CASE REPORT

WILEY

Recurrent infection triggered encephalopathy syndrome in a pediatric patient with *RANBP2* mutation and severe acute respiratory syndrome coronavirus 2 infection

Jiaqi Li[1] | Feng Huo[1] | Shuo Wang[1] | Yimu Fan[1] | Jie Wu[1] | Zhezhe Zhang[1] | Shuangjun Liu[1] | Quan Wang[1,2]

[1]Emergency Department, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
[2]Pediatric Intensive Care Unit, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

Correspondence
Quan Wang, Pediatric Intensive Care Unit, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing 100045, China.
Email: wq_bch@163.com

Received: 5 August 2023
Accepted: 31 October 2023

ABSTRACT

Introduction: Acute necrotizing encephalopathy (ANE), a fatal subtype of infection-triggered encephalopathy syndrome (ITES), can be triggered by many systemic infections. *RANBP2* gene mutations were associated with recurrent ANE.

Case presentation: Here we report a 1-year-old girl with recurrent ITES and *RANBP2* mutation. She was diagnosed with influenza-associated encephalopathy and made a full recovery on the first episode. After severe acute respiratory syndrome coronavirus 2 infection, the patient presented with seizures and deteriorating mental status. Brain magnetic resonance imaging revealed necrotic lesions in bilateral thalami and pons. Methylprednisolone, immunoglobulin, and interleukin 6 inhibitors were administered. Her consciousness level was improved at discharge. Nineteen cases of 2019 coronavirus disease-related ANE have been reported, of which 22.2% of patients died and 61.1% had neurologic disabilities. *RANBP2* gene mutation was found in five patients, two of whom developed recurrent ITES.

Conclusion: Patients with *RANBP2* mutations are at risk for recurrent ITES, may develop ANE, and have a poor prognosis after relapse.

KEYWORDS

Acute necrotizing encephalopathy, SARS-CoV-2, COVID-19, *RANBP2*

INTRODUCTION

Since the end of 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has gradually become prevalent worldwide. SARS-CoV-2 can cause acute necrotizing encephalopathy (ANE), the most severe and fatal subtype of infection-triggered encephalopathy syndrome (ITES), in both children and adults.[1–17] Studies have found that *RANBP2* missense mutations predispose individuals to ANE. Neilson et al.[18] reported familial, recurrent

DOI: 10.1002/ped4.12406

ANE (also termed ANE1) cases for the first time and confirmed that missense mutations in the *RANBP2* gene are responsible for the genetic susceptibility to ANE.[19] To date, five patients with ANE associated with the 2019 coronavirus disease (COVID-19) have been reported to carry the *RANBP2* gene mutation.[3,4,6,9] Here we report a case of recurrent ITES in a pediatric patient with *RANBP2* gene mutation who was diagnosed with influenza-associated encephalopathy and COVID-19-related ANE successively.

CASE REPORT

A 1-year-and-3-month-old girl was admitted to our intensive care unit for fever, decreased level of consciousness, and convulsion. She developed fever and weakness after exposure to SARS-CoV-2-infected family members and became drowsy but arousable in the first 72 hours. Eighty-four hours after onset, she experienced several episodes of generalized tonic-clonic seizures that lasted for 2 minutes each time and then deteriorated into a coma. On admission, her Glasgow Coma Scale (GCS) was E4, V1 and M5. Her breath pattern was irregular, with a diameter of 2 mm in both pupils which were symmetric and sluggish. She had chemosis, hypertonia, hyperreflexia, and a positive Babinski sign. The nasopharyngeal swab polymerase chain reaction test was positive for SARS-CoV-2 and negative for Influenza A/B. A lumbar puncture was performed, and cerebrospinal fluid (CSF) pressure was normal. CSF analysis showed a normal glucose level (3.76 mmol/L), and elevated protein level (1.04 g/L) without pleocytosis (2/mm^3). Tests for pathogens such as bacteria, viruses (including SARS-CoV-2), and fungi in CSF were negative. Non-contrast head computer tomography (CT) scan on day 1 showed a small hypodense lesion on the left thalamus (Figure 1).

