Journal of
Medical Case Reports

CASE REPORT

Open Access

Acute necrotizing encephalopathy in an adult presenting with typical imaging findings and distinctive cerebrospinal fluid characteristics: a case report

Yan Wang[1], Mianwang He[1], Hong Zhao[1], Fei Yang[1*], Jiatang Zhang[1] and Shengyuan Yu[1]

Abstract

Background Acute necrotizing encephalopathy is a rare, clinically distinct subgroup of acute encephalopathy, which may be a complication of coronavirus disease 2019.

Case presentation A 22-year-old male of Han Chinese with a yellow complexion presented with fever, psychological and behavioral abnormalities, seizures, and coma. Cerebrospinal fluid tests indicated leukocytosis, high protein concentrations, and significantly elevated levels of neuron-specific enolase, interleukin-2, interleukin-6, and interleukin-8. Magnetic resonance imaging revealed restricted diffusion in the bilateral thalami and splenium of the corpus callosum, and no hemorrhagic signals were detected on susceptibility-weighted imaging. Hyperintense and hypointense lesions in the bilateral thalami, brainstem, cerebellum, and splenium of the corpus callosum were observed in T1- and T2-weighted sequences without gadolinium enhancement. At the 6-month follow-up, the T1 and T2 sequences showed significant atrophy in the cerebellar hemispheres and brachium pontis and an enlarged fourth ventricle. After symptomatic and immunotherapy treatment, the prognosis was good.

Conclusion We report a rare case of a 22-year-old male diagnosed acute necrotizing encephalopathy showing typical imaging findings and distinctive cerebrospinal fluid presentation. In adults, heightened awareness of acute necrotizing encephalopathy is crucial because early recognition and treatment have the potential to enhance prognosis.

Keywords Acute necrotizing encephalopathy, Adult, Cerebrospinal fluid, Imaging, Treatment

Background

Acute necrotizing encephalopathy (ANE) is a rare, clinically distinct subtype of acute encephalopathy [1]. ANE is a complication of influenza and other viral infections associated with an intracranial cytokine storm that disrupts the blood–brain barrier and triggers brain edema, petechial hemorrhage, and necrosis [2]. It is characterized by rapid onset, a fulminant course, and low morbidity and high fatality rates [1], which is most common in children [3]. The radiological findings typically reveal multifocal and symmetrical brain lesions, predominantly impacting the bilateral thalamus, basal ganglia, brainstem, and cerebellar white matter [4]. The disease is often misdiagnosed in adults owing to its relative rarity, leading to the frequent oversight of the optimal treatment period. With the global spread of coronavirus disease 2019 (COVID-19,) a wide spectrum of neurological complications has emerged, including Guillain–Barre syndrome,

*Correspondence:
Fei Yang
yangfeiyanbian@163.com
[1] The First Medical Center, Department of Neurology, Chinese PLA General Hospital, Fuxing Road 28, Haidian District, Beijing 100853, China

acute cerebrovascular disease, encephalitis, and encephalopathy [5]. Among them, there has been an increase in reported cases of adult necrotizing encephalopathy, but owing to the serious condition of this disease, good prognosis is observed in a minority of patients [5, 6]. Here, we report a rare adult case of ANE with typical imaging findings and distinctive cerebral spinal fluid (CSF) presentation who recovered.

Case presentation

A 22-year-old male of Han Chinese with a yellow complexion presented with sudden fever for 10 days, psychological and behavioral abnormalities for 3 days, and seizures and coma for 2 days. When his condition did not improve with symptomatic treatment at a local hospital, he was admitted to our hospital. Neurological evaluation revealed a therapeutic coma, diminished limb activity with hypotonia, no tendon reflex, a positive bilateral Babinski sign, and a meningeal irritation sign. The patient had contracted COVID-19 2 months prior. He had increased intracranial pressure (> 330 mm H_2O), and CSF tests indicated leukocytosis (164×10^6/L), high protein concentrations (1619.3 mg/L), and significantly elevated levels of neuron-specific enolase (NSE, 306.6 ng/mL), interleukin-2 (1404 μ/mL), interleukin-6 (822 pg/mL), and interleukin-8 (1817 pg/mL). His CSF glucose and chloride levels were normal. Metagenomic next-generation sequencing and neural autoantibody tests of serum and CSF were negative. Serum levels of immunoglobulin G (IgG)- and immunoglobulin M (IgM)-specific antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were detected. Computed tomography of his brain was unremarkable. Electroencephalography revealed single spikes in the left prefrontal and frontal areas. Needle electromyography showed fibrillation potentials and positive sharp waves in the left first dorsal interosseous (LFDI), biceps femoris (BF), and bilateral tibialis anterior (BLA) regions. No motor unit potential was evident in the LFDI or BF regions; however, long-duration, high-amplitude unit potentials were apparent in the BLA region. The compound muscle action potential amplitudes of the common peroneal nerve were markedly reduced bilaterally (left 0.5 mV and right 0.2 mV). The F-waves of the left ulnar and tibial regions could not be elicited. As tracheal intubation and mechanical ventilation had commenced, magnetic resonance imaging (MRI) of the brain was not possible upon arrival at the hospital. He remained unconscious after sedation was discontinued with a Glasgow Coma Scale (GCS) score of 3 and a Full Outline of Unresponsiveness (FOUR) score of 5.

