Journal of Neurological Disorders

J Neurol Disord
Volume 11:3, 2023

Case Report Open Access

The Case of Acute Necrotizing Encephalopathy in an Adolescent with COVID-19

Ling Liu[1,4], Rong Ou[1,4], ZongWen Chen[1,4], Wen Zhong[2,4#] and Hongxia Chen[3,4*]

[1]*Department of Pediatrics, Chongqing University, China*
[2]*Department of Radiology, Chongqing University, China*
[3]*Department of Hematology, Chongqing University, China*
[4]*Department of Medicine, Chongqing University, China*

Abstract

Introduction: Acute Necrotizing Encephalopathy (ANE) is a rare severe disease with high mortality or severe neurological sequelae characterized by rapid onset of consciousness disturbance and symmetric bilateral thalamic necrosis shown on imaging. To date, there have been limited investigations on SARS-CoV-2-related ANE, mainly in the form of case reports.

Case presentation: A previously healthy 13-year-old girl presented with rapid deterioration of consciousness, status epilepticus, elevated aminotransferase, and symmetrical multi-focal brain lesions on MRI images during the Omicron pandemic. She accepted mechanical ventilation and had a good response to plasma exchange and continuous blood purification, intravenous immunoglobulin and high-dose methylprednisolone.

Conclusion: ANE is a rapidly progressing disease that necessitates prompt detection through a combination of clinical presentation and imaging modalities. It is of paramount importance to enhance the awareness and knowledge of pediatricians regarding SARS-CoV-2-related encephalopathy. Upon diagnosis, treatment with high-dose intravenous methylprednisolone and IVIG should be contemplated. Additionally, plasma exchange and continuous blood purification could help alleviate liver damage in patients with ANE.

Keywords: Acute Necrotizing Encephalopathy (ANE) • Covid-19 • Adolescent

Introduction

Acute Necrotizing Encephalopathy (ANE) is a rare severe disease with high mortality or severe neurological sequelae characterized by rapid onset of consciousness disturbance and symmetric bilateral thalamic necrosis shown on imaging. ANE is commonly triggered by viral infection, predominantly influenza virus infection. In the last three years of the global epidemic of severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) infection, ANE has become one of the major co-occurring diseases causing severe illness and death in children with Coronavirus disease-2019 (COVID-19). However, there have been limited investigations on SARS-CoV-2-related ANE, mainly in the form of case reports. This study reports on a child diagnosed with ANE during the Omicron variant surge who had COVID-19 and presented with rapid deterioration of consciousness, status epilepticus, elevated aminotransferase, and symmetrical multi-focal brain lesions on MRI images. The case highlights the potential severity of ANE in children with COVID-19 and underlines the necessity for further research to elucidate the underlying mechanisms and develop optimal therapeutic approaches.

***Address for Correspondence:** Hongxia Chen, Department of Hematology, Chongqing University, China, Email: 112708410@qq.com*

***Note:** Wen Zhong and Hongxia Chen contributed equally to this work, so they will be chosen to have joint Corresponding authorship.*

Received: 16-May-2023, Manuscript No. jnd-23-98893; **Editor assigned:** 18-May-2023, PreQC No. P-98893 (PQ); **Reviewed:** 01-June-2023; QC No. Q-98893; **Revised:** 06-June-2023; Manuscript No. R-98893 (R); **Published:** 13-June-2023, **DOI:** 10.4172/2329-6895.11.3.553

Case Report

A previously healthy 13-year-old girl presented with four episodes of brief tonic seizures without an interictal return to the baseline clinical state for twelve hours after one day of fever, pharyngalgia, vomiting and diarrhoea. She tested positive for SARS-CoV-2 antigen *via* colloidal gold method or ORF1ab and N gene *via* real-time fluorescent quantitative polymerase chain reaction (RT-qPCR) using a nasopharyngeal swab sample. She had received two shots of the COVID-19 vaccine more than 6 months before her infection. She was admitted to the Intensive Care Unit in a coma. Upon physical examination, the patient was febrile with irregular breathing, shortness of breath without Cyanosis, and Sinus Tachycardia, but hemodynamically stable. Neurological examination revealed reduced consciousness (Glasgow Coma Scale score of 6: E1V2M3). The cough reflex was weak, and her pupils were 3 mm and insensitive to light. Abdominal reflexes were absent, and both upper limbs were flexed and hypertonic. Tendon reflexes, signs of meningeal irritation, and pyramidal signs were negative. Other systemic examinations were normal.