Past history: She was admitted to the neurology department due to fever and convulsion at the age of 8 months and tested positive for influenza B. CSF study showed normal glucose, protein (3.18 mmol/L and 0.40 g/L, respectively) and no pleocytosis (7/mm^3). CSF pathogens, oligoclonal bands, anti-myelin oligodendrocyte glycoprotein, and anti-neural-antigen antibodies were negative. Brain magnetic resonance imaging (MRI) revealed edema and scattered patchy/nodular increased signal intensity in the bilateral cerebral hemisphere on T2-weighted-fluid-attenuated inversion recovery (T2-FLAIR) images with meningeal thickening and enhancement on T1 post-contrast images (Figure S1). She was diagnosed with influenza-associated encephalopathy. Whole-exome sequencing was performed, and *RANBP2* heterozygous mutation (c.1754C>T p.T585M and c.6952G>A p.D2318N) was found. After treatment with oseltamivir and intravenous immunoglobulin (IVIG) (2 g/kg), she made a full recovery and was discharged home with a modified Rankin Scale (mRS) score of 0. She had reached normal developmental milestones, and no abnormal T1, T2, or FLAIR signal was found on the follow-up brain MRI at 12 months of age.

Family history: One of her mother's cousins had a history of febrile seizures during childhood and was later diagnosed with epilepsy.

As soon as she was admitted, high-dose methylprednisolone (30 mg/kg for 5 days) and IVIG (1 g/kg for 2 days) were administered. Seizures were controlled by midazolam and levetiracetam. Non-invasive ventilation was used for respiratory support and cocktail therapy including coenzyme Q10, levocarnitine, vitamin B1, B2, B6, and B12 was used for potential mitochondrial dysfunction. On day 3, her consciousness level further decreased (GCS 5: E1V1M3) with pupillary asymmetry and diminished pupillary light reflex. Intubation and invasive mechanical ventilation were performed. The second head CT scan showed swelling and hypodensities in the bilateral basal ganglia, thalamus,

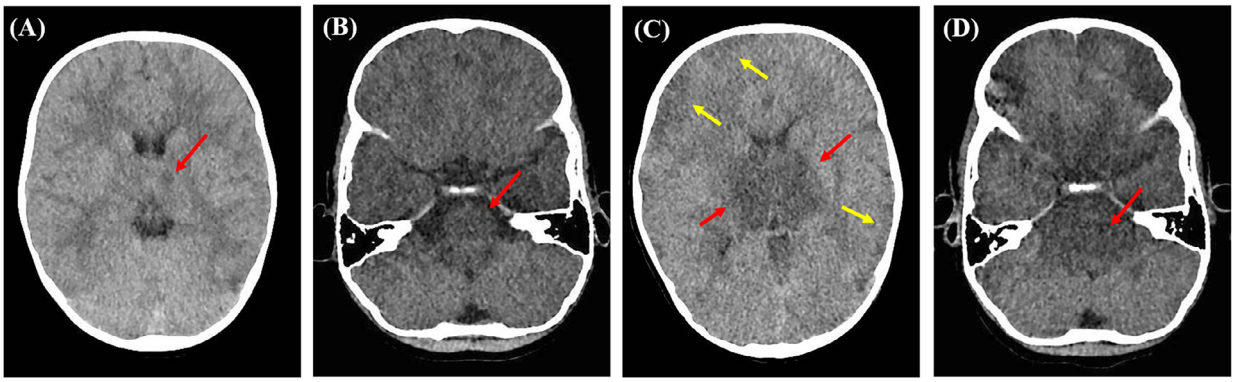

FIGURE 1 The head computer tomography scan on day 1 and day 4. (A) Hypodensity in the left thalamus (red arrow) on day 1. (B) Normal brain stem (red arrow) on day 1. (C) Bilateral symmetric hypodensity of basal ganglia and thalamus (red arrow) with multiple hypodensities in the cerebral cortex (yellow arrow) on day 4. (D) Symmetric hypodensity of brain stem (red arrow) on day 4.