The clinical manifestations and CSF characteristics excluded autoimmune or viral encephalitis. Given the history of COVID-19, radiculopathy, and elevated CSF NSE levels, ANE was suspected. On days 11 and 12 after onset, we initiated methylprednisolone (240 mg for 10 days, then gradually reduced the dose) and intravenous immunoglobulin (30 g for 5 days). Levetiracetam (1.5 g every 12 hour) and phenobarbital sodium (intramuscular, 200 mg every 8 hour) were used to treat the seizures, and the ganciclovir (intravenous, 0.25 g every 12 hour) was administered used for antiviral therapy. In addition to these, symptomatic and supportive treatments were sufficient. Repeated lumbar punctures revealed that intracranial pressure, and CSF leukocyte, protein, interleukin, and NSE levels gradually decreased toward normal (Figs. 1, 2), and the clinical symptoms improved slowly.

One month later, the patient emerged from the coma and could follow simple instructions. He was weaned from mechanical ventilation over 8 weeks, after which MRI of his brain was performed. Diffusion-weighted imaging (DWI) revealed symmetrical bilateral hyperintense lesions in the thalami and splenium of the corpus callosum (Fig. 3). Apparent diffusion coefficient (ADC) imaging did not show the typical tricolor pattern in the bilateral thalami but did show a slightly hyperintense signal in the splenium of the corpus callosum (Fig. 3). Susceptibility-weighted imaging (SWI) showed no hemorrhagic signals and enhanced scan was normal (Fig. 3). Hyperintense and hypointense lesions were observed in T2WI and T1WI sequences, respectively, in the splenium of the corpus callosum, bilateral thalami, brainstem, and brachium pontis, indicating malacia and necrosis. Slight cerebellar atrophy was seen in coronal MRI (Fig. 4). Together, the imaging findings are consistent with the diagnosis of ANE.

The patient received rehabilitation treatment and at 6-month follow-up he was conscious, answered questions accurately, and could eat independently. His level of consciousness and cerebral cortical functions recovered (GCS score of 15 and FOUR score of 16), his motor function improved, and his upper limb muscle strength was restored to grade 5; however, mild ataxia persisted. He experienced no further seizures or fever. The patient did not regain lower limb muscle strength, which remained at grade 0, and his deep tendon reflex was absent due to severe nerve root damage. Follow-up motor nerve conduction studies revealed the absence of motor evoked responses in bilateral tibial nerves and common peroneal nerve. The levels of leukocytes, proteins, NSE, and interleukins in CSF were normal (Figs. 1, 2). Follow-up DWI revealed persistent hyperintensities in the thalami and splenium of the corpus callosum, which were diminished compared with previous scans (Fig. 3). The 8-week and 6-month ADC, SWI, and enhanced scan findings did not

