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Case report

Case report: Influenza A virus and Human herpesvirus 1 infection-associated acute encephalopathy in children with the mutations in the *SLC25A19* and*TICAM1* gene, respectively

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ABSTRACT

Background: Infection-associated acute encephalopathy (AE) is a clinical condition caused by a variety of pathogens, particularly common viruses. In some cases, this condition could be characterized by a sudden onset and a rapid progression, leading to severe neurological sequelae, including acute encephalopathy with biphasic seizures and late reduced diffusion, hemorrhagic shock and encephalopathy syndrome, etc.
Case presentation: In this study, it was reported that three previously healthy children developed acute encephalopathy/encephalitis symptoms with different neurological sequelae after either Influenza A Virus or Human Herpesvirus 1 infection, presenting with fever and convulsions. What's more, after performing the gene exon detection for these three children, it was found that there are abnormal genes corresponding to their neurological sequelae, including *SLC25A19* and *TICAM1*.
Conclusions: Therefore, comparing to children with common encephalitis, for children with encephalitis whose progression is rapid and clinical manifestations such as recurrent fever and frequent convulsions is difficult to improve, whole-exome sequencing can be a valuable tool for identifying encephalitis-associated genetic variants and providing strong evidence for prognostic prediction.

Introduction

Infection-associated acute encephalopathy (AE) is characterized by convulsions, prolonged impairment of consciousness, as well as pyrexia, frequently resulting in severe neurological sequelae and even death in vulnerable cohorts of infants and young children [1]. In Japan, the mean age at onset of acute necrotizing encephalopathy is approximately 4 years, with most cases occurring in infancy and early childhood (0–5 years) [2]. From a retrospective study of 983 AE patients, viral infections were found to be closely associated with the development of AE, among which Influenza virus appeared to be the most common (263 cases, 26.6%), followed by Human herpesvirus-6 (HHV-6, 168 cases, 17.0%), Rotavirus (40 cases, 4.0%), Respiratory syncytial virus (RSV, 17 cases, 1.7%), Mumps virus (9 cases, 0.9%), Adenovirus (7 cases, 0.7%), Human herpesvirus-7 (HHV-7, 6 cases, 0.6%), Herpes simplex virus (HSV, 6 cases, 0.6%), Norovirus (5 cases, 0.5%), Epstein Barr virus (EBV, 3 cases, 0.3%), Varicella-zoster virus (VZV, 3 cases, 0.3%), Human parechovirus (2 cases, 0.2%), and Measles virus (1 case, 0.1%)[2]. Here, we reported 3 cases of AE patients admitted to the Pediatric Intensive Care Unit (PICU) of Luoyang Maternal and Child Health Hospital from January 2019 to December 2021. These subjects all carried AE-associated genetic variants, which did not seem to be much of a problem to the growth and development until the onset of acute infection. All of a sudden, they all had severe neurological problems related to and/or similar to the phenotypes of these genetic variants. These patients also ended up with a poor prognosis as evidenced by varying degrees of neurological sequelae found at follow-up visits.

Abbreviations: AE, Acute encephalopathy; WES, whole-exome sequencing.

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Case report

Case 1

Patient 1 was a 19-month-old girl, who had suffered from fever and cough for 1 day and convulsions for 5 h. On February 1, 2019 (day 1), she was transferred to our hospital after injection of diazepam and Luminal which failed to manage the symptom of convulsion. Physical examination: body temperature (T) 37.3 °C, pulse (P) 194 beats/min, respiratory rate (R) 54 breaths/min, blood pressure (BP) 88/52 mmHg, mental confusion, Kussmaul breathing, high endurance of deep cervical flexor muscle, blue skin below the wrists and ankles, blue lips, audible rhonchi over both lungs, three concave sign positive, no specific abnormalities found in cardiac and abdominal examinations, cold extremities, capillary refill time (CRT) 3 s. The patient's patellar reflex was hyperactive, but no pathological reflexes were elicited. Diagnostic tests: (1) arterial blood gas test: metabolic acidosis, hyperlactatemia (lactate 9.8 mmol/L); (2) Influenza A antigen test (throat swabs, colloidal gold