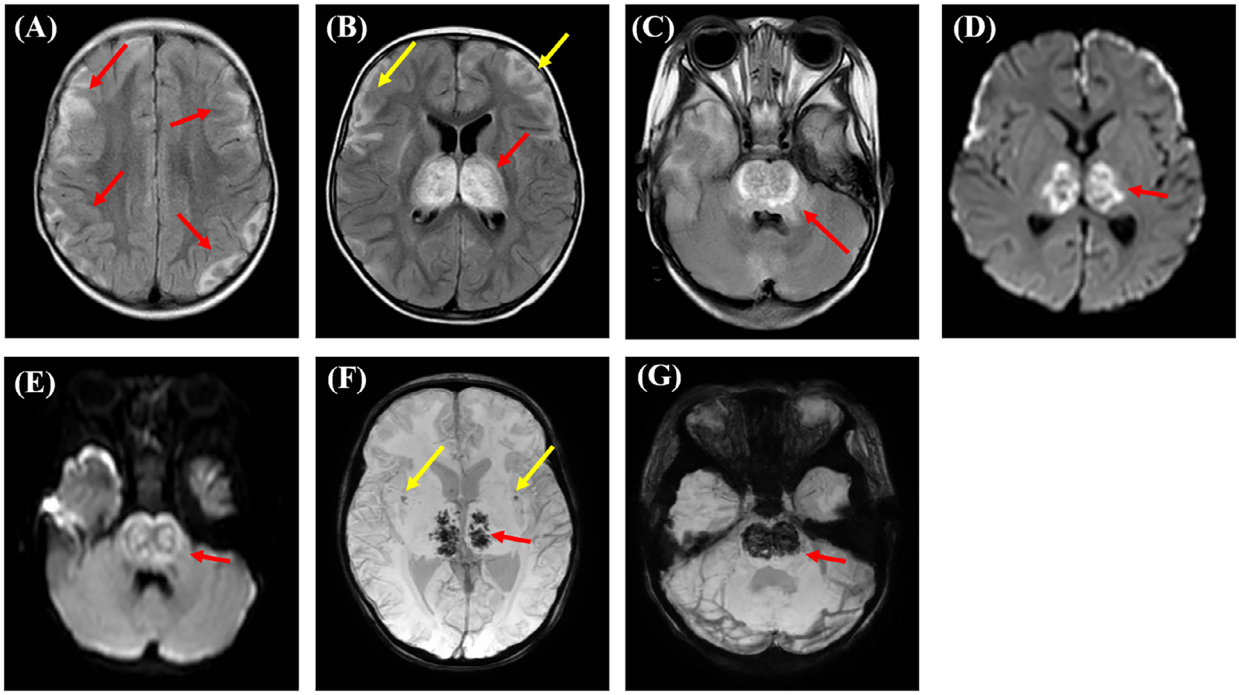

FIGURE 2 Non-contrast magnetic resonance imaging of acute necrotizing encephalopathy on day 10. (A–C) T2-weighted-fluid-attenuated inversion recovery (T2-FLAIR) showed swelling and increased signal intensity in cortical and subcortical regions of bilateral frontal and parietal lobes (A, red arrows and B, yellow arrows) and symmetrically increased signal intensity in thalami and pons (B and C, red arrows). (D, E) Diffusion-weighted image (DWI) showed increased signal intensity in the bilateral thalami and pons with restricted diffusion and cytotoxic edema (red arrows). (F, G) Hemorrhage was indicated by signal intensity decrease within the insular cortex (yellow arrows) bilateral thalami and pons (red arrows) on susceptibility-weighted images (SWI).

brainstem, and cerebral cortex (Figure 1). COVID-19-related ANE was suspected and tocilizumab 12 mg/kg was injected intravenously. On day 9, her consciousness and respiratory function were improved (GCS 7T: E2VTM5) and she was extubated. Non-contrast MRI and magnetic resonance spectroscopy of the brain on day 10 confirmed symmetric hemorrhagic and necrotic lesions in the thalamus and brainstem (Figures 2 and 3), and the definite diagnosis was acute hemorrhagic necrotizing encephalopathy. Electroencephalogram showed excessive generalized continuous slow waves without epileptiform discharges. A second lumbar puncture was performed after tocilizumab therapy and the interleukin 6 (IL-6) level in CSF was 59.69 pg/mL (reference range: < 6 pg/mL). She was discharged and transferred to a rehabilitation facility on day 28 without the need for respiratory or cardiovascular support. Her consciousness level improved with a GCS of 10 (E4V1M5) and an mRS score of 5. She still had pupillary asymmetry, lower limb hypertonia, impaired brain stem reflex, and positive Babinski sign. Improvement was noted with the normalization of the right pupillary light reflex and upper limb muscle tone.