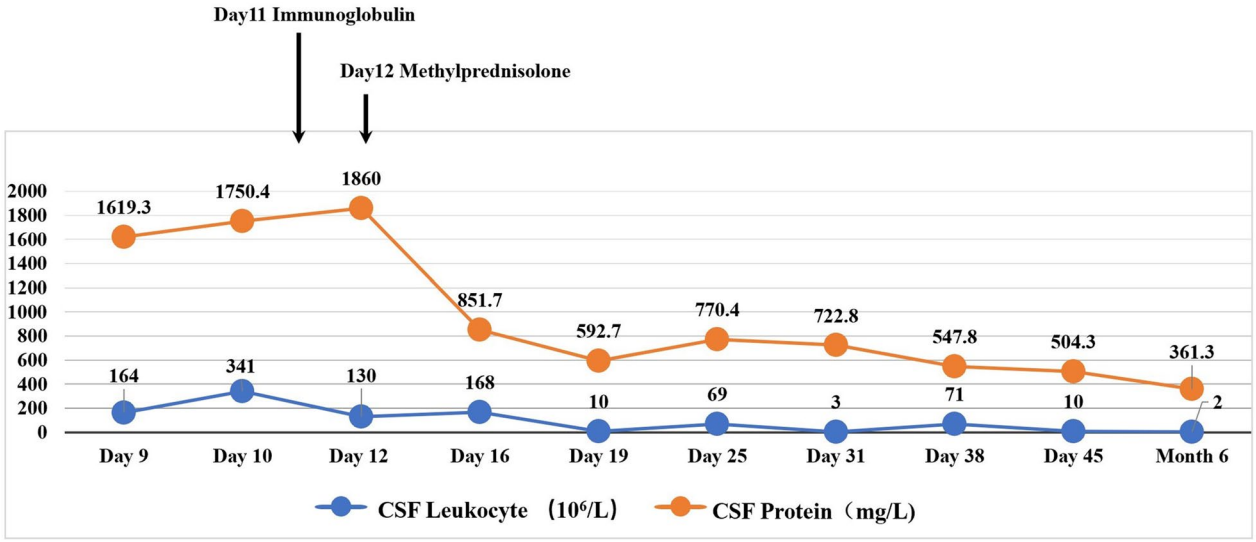

Fig. 1 Leukocyte and protein levels in cerebral spinal fluid. Treatment with methylprednisolone and immunoglobulin gradually decreased leukocyte and protein levels in cerebral spinal fluid toward normal

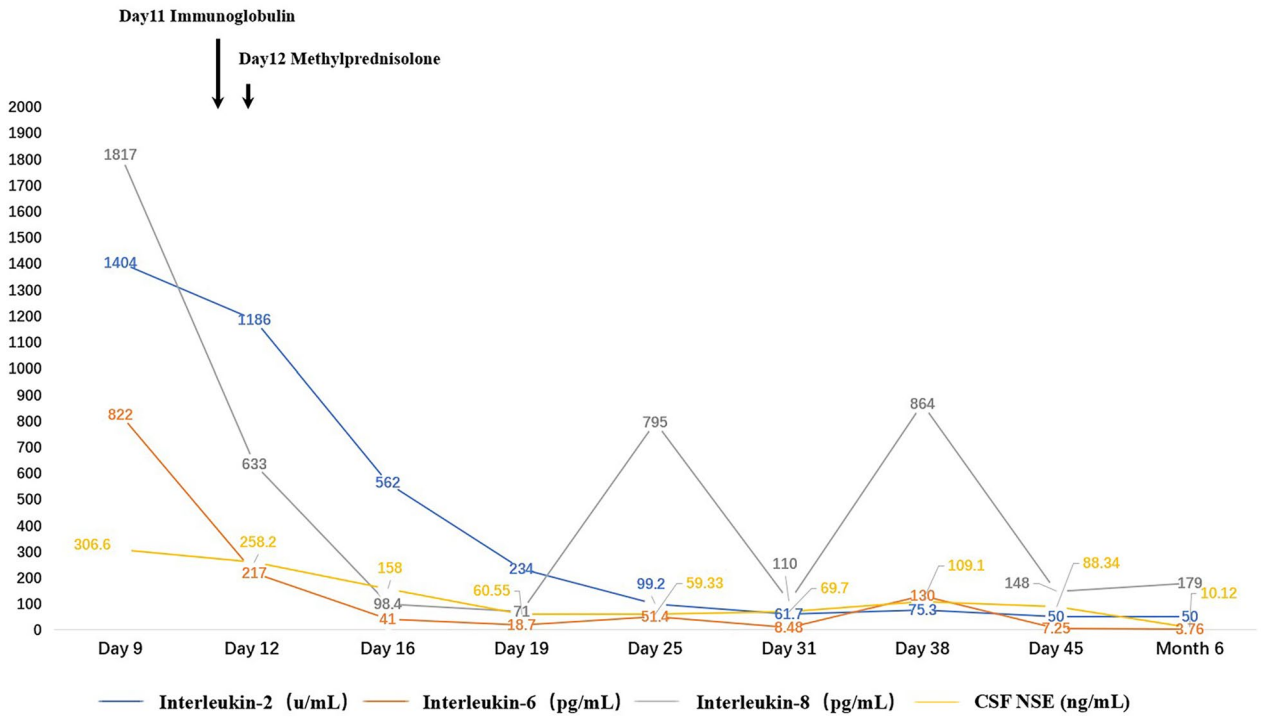

Fig. 2 Levels of interleukins and neuron-specific enolase in cerebral spinal fluid. Treatment with methylprednisolone and immunoglobulin gradually decreased interleukin and neuron-specific enolase levels in cerebral spinal fluid toward normal