Laboratory workup revealed abnormal values for several markers, including elevated levels of alanine aminotransferase (2087 u/L), aspartate aminotransferase (3576 u/L), lactate dehydrogenase (>2554.4 u/L), plasma ammonium (77.3 umol/L), and procalcitonin (14.97 ng/mL). Serum levels of cytokines revealed increased interleukin (IL)-6 (14.28 pg/mL), while IL-10, IL-17, tumor necrosis factor (TNF)-α, interferon (IFN)-γ were normal. Coagulation tests showed prolonged prothrombin time (20.8 s), elevated D-dimer (18.97 mg/L) and fibrinogen degradation products (44.1 mg/L), and normal activated partial thromboplastin time and fibrinogen. The initial complete blood count showed lymphopenia (940/mm^3) and thrombocytopenia (73,000/mm^3). Thyroid function test indicated decreased triiodothyronine and normal tetraiodothyronine and thyroid-stimulating hormone. Troponin, immunoglobulin, cholesterol, triglyceride, electrolyte, creatinine, albumin, bile acid, C-reactive protein (CRP), anti-nucleic antibody, autoimmune liver disease antibodies, α1-antitrypsin, and ceruloplasmin were all normal. Polymerase chain reaction for Respiratory Syncytial Viral (RSV), Adenovirus, Influenza A virus, Influenza B virus, Parainfluenza virus type I and Parainfluenza virus type III, performed on

a nasopharyngeal swab, was negative. Blood culture was negative. A lumbar puncture was performed, and the open pressure was 14 cm H_2O. Cerebrospinal Fluid (CSF) showed significantly elevated protein levels (1.47 g/L) without pleocytosis (Table 1). Gram stain, ink stain, acid-fast stain, and culture were negative. Electroencephalogram showed diffuse 1.0 Hzδ-3.0 Hzδ slow background activity without epileptiform discharges. Chest X-ray and a non-contrast computed tomography of the head revealed no apparent lesions on day 2. Brain Magnetic Resonance Imaging (MRI) without contrast was performed on day 6 and revealed bilateral symmetric hyper intensities in both thalamus, cerebellar hemispheres, frontal lobes, temporal lobes, parietal lobes, occipital lobes, periventricular white matter, centrum semiovale, and corpus callosum during T2-weighted and Fluid Attenuated Inversion Recovery (FLAIR) images (Figures 1 and 2). Diffusion Weighted Imaging (DWI) showed a slightly higher signal, and Apparent Diffusion Coefficient (ADC) showed no definite decrease. No obvious abnormal signals were observed in the brain stem, cisterna and sulci. No enlargement of the ventricular system was observed. These imaging findings were compatible with the ANE of childhood.

Table 1. Acute necrotizing encephalopathy laboratory values

	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 14
White blood cell/mm^3	7,020		5,600	10,420		7,150		12,060
Neutrophil/mm^3	5,930		4,650	9,080		5,780		9,040
Lymphocyte/mm^3	940		600	520		740		2,060
Platelet/mm^3	73,000		65,000	1,00,000		1,97,000		8,01,000
C-reactive Protein, mg/L	<0.5			2.38		1		<0.5
Procalcitonin, ng/mL	14.97			1.76				
Interleukin-6, pg/mL	14.28		15.23			2.87		
Alanine aminotransferase, U/L	2087		781.1		237.5		144.3	29.6
Aspartate aminotransferase, U/L	3576		481.4		29.5		31.3	31.3
Lactate dehydrogenase, U/L	>2554.4		445		190		196	196
D-dimer, mg/L	18.97	1.5	0.82		0.69			1.95
Prothrombin time, s	20.8	13.4	12.3		12.3			
Activated partial thromboplastin times	33.1	32	25.4		24.6			
Fibrinogen, g/L	2.22	1.27	1.66		3.05			
Cerebrospinal fluid protein, g/L		1.47		1.07			0.55	0.36
Cerebrospinal white blood cell/mm^3		4		1			0	0