Follow-up: At the first follow-up (one and a half months after discharge), the patient was still undergoing rehabilitation with an mRS score of 5 and a GCS of 14 (E4V4M6), and no convulsive seizures were observed. Her mental status did not improve further at the second follow-up (seven and a half months after discharge).

DISCUSSION

ANE is a relatively rare disease and the exact incidence rate is still unknown. A variety of pathogens can induce ANE, with influenza and human herpesvirus-6 (HHV-6) being the most common pathogens causing ANE.[20] "SARS-CoV-2", "COVID-19" and "acute necrotizing encephalopathy" were used as keywords to retrieve papers from the literature in Pubmed and Web of Science databases. Twenty-one COVID-19-related ANE cases were reported from 2019 to 2023 and detailed patient information for the 19 cases was summarized in Table S1. The ages of the 19 patients ranged from 2 months to 70 years, including nine children aged between 2 months and 11 years. Nine patients were female (9/19, 47.4%). The duration from onset to consciousness deterioration ranged from 2 to 21 days (the median is 4 days). Eleven patients (11/16, 68.7%) required mechanical ventilation, and 47.4% of patients (9/19) experienced convulsive seizures. After excluding one case without a prognosis report, only 3 patients (3/18, 16.7%) made a full

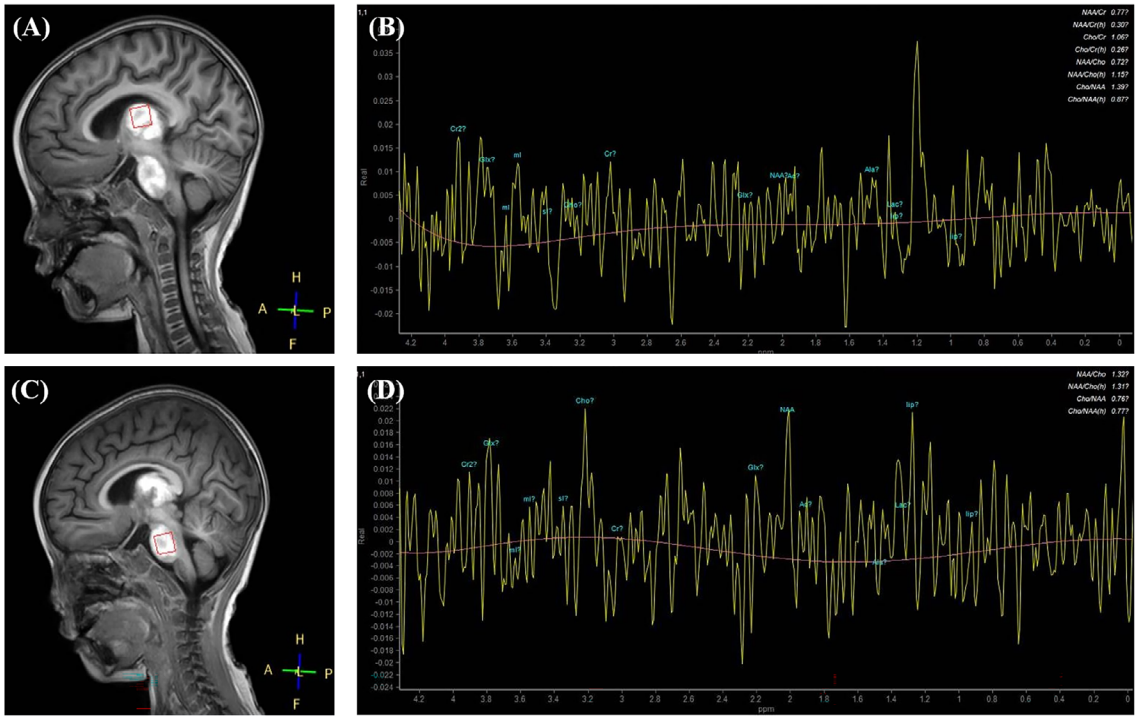

FIGURE 3 Magnetic resonance spectroscopy of acute necrotizing encephalopathy on day 10. (A, B) A lip peak at 1.2 ppm was shown in the left thalamus without *N*-acetylaspartate (NAA), choline (Cho), and creatine (Cr) peaks, suggesting necrotic tissue. (C, D) Significantly reduced NAA, Cho, and Cr peaks were found in the left pons, indicating severe neuron damage.