differ (Fig. 3). T1WI and T2WI sequences showed significant atrophy in the cerebellar hemispheres and brachium pontis and an enlarged fourth ventricle (Fig. 4). Overall, the follow-up findings were satisfactory and the prognosis was good.

Discussion

ANE is a rare, rapidly progressing encephalopathy characterized by altered consciousness, seizures, focal neurological deficits, and a high mortality rate [7]. Its etiology and pathogenesis are unknown but thought

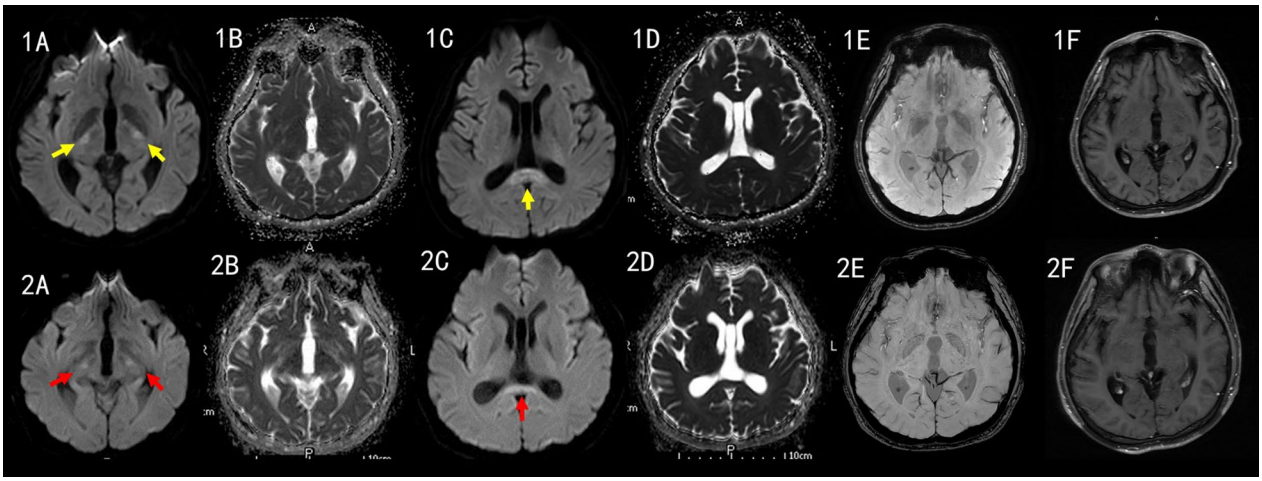

Fig. 3 Changes in magnetic resonance imaging over time. Upper row: Findings at 8 weeks. Diffusion-weighted images show symmetrical hyperintensity in the bilateral thalami and splenium of the corpus callosum (**1A, 1C**, yellow arrows) with no significant enhancement (**1F**). Apparent diffusion coefficient images showed no typical tricolor patterns on bilateral thalami (**1B**) and a slightly hyperintense signal in the splenium of the corpus callosum (**1D**). Susceptibility-weighted imaging showed no evidence of hemorrhage in the thalami (**1E**). Lower row: findings at the 6-month follow-up. Compared to the 8-week findings, diffusion-weighted images hyperintensity was diminished in the thalami and splenium of the corpus callosum (**2A, 2C**, red arrows). No changes were seen in apparent diffusion coefficient, susceptibility-weighted imaging, and contrast-enhanced-magnetic resonance images (**2B, 2D, 2E, 2F**)