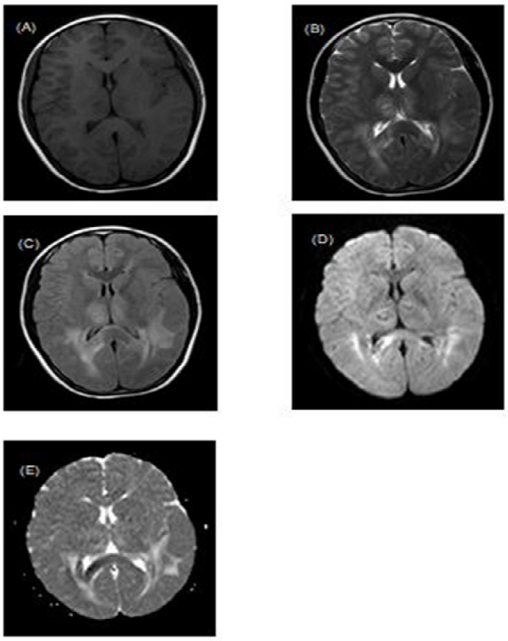

Figure 1. (A) Brain MRI on day 6 revealing decreased signal on T1 (B) Increased signal on T2, (C) Fluid-attenuated inversion recovery sequence (D) and diffusion-weighted sequence (E) and decreased apparent diffusion coefficient value in the bilateral thalami, periventricular white matter and the splenium of the corpus callosum

The patient was treated with antibiotics, anticonvulsive drugs, hepato-protective drugs, and mannitol, followed by intravenous low-dose methylprednisolone (2 mg/kg/day for 4 days). There was no seizure attack during hospitalization. Given the severe liver damage, plasma exchange and continuous blood purification were performed on day 3. However, she experienced respiratory failure under oxygen inhalation with a double nasal catheter, necessitating mechanical ventilation and intravenous immunoglobulin (IVIG) (0.5 g/kg/day for 4 days) on day 4, followed by high-dose intravenous methylprednisolone (30 mg/kg/day for 3 days) on day 6. Meanwhile, her cough reflex recovered, and she was taken off the ventilator on day 6. She was in a vigil coma on day 11 when the CSF protein level returned to normal. On day 18, she regained consciousness with a GCS of 12: E4V2M6, and her temperature returned to normal. She regained the ability to take care of herself and was discharged home on day 25 with residual deficits, including debilitation, right upper limb strength decline, fine motor disorder, declining math skills, memory loss and myopia which persisted after one-month follow-up.

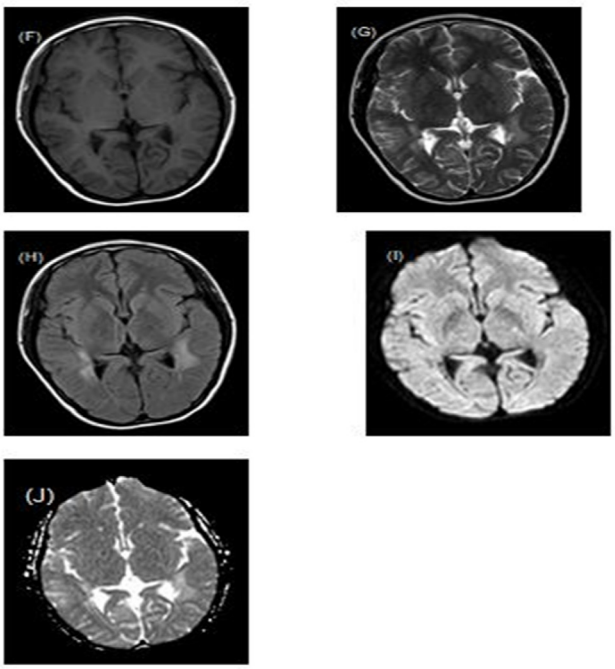

Figure 2. Repeat brain MRI on day 60 revealing remarkable absorption of lesions (F-J)