recovery, four patients (4/18, 22.2%) died, and 11 patients (11/18, 61.1%) had a neurologic disability. Sakuma et al.[21] reported 31 pediatric patients with COVID-19-related ITES (including two ANE cases) and nine patients (29%) had severe neurological sequelae or died. Levine et al.[22] summarized 87 cases of non-SARS-CoV-2-induced ANE with a 30% mortality rate and a full recovery rate of less than 10%. Jing et al.[23] reported 96 cases of non-COVID-19-related ANE-carrying *RANBP2* gene mutations, with a mortality rate of 25.4% and a full recovery rate of 22.5%. The overall prognosis of COVID-19-related ANE is comparable to that of ANE induced by other infections.

RANBP2 missense mutations are the most prevalent susceptibility alleles for familial and recurrent ANE, with an incomplete penetrance rate of 40%.[22] The family history of our patient is unremarkable. Only one family member from her mother's side had a history of febrile seizures. The *RANBP2* gene encodes a protein called Nup358, which consists of 3224 amino acids. Nup358 contains a leucine-rich region and four RanBP1 homologous (RBH) domains.[24] A total of 10 pathogenic mutations have been reported, seven of which are located in the leucine-rich region, with the Thr585Met (T585M) mutation accounting for the majority of cases.[3,23] In the literature review, five patients (cases 4, 5, 7, 8, and 11) carried *RANBP2* mutation, two of which (cases 4 and 8) presented with recurrent ITES with severe neurological impairment. Case 8 was a 10-year-old girl who was diagnosed with atypical acute disseminated encephalomyelitis due to influenza infection on the first episode and fully recovered after treatment. Similar to our patient, she had ANE after SARS-CoV-2 infection on the second episode without multi-organ failure and she remained unconscious (GCS 7) after treatment. Case 4 was a 2-year-old boy who experienced two episodes of COVID-19-related ANE. On the second attack, a brain MRI showed new areas of necrosis and worsening signal abnormalities. The other three cases (cases 5, 7, and 11) had only one episode of COVID-19-related ANE, of which case 11 died on the sixth day of admission with no response to remdesivir and dexamethasone. In addition to carrying the same T585M mutation as cases 5, 8, and 11 (Table S1), our patient also inherited the D2318N mutation from her father, which has not been reported yet. The amino acid alteration is located at RBH domain 3, which may abolish the binding of Ran GDP/GTP to the RBH domain, thus affecting the function of RANBP2/Nup358.[25] The pathogenicity of D2318N mutation remains to be investigated.

Compared to *RANBP2* mutation negative ANE (also known as sporadic ANE) patients, ANE1 patients are more likely to develop lesions at amygdalae, hippocampi, and medial temporal lobes while transaminitis and disseminated

intravascular coagulation is less common.[20,22,23] In addition, there have been no reports of recurrence in sporadic ANE patients. Nurin et al.[26] reported 20 pediatric patients with non-SARS-CoV-2 induced ANE. Among the seven patients with *RANBP2* mutations, three experienced recurrent ITES and one died during recurrence. No relapses were found in *RANBP2* mutation-negative patients. Esra et al.[27] presented nine pediatric ANE cases with *RANBP2* gene mutations and influenza was detected in seven patients. Two patients experienced recurrent attacks, one of which had a total of three relapses and died on the third recurrence after Influenza B infection, suggesting that *RANBP2* mutation carriers are predisposed to recurrent ITES and may be at greater risk of death in the course of relapse. Case 8 and our patient developed acute encephalopathy after initial influenza infection with relatively mild symptoms and inconsistent neuroimaging abnormalities with ANE. Both patients made a full recovery after treatment. However, typical ANE changes were found on brain CT/MRI after SARS-CoV-2 infection with poor prognosis due to severe neurological impairment. Therefore, we presume that individuals carrying *RANBP2* mutations have a higher risk of recurrent ITES after viral infection and their worse clinical course and poor prognosis are also related to relapse. Although various hypotheses have been proposed, such as genetic susceptibility, direct invasiveness, dependent enhancement of vaccine-related antibodies, and cytokine storm, the exact mechanisms are unclear.[28] Interestingly, recent studies found that SARS-CoV-2 affects the gene expression and function of RANBP2,[29,30] which might be involved in the pathogenesis of COVID-19-related ANE in patients with *RANBP2* gene mutations. There is no evidence to support that SARS-CoV-2 is more likely to induce ANE than other viruses in *RANBP2* mutation-positive individuals. Future studies need to further investigate the differences in mechanisms of ANE induced by different pathogens under the same genetic background and the impact on patient prognosis.