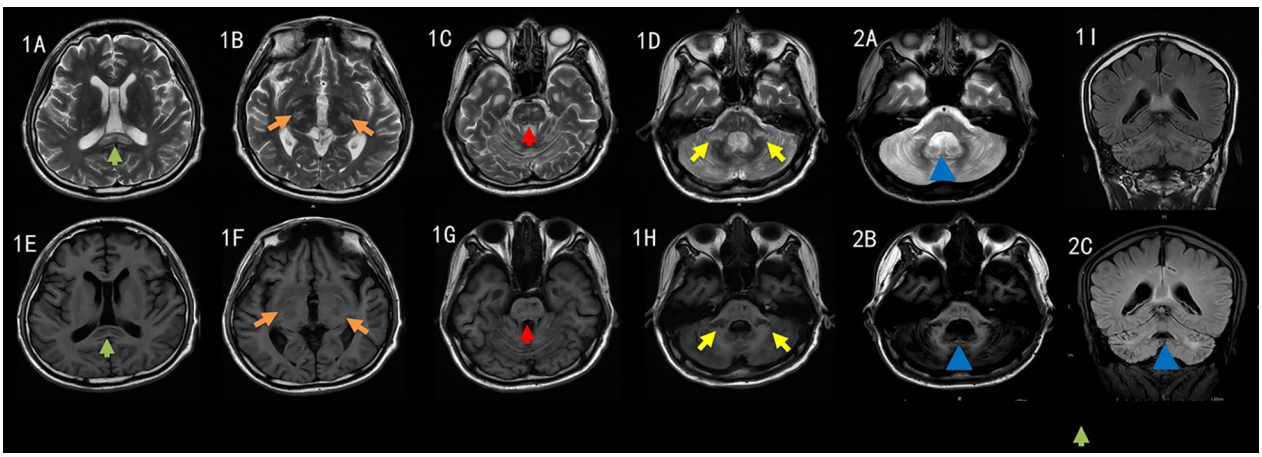

Fig. 4 Changes in T1-weighted, T2-weighted and FLAIR imaging over time. Findings at 8 weeks (1): hyperintense and hypointense lesions on T1- and T2-weighted images, respectively, in the splenium of the corpus callosum (**1A**, **1E**, green arrow), bilateral thalami (**1B, 1F**, orange arrows), brainstem (**1C**, **1G**, red arrow), and brachium pontis (**1D**, 1H, yellow arrows). Slight cerebellar atrophy is seen in coronal magnetic resonance images (**1I**). Findings at the 6-month follow-up (2): follow-up imaging showed significant atrophy in the cerebellum and brachium pontis and an enlarged fourth ventricle (**2A–2C**, blue triangles)

to involve a cytokine storm, dysfunction of the blood–brain barrier, and direct viral-mediated endotheliopathy [8]. Moreover, environmental factors, which may contribute to antecedent infections, and host factors including individual susceptibility and gene modifications may be involved [9]. ANE has been linked to various infectious pathogens, including influenza A and B, herpes simplex virus, and SARS-CoV-2 [10].

The existing literature has previously reported a higher incidence of ANE in infants and young children, while it is considered rare among adults [4]. However, since the emergence of the COVID-19, there has been a significant increase in the prevalence rate of ANE. The possible reason for this phenomenon could be attributed to the fact that the SARS-CoV-2 triggers a hyperactive immune response [5]. This patient had COVID-19 infection

2 months prior to admission and tested serum positive for SARS-CoV-2 IgM upon admission. Considering the persistent positivity of SARS-CoV-2 IgM, we suspect a correlation between the current clinical course and the previous COVID-19 infection.

Although the absence of CSF leukocytosis is one of the diagnostic criteria for ANE [4, 11], our patient exhibited CSF leukocytosis. A cytokine storm or hyperinflammatory state can induce leukocyte chemotaxis, which may cause CSF leukocytosis. Therefore, CSF leukocytosis may occur in not only inflammatory encephalitis but also ANE. Although elevated NSE levels in CSF have been reported in patients with subarachnoid hemorrhage and severe epilepsy [12, 13], the levels in our patient were higher, indicating severe neuronal necrosis and disintegration [14] in accordance with the pathophysiological mechanisms of ANE. This may be a useful diagnostic indicator for ANE. Lower extremity motor function was severely impaired in our patient, which was most likely due to an inflammatory cytokine storm related to nerve root damage. We found no previous reports of radiculopathy associated with ANE in literature.

