pediatr 2021;67(3). https://doi.org/10.1093/jtrapej/fmaa070. Jul 2.
20. Harapan BN, Yoo HJ. Neurological symptoms, manifestations, and complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 19 (COVID-19). J Neurol. Sep 2021;268(9):3059–71. https://doi.org/10.1007/s00415-021-10406-y.
21. Tso WW, Kwan MY, Wang YL, Leung LK, Leung D, Chua GT, et al. Severity of SARS-CoV-2 Omicron BA. 2 infection in unvaccinated hospitalized children: comparison to influenza and parainfluenza infections. Emerg Microb Infect 2022:1–29 (just-accepted).
22. Chen CS, Chang CH, Hu CF, Jian MJ, Chung HY, Chang CK, et al. Critical pediatric neurological illness associated with COVID-19 (Omicron BA.2.3.7 variant) infection in Taiwan: Immunological assessment and viral genome analysis in tertiary medical center. Int J Infect Dis. Sep 8 2022;124:45–8. https://doi.org/10.1016/j.ijid.2022.09.001.
23. Zhang Q, Bastard P, Liu Z, Le Pen J, Moncada-Velez M, Chen J, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science 2020;370:eabd4570.
24. Oshiumi H, Okamoto M, Fujii K, Kawanishi T, Matsumoto M, Kolke S, et al. The TLR3/TICAM-1 pathway is mandatory for innate immune responses to poliovirus infection. J Immunol 2011;187(10):5320–7.
25. Li S, Zheng X, Hu Y, You K, Wang J. RNF31 mediated ubiquitination of A20 aggravates inflammation and hepatocyte apoptosis through the TLR4/MyD88/NF-κB signaling pathway. Chem Biol Interact 2021;348:109623.