The optimal treatment regimen for ANE remains controversial due to the lack of high-quality clinical trials. Studies have shown that early use of glucocorticoids and IVIG is protective in ANE.[31] Koh et al.[32] found that early use of tocilizumab may improve clinical outcomes and prevent disability in ANE children, even if some patients had normal serum IL-6. In our case, early treatment with high-dose glucocorticoids, IVIG, and IL-6 blockade resulted in a significant improvement in GCS (5→14) at follow-up, but no significant improvement in mRS, which may be related to the limited follow-up period. In addition, the timing, dosage, and frequency of administration of tocilizumab are still uncertain. Future studies with larger sample sizes and longer follow-up periods are warranted to investigate the long-term prognosis of COVID-19-related ANE.

The early findings of neuroimaging are unremarkable for the majority of ANE patients, especially since the result of the head CT scan may be normal on admission,[33] which may delay diagnosis and treatment. In our case, low-density lesions in bilateral thalami and brain stems were detected on the follow-up head CT scan on the 4th day of hospitalization. Brain MRI may be helpful for the early detection of ANE as the patient's condition permits. During the viral epidemic season, clinicians should be aware that children with high fever, convulsive seizures, and impaired consciousness may develop ANE. Therapeutic intervention should be provided and neuroimaging should be closely monitored in the early stages. In addition, genetic testing is available for screening *RANBP2* mutation carriers in patients with a history of acute encephalopathy or epilepsy after febrile illness and may help identify patients at high risk for recurrent ITES and ANE. The genetic test results are important for both medical care providers and families, as they may lead to early intervention to improve the prognosis. Since the inheritance of *RANBP2* mutation is autosomal dominant with incomplete penetrance, genetic counseling and assessment of other family members may also be important. Patients and family members need to understand the inheritance pattern, and the implications of incomplete penetrance and take more proactive action such as social distancing or vaccination to avoid infections in the epidemic season of pathogens that may induce ANE.

COVID-19-related ANE is characterized by high mortality and disability rates. Patients with pathogenic mutations of *RANBP2* are predisposed to recurrent ITES and may develop ANE, with a higher risk of poor prognosis during the relapse. When neuroimaging findings are atypical for ANE, clinical manifestations, and genetic evaluation may help in the early identification of high-risk patients.

CONSENT FOR PUBLICATION

Consent was obtained from the patient's guardian.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Mierzewska-Schmidt M, Baranowski A, Szymanska K, Ciaston M, Kuchar E, Ploski R, et al. The case of fatal acute hemorrhagic necrotizing encephalitis in a two-month-old boy with COVID-19. *Int J Infect Dis.* 2022;116:151-153. DOI: 10.1016/j.ijid.2021.12.334
2. Lazarte-Rantes C, Guevara-Castañón J, Romero L, Guillén-Pinto D. Acute necrotizing encephalopathy associated with SARS-CoV-2 exposure in a pediatric patient. *Cureus.* 2021;13:e15018. DOI: 10.7759/cureus.15018