The typical neuroradiological features of ANE are multifocal, symmetrical brain lesions in the bilateral thalami, brainstem, cerebral white matter, and cerebellum [2], all of which were found in our patient. At the 6-month follow-up, DWI showed persistent hyperintensity in the bilateral thalami and splenium of the corpus callosum. This finding has previously been reported in intravascular lymphoma, hereditary diffuse leukoencephalopathy with spheroids, and stroke [15–17], but not in ANE. In our case, persistent hyperintensity in DWI accompanied by a slightly elevated ADC signal may have resulted from either a continuous increase in vascular permeability or inflammatory response causing focal vasogenic edema, or the T2 shine-through effect. Further study is needed to determine the mechanisms underlying this phenomenon.

Previous neuroimaging studies of ANE on ADC have described a laminar or tricolor pattern in the center of thalamic lesions with hemorrhage and necrosis, surrounding the central thalamic lesions due to cytotoxic edema, and in the periphery of the lesion suggesting vasogenic edema [2, 3]. Our patient did not exhibit these findings, possibly because the neuroradiological features of ANE are characterized by dynamic changes during the clinical course corresponding to pathophysiological changes from edema to necrosis [2, 18]. However, MRI was performed 2 months after our patient emerged from a coma when the acute swelling of oligodendrocytes and extravasations had improved with only necrosis and malacia remaining. Perivascular hemorrhage is a pathophysiological feature of ANE, which may appear as a hypointensity in SWI [2, 7] in some cases. A previous study of patients with ANE found that hemorrhagic lesions in MRI indicated severe neurological sequelae [19]. No definite hemorrhage was seen in SWI in our patient, possibly because he received early immunotherapy and endothelial injury was less severe.

Currently, there are no recommended therapies for ANE. The majority of cases have received intensive care, symptomatic and empirical treatment (antiviral therapy), and immunomodulatory agents [2]. Given that the pathogenesis of ANE may involve elevated cytokine levels secondary to a viral infection via immune-mediated mechanisms, immunomodulatory therapies that suppress cytokine production have the potential to improve the outcome of ANE. Intravenous glucocorticoids, immunoglobulin, and plasma exchange in the early stages of the disease had been considered effective [2, 20, 21]. The patient was transferred to our hospital on day 10 after the onset of illness; we initiated glucocorticoid and immunoglobulin as soon as possible and the therapeutic effect was satisfactory.

Given the severity of ANE, most patients cannot undergo imaging studies in the early stage, compromising prognosis. Our case demonstrates that in the absence of imaging evidence neurologists should consider ANE in patients who present with severe new-onset disturbed consciousness, refractory seizures, and significantly elevated CSF NSE levels. Elevated leukocyte levels in the CSF are not an exclusion criterion. Early diagnosis and prompt immunomodulatory treatment may offer a good long-term outcome.

Conclusion

We report the case of a 22-year-old male diagnosed with ANE with typical imaging and distinctive CSF presentation. He had a relatively good prognosis after prompt treatment. In adults, heightened awareness of ANE is crucial because early diagnosis and treatment may be lifesaving.

Abbreviations

ANE	Acute necrotizing encephalopathy
COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
CSF	Cerebral spinal fluid
NSE	Neuron-specific enolase
LFDI	Interosseous
BF	Biceps femoris
BLA	Bilateral tibialis anterior
MRI	Magnetic resonance imaging
GCS	Glasgow Coma Scale
FOUR	Full outline of unresponsiveness
DWI	Diffusion-weighted imaging
ADC	Apparent diffusion coefficient
SWI	Susceptibility-weighted imaging

Acknowledgements
Our thanks to the this patient and his family for understanding the hardships and uncertainties that such an extraordinary clinical picture has implied and for their collaboration in the hope of his case helping other patients.

Author contributions
YW collected the data and designed and drafted the manuscript; MWH and HZ participated in the data collection, the design of this article and helped to draft the manuscript; FY, JTZ, and SYY gave instructions. All authors read and approved the final manuscript.

Funding
This work was not funded by any grants.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Chinese PLA General Hospital. Written informed consent was obtained from the patient.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declares that they have no competing interests.