Discussion

The patient was the only one who developed COVID-19-related life-threatening neurologic involvement in our hospital. Similarly, SARS-CoV-2-related ANE of childhood has been reported to be rare worldwide. Prior literature indicated that pre-existing neurologic complex chronic condition was a substantial risk factor for neurologic complications in COVID-19 patients [1]. However, our patient and the reported children with ANE and COVID-19 were all previously healthy, with a wide range of 5 weeks to 13 years old [1-4], and were similar to cases of influenza-associated ANE [1], suggesting that neurological comorbidity might not be a predisposing factor for ANE. A recent study found that highly elevated level of PCT>4.25 ng/mL might serve as an early indicator for influenza-associated ANE with a specificity and sensitivity of 100.0% and 73.3%, respectively [5,6]. However, it should be noted that not all children with ANE caused by COVID-19 exhibit high PCT level [2], and ANE typically exhibits normal or slightly elevated level of CRP opposite to PCT [6]. Additionally, a higher neutrophil-to-lymphocyte ratio (median, 12.2) and frequency of D-dimer level greater than 3 mg/L fibrinogen equivalent units (49%) were reported among those with fatal neurologic conditions caused by COVID-19 [1]. Our patient showed the highest D-dimer level of 18.97 mg/L on day 2 and a neutrophil-to-lymphocyte ratio 17.5 on day 5, indicating the severity of the disease.

The patient fulfilled all the diagnostic criteria for ANE [1], except that the detection of SARS-CoV-2 PCR in CSF was unavailable in our laboratory, and CSF autoimmune tests were not conducted. Nonetheless, based on the typical clinical manifestations, CSF and MRI findings, a diagnosis of COVID-19 associated with ANE was established. So the patient was treated with intravenous methylprednisolone and immunoglobulin, plasma exchange and continuous blood purification. To the best of our knowledge, this is the first report of plasma exchange and continuous blood purification being used in SARS-CoV-2-related ANE in children, which resulted in a rapid decline of alanine transaminase from 2087 u/L to 481.4 u/L, and aspartate aminotransferase from 3756 u/L to 781.1 u/L, respectively, on day 4. We observed that early low-dose glucocorticoids, plasma exchange and continuous blood purification, did not enhance prognosis. The patient recovered from respiratory failure with intravenous immunoglobulin and high-dose methylprednisolone, without the use of anti-SARS-CoV-2 drugs, indicating an immune-mediated cause. Furthermore, recent evidence suggests that tocilizumab, an anti-IL-6 monoclonal antibody, may benefit children with severe ANE [2,3,5]. However, determining the optimal combined treatments remains challenging due to the rarity of this condition.

SARS-CoV-2 has been validated to be neuroinvasive [1], but the pathophysiology of ANE may be related to an intense cytokine storm rather than direct viral invasion. Several studies have demonstrated that SARS-CoV-2 nucleic acid is not detected in CSF in children with ANE [2,3]. Additionally, the virus may not cause symmetrical brain lesions. Adult ANE showed elevation of IL-6 in CSF and serum [1], which was highly related with severe COVID-19 and may serve as a potential treatment target. Meanwhile, other pro-inflammatory cytokines, including TNF-α, IL-10, and IL-1, were also detected in patients with severe COVID-19 [7-12]. The cytokine storm may impair the blood-brain barrier (BBB) and activate microglia and astrocytes, leading to the secretion of inflammatory mediators and resulting in neurotoxicity. In our study, IL-6 level was not a very high concentration with normal IL-10 and TNF-α, suggesting of not a simple cytokine dysregulation. SARS-CoV-2, through ACE2 receptors expressed on cerebrovascular endothelial cells, can initiate vasculitis and coagulation cascade which can promote hypoxic-ischemic injury and infarcts [2]. The biopsy conducted on the right thalamus of SARS-CoV-2-related ANE patient revealed perivascular neutrophilic inflammation, indicating small vessel vasculitis with significant hemorrhage and necrosis [2]. Therefore, we cannot exclude the possibility that SARS-CoV-2 may invade brain tissues *via* damaged BBB or cerebrovascular endothelial cells despite negative detection in CSF. A brain biopsy may provide further insights into the underlying pathogenesis.