3. Wu D, Zheng Y, Li Y, Peng M, Lin H, Wang K. Exploring the molecular and clinical spectrum of COVID-19-related acute necrotizing encephalopathy in three pediatric cases. *J Hum Genet.* 2023;68:769-775. DOI: 10.1038/s10038-023-01171-z. Online ahead of print.
4. Olubiyi OI, Zamora C, Jewells V, Hunter SE. Recurrent acute hemorrhagic necrotizing encephalopathy associated with RAN-binding protein-2 gene mutation in a pediatric patient. *BJR Case Rep.* 2022;8:20220019. DOI: 10.1259/bjrcr.20220019
5. Wang PY, Yang MT, Liang JS. Acute necrotizing encephalopathy caused by SARS-CoV-2 in a child. *Pediatr Neonatol.* 2022;63:642-644. DOI: 10.1016/j.pedneo.2022.06.003
6. Forest C, Laudisi M, Malaventura C, Tugnoli V, Pellino G, Marangoni E, et al. Pediatric recurrent acute necrotizing encephalomyelitis, RANBP2 genotype and Sars-CoV-2 infection: diagnosis, pathogenesis and targeted treatments from a case study. *Eur J Paediatr Neurol.* 2023;42:117-121. DOI: 10.1016/j.ejpn.2022.12.010
7. Ho JHY, Lee CYM, Chiong YK, Aoyama R, Fan LJ, Tan AHS, et al. SARS-CoV-2-related acute necrotizing encephalopathy of childhood with good response to tocilizumab in an adolescent. *Pediatr Neurol.* 2023;139:65-69. DOI: 10.1016/j.pediatrneurol.2022.11.010
8. Breit H, Radaideh Y, John S. Acute necrotizing encephalopathy due to SARS-CoV-2 in a pregnant female. *Neurol Sci.* 2021;42:3991-3994. DOI: 10.1007/s10072-021-05518-2
9. Pongpitakmetha T, Hemachudha P, Rattanawong W, Thanapornsangsuth P, Viswanathan A, Hemachudha T. COVID-19 related acute necrotizing encephalopathy with extremely high interleukin-6 and *RANBP2* mutation in a patient with recently immunized inactivated virus vaccine and no pulmonary involvement. *BMC Infect Dis.* 2022;22:640. DOI: 10.1186/s12879-022-07610-0
10. Ciolac D, Crivorucica I, Zota E, Gorincioi N, Efremova D, Manea D, et al. Extensive cerebellar involvement and cognitive impairment in COVID-19-associated acute necrotizing encephalopathy. *Ther Adv Neurol Disord.* 2021;14:1756286420985175. DOI: 10.1177/1756286420985175
11. Rettenmaier LA, Abdel-Wahed L, Abdelmotilib H, Conway KS, Narayanan N, Groth CL. COVID-19-associated necrotizing encephalopathy presenting without active respiratory symptoms: a case report with histopathology. *J Neurovirol.* 2022;28:172-176. DOI: 10.1007/s13365-021-01042-3
12. Delamarre L, Gollion C, Grouteau G, Rousset D, Jimena G, Roustan J, et al. COVID-19-associated acute necrotising encephalopathy successfully treated with steroids and polyvalent immunoglobulin with unusual IgG targeting the cerebral fibre network. *J Neurol Neurosurg Psychiatry.* 2020;91:1004-1006. DOI: 10.1136/jnnp-2020-323678
13. Virhammar J, Kumlien E, Fällmar D, Frithiof R, Jackmann S, Sköld MK, et al. Acute necrotizing encephalopathy with SARS-CoV-2 RNA confirmed in cerebrospinal fluid. *Neurology.* 2020;95:445-449. DOI: 10.1212/WNL.0000000000010250
14. Bansal P, Fory EK, Malik S, Memon AB. Clinical course of a patient with radiographically described acute necrotizing encephalopathy. *Radiology.* 2020;297:E278-E280. DOI: 10.1148/radiol.2020203132
15. Dixon L, Varley J, Gontsarova A, Mallon D, Tona F, Muir D, et al. COVID-19-related acute necrotizing encephalopathy with brain stem involvement in a patient with aplastic anemia. *Neurol Neuroimmunol Neuroinflamm.* 2020;7:e789. DOI: 10.1212/NXI.0000000000000789
16. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging features. *Radiology.* 2020;296:E119-E120. DOI: 10.1148/radiol.2020201187
17. Ziemele D, Ķauķe G, Skrējāne K, Jaunozoliņa L, Karelis G. A fatal case of COVID-19-associated acute necrotizing encephalopathy. *Eur J Neurol.* 2021;28:3870-3872. DOI: 10.1111/ene.14966
18. Neilson DE, Eiben RM, Waniewski S, Hoppel CL, Varnes ME, Bangert BA, et al. Autosomal dominant acute necrotizing encephalopathy. *Neurology.* 2003;61:226-230. DOI: 10.1212/01.wnl.0000073544.28775.1a
19. Neilson DE, Adams MD, Orr CM, Schelling DK, Eiben RM, Kerr DS, et al. Infection-triggered familial or recurrent cases of acute necrotizing encephalopathy caused by mutations in a component of the nuclear pore, *RANBP2*. *Am J Hum Genet.* 2009;84:44-51. DOI: 10.1016/j.ajhg.2008.12.009
20. Shukla P, Mandalla A, Elrick MJ, Venkatesan A. Clinical manifestations and pathogenesis of acute necrotizing encephalopathy: the interface between systemic infection and neurologic injury. *Front Neurol.* 2021;12:628811. DOI: 10.3389/fneur.2021.628811
21. Sakuma H, Takanashi JI, Muramatsu K, Kondo H, Shiihara T, Suzuki M, et al. Severe pediatric acute encephalopathy syndromes related to SARS-CoV-2. *Front Neurosci.* 2023;17:1085082. DOI: 10.3389/fnins.2023.1085082
22. Levine JM, Ahsan N, Ho E, Santoro JD. Genetic acute necrotizing encephalopathy associated with RANBP2: clinical and therapeutic implications in pediatrics. *Mult Scler Relat Disord.* 2020;43:102194. DOI: 10.1016/j.msard.2020.102194
23. Jiang J, Wang YE, Palazzo AF, Shen Q. Roles of nucleoporin RanBP2/Nup358 in acute necrotizing encephalopathy type 1 (ANE1) and viral infection. *Int J Mol Sci.* 2022;23:3548. DOI: 10.3390/ijms23073548
24. Yokoyama N, Hayashi N, Seki T, Panté N, Ohba T, Nishii K, et al. A giant nucleopore protein that binds Ran/TC4. *Nature.* 1995;376:184-188. DOI: 10.1038/376184a0
25. Yaseen NR, Blobel G. Two distinct classes of Ran-binding sites on the nucleoporin Nup-358. *Proc Natl Acad Sci U S A.* 1999;96:5516-5521. DOI: 10.1073/pnas.96.10.5516
26. Chatur N, Yea C, Ertl-Wagner B, Yeh EA. Outcomes in influenza and *RANBP2* mutation-associated acute necrotizing encephalopathy of childhood. *Dev Med Child Neurol.* 2022;64:1008-1016. DOI: 10.1111/dmcn.15165
27. Sarigecili E, Ucar HK, Havali C, Cansu A, Aydin K. Acute necrotizing encephalopathy associated with *RANBP2* mutation: value of MRI findings for diagnosis and intervention. *Acta Neurol Belg.* 2023;123:571-582. DOI: 10.1007/s13760-022-02166-x
28. Qin N, Wang J, Peng X, Wang L. Pathogenesis and management of acute necrotizing encephalopathy. *Expert Rev*