Received: 9 July 2024 Accepted: 6 February 2025
Published online: 08 March 2025

References

1. Qin N, Wang J, Peng X, Wang L. Pathogenesis and management of acute necrotizing encephalopathy. Expert Rev Neurother. 2023;23(7):641–50.
2. Wu X, Wu W, Pan W, Wu L, Liu K, Zhang HL. Acute necrotizing encephalopathy: an underrecognized clinicoradiologic disorder. Mediators Inflamm. 2015;2015: 792578.
3. Wu L, Peng H, Jiang Y, He L, Jiang L, Hu Y. Clinical features and imaging manifestations of acute necrotizing encephalopathy in children. Int J Dev Neurosci. 2022;82(5):447–57.
4. Mizuguchi M. Acute necrotizing encephalopathy of childhood: a novel form of acute encephalopathy prevalent in Japan and Taiwan. Brain Dev. 1997;19(2):81–92.
5. Zamani R, Pouremamali R, Rezaei N. Central neuroinflammation in Covid-19: a systematic review of 182 cases with encephalitis, acute disseminated encephalomyelitis, and necrotizing encephalopathies. Rev Neurosci. 2022;33(4):397–412.
6. Wang ML, Liu R, Zhang LM, Zhao B, Jia R, Zhao Y, *et al*. Clinical experience in the diagnosis and treatment of adult acute necrotizing encephalopathy. NeuroImmunoModulation. 2022;29(4):468–75.
7. Ziemele D, Ķauķe G, Skrējāne K, Jaunozoliņa L, Karelis G. A fatal case of COVID-19-associated acute necrotizing encephalopathy. Eur J Neurol. 2021;28(11):3870–2.
8. Mullaguri N, Sivakumar S, Battineni A, Anand S, Vanderwerf J. COVID-19 related acute hemorrhagic necrotizing encephalitis: a report of two cases and literature review. Cureus. 2021;13(4): e14236.
9. Neilson DE. The interplay of infection and genetics in acute necrotizing encephalopathy. Curr Opin Pediatr. 2010;22(6):751–7.
10. Zhu HM, Liu ZS. Advances in clinical and imaging studies of acute necrotizing encephalopathy. Zhonghua Er Ke Za Zhi. 2017;55(11):865–8.
11. Lin YY, Lee KY, Ro LS, Lo YS, Huang CC, Chang KH. Clinical and cytokine profile of adult acute necrotizing encephalopathy. Biomed J. 2019;42(3):178–86.
12. Moritz S, Warnat J, Bele S, Graf BM, Woertgen C. The prognostic value of NSE and S100B from serum and cerebrospinal fluid in patients with spontaneous subarachnoid hemorrhage. J Neurosurg Anesthesiol. 2010;22(1):21–31.
13. Mu RZ, Liu S, Liang KG, Jiang D, Huang YJ. A meta-analysis of neuron-specific enolase levels in cerebrospinal fluid and serum in children with epilepsy. Front Mol Neurosci. 2020;13:24.
14. Lamers KJ, van Engelen BG, Gabreëls FJ, Hommes OR, Borm GF, Wevers RA. Cerebrospinal neuron-specific enolase, S-100 and myelin basic protein in neurological disorders. Acta Neurol Scand. 1995;92(3):247–51.
15. Rivers CS, Wardlaw JM, Armitage PA, *et al*. Persistent infarct hyperintensity on diffusion-weighted imaging late after stroke indicates heterogeneous, delayed, infarct evolution. Stroke. 2006;37(6):1418–23.
16. Kageyama T, Yamanaka H, Nakamura F, Suenaga T. Persistent lesion hyperintensity on brain diffusion-weighted MRI is an early sign of intravascular lymphoma. BMJ Case Rep. 2017;2017:bcr2017220099.
17. Terasawa Y, Osaki Y, Kawarai T, *et al*. Increasing and persistent DWI changes in a patient with hereditary diffuse leukoencephalopathy with spheroids. J Neurol Sci. 2013;335(1–2):213–5.
18. Mizuguchi M, Abe J, Mikkaichi K, *et al*. Acute necrotising encephalopathy of childhood: a new syndrome presenting with multifocal, symmetric brain lesions. J Neurol Neurosurg Psychiatry. 1995;58(5):555–61.
19. Kim JH, Kim IO, Lim MK, *et al*. Acute necrotizing encephalopathy in Korean infants and children: imaging findings and diverse clinical outcome. Korean J Radiol. 2004;5(3):171–7.
20. Bassuk AG, Burrowes DM, McRae W. Acute necrotizing encephalopathy of childhood with radiographic progression over 10 hours. Neurology. 2003;60(9):1552–3.
21. Okumura A, Mizuguchi M, Kidokoro H, *et al*. Outcome of acute necrotizing encephalopathy in relation to treatment with corticosteroids and gammaglobulin. Brain Dev. 2009;31(3):221–7.

Publisher's Note