Conclusion

In summary, ANE is a rapidly progressing disease that necessitates prompt detection through a combination of clinical presentation and imaging modalities. It is of paramount importance to enhance the awareness and knowledge of pediatricians regarding SARS-CoV-2-related encephalopathy. Upon diagnosis, treatment with high-dose intravenous methylprednisolone and IVIG should be contemplated. Additionally, plasma exchange and continuous blood purification could help alleviate liver damage in patients with ANE.

Funding

This project was supported by Natural Science Foundation of Chongqing (No.cstc2020jcyj-msxmX0969).

Acknowledgement

The authors would like to thank Chongqing University Three Gorges Hospital, SARS-CoV-2 laboratory and medical team that are fighting against the illness.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics Statement

The study involving human participants was reviewed and approved by the Ethics Committee of Chongqing University Three Gorges Hospital (Approval number: 2023 NO.27). Written informed consent of participants was waived with an approval by the Institutional Review Board.

Author Contributions

All authors participated in study design and conceptualization of the study. LL and RO collected data. LL performed the literature review for this article and was a major contributor in writing the manuscript. HC reviewed and revised the manuscript. All authors read and approved the final manuscript.

References

1. Antoon, JW, Hall M, Howard LM and Herndon A, et al. "COVID-19 and Acute Neurologic Complications in Children." *Pediatrics* 150(2022): e2022058167.
2. Khan, M, Bhattarai S, Boyce TG and Hayek RA, et al. "Acute Necrotizing Encephalopathy Associated with Coronavirus Disease 2019 in an Infant." *J Pediatr* 247(2022): 160-162.
3. Wang, PY, Yang MT and Liang JS. "Acute Necrotizing Encephalopathy Caused by SARS-CoV-2 in a Child." *Pediatr Neonatol* 63(2022): 642-644.
4. Lazarte, RC, Guevara CJ, Romero L and Pinto GD. "Acute Necrotizing Encephalopathy Associated With SARS-CoV-2 Exposure in a Pediatric Patient." Cureus 13(2021): e15018.
5. Ho, JHY, Lee CYM, Chiong YK and Aoyama R, et al. "SARS-CoV-2-Related Acute Necrotizing Encephalopathy of Childhood With Good Response to Tocilizumab in an Adolescent." *Pediatr Neurol* 139(2023): 65-69.
6. Song, Y, Li S, Xiao W and Shen J, et al. "Influenza-Associated Encephalopathy and Acute Necrotizing Encephalopathy in Children: A Retrospective Single-Center Study." *Med Sci Monit* 27(2021): e928374.
7. LaRovere, KL, Riggs BJ, Poussaint TY and Young CC, et al. "Neurologic Involvement in Children and Adolescents Hospitalized in the United States for COVID-19 or Multisystem Inflammatory Syndrome." *JAMA Neurol* 78(2021):536-547.
8. Mizuguchi, M, Ichiyama T, Imataka G and Okumura A, et al. "Guidelines for the Diagnosis and Treatment of Acute Encephalopathy in Childhood." *Brain Dev* 43(2021): 2-31.
9. Stein, SR, Ramelli SC, Grazioli A and Chung JY, et al. "SARS-CoV-2 Infection and Persistence in the Human Body and Brain at Autopsy." Nature 612(2022): 758-763.
10. Lin, YY, Lee KY, Ro LS and Lo YS, et al. "Clinical and Cytokine Profile of Adult Acute Necrotizing Encephalopathy." *Biomed J* 42(2019): 178-186.
11. Boldrini, M, Canoll PD and Klein RS. "How COVID-19 Affects the Brain." *JAMA Psychiatry* 78(2021): 682-683.
12. Rettenmaier, LA, Abdel-Wahed L, Abdelmotilib H and Conway KS, et al. "COVID-19-Associated Necrotizing Encephalopathy Presenting without Active Respiratory Symptoms: A Case Report with Histopathology." *J Neurovirol* 28(2022): 172-176.

How to cite this article: Liu, L, Ou R, Chen ZW and Zhong W, et al. "The Case of Acute Necrotizing Encephalopathy in an Adolescent with COVID-19." *J Neurol Disord*. 11 (2023):553.