Neurother. 2023;23:641-650. DOI: 10.1080/14737175.2023.2224503
29. Bock JO, Ortea I. Re-analysis of SARS-CoV-2-infected host cell proteomics time-course data by impact pathway analysis and network analysis: a potential link with inflammatory response. *Aging.* 2020;12:11277-11286. DOI: 10.18632/aging.103524
30. Lee JG, Huang W, Lee H, van de Leemput J, Kane MA, Han Z. Characterization of SARS-CoV-2 proteins reveals Orf6 pathogenicity, subcellular localization, host interactions and attenuation by Selinexor. *Cell Biosci.* 2021;11:58. DOI: 10.1186/s13578-021-00568-7
31. Okumura A, Mizuguchi M, Kidokoro H, Tanaka M, Abe S, Hosoya M, et al. Outcome of acute necrotizing encephalopathy in relation to treatment with corticosteroids and gammaglobulin. *Brain Dev.* 2009;31:221-227. DOI: 10.1016/j.braindev.2008.03.005
32. Koh JC, Murugasu A, Krishnappa J, Thomas T. Favorable outcomes with early interleukin 6 receptor blockade in severe acute necrotizing encephalopathy of childhood. *Pediatr Neurol.* 2019;98:80-84. DOI: 10.1016/j.pediatrneurol.2019.04.009
33. Larsh T, Hsich G. Temporal course of imaging and laboratory findings in a child with fulminant acute necrotizing encephalopathy. *Pediatr Neurol.* 2020;102:74-75. DOI: 10.1016/j.pediatrneurol.2019.05.003

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Li J, Huo F, Wang S, Fan Y, Wu J, Zhang Z, et al. Recurrent infection triggered encephalopathy syndrome in a pediatric patient with *RANBP2* mutation and severe acute respiratory syndrome coronavirus 2 infection. *Pediatr Investig*. 2023;7:290–296. https://doi.org/10.1002/ped4.12406