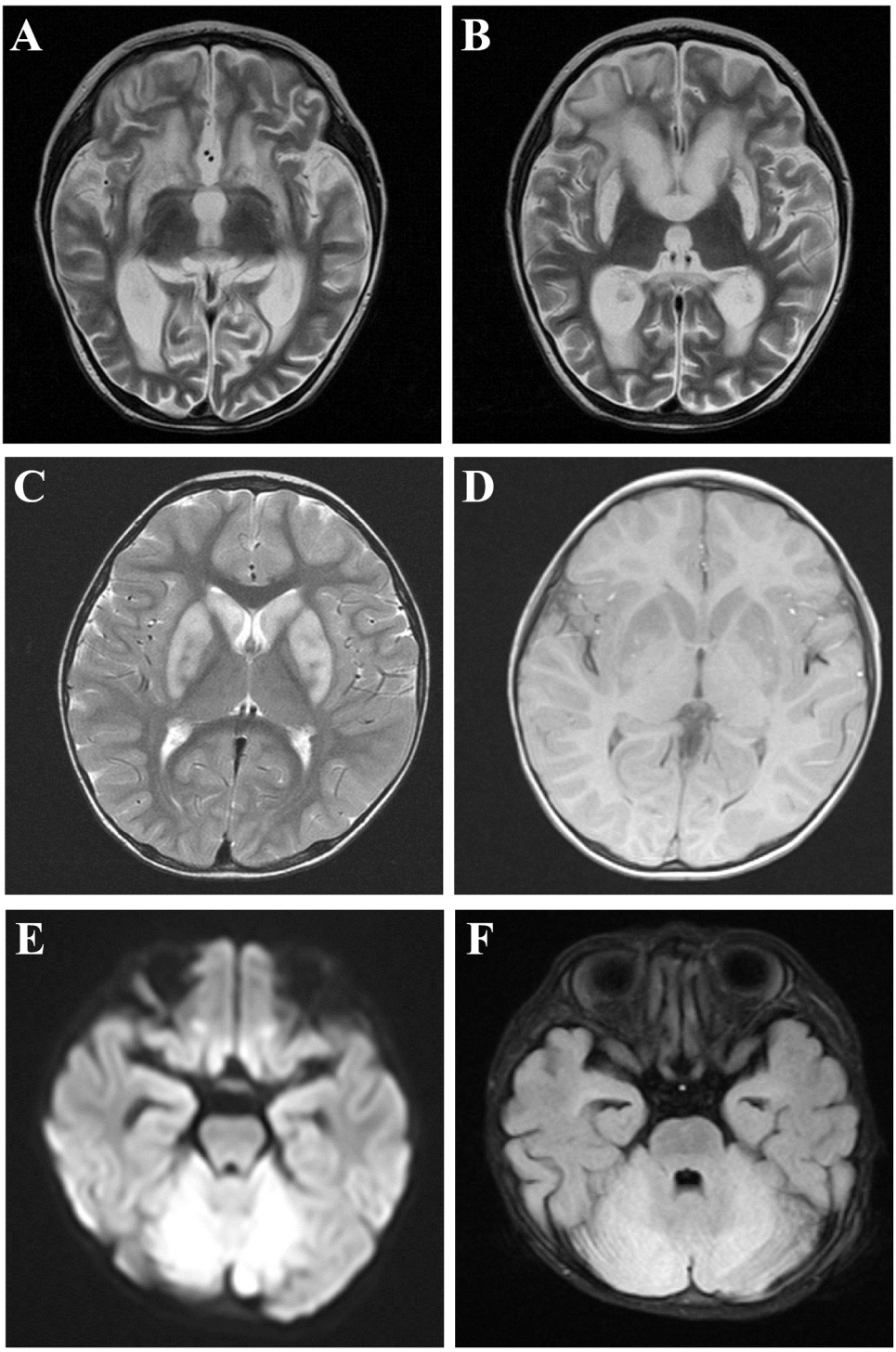

Fig. 1. Cranial magnetic resonance imaging of the four patients. (A~B) patient 1, T2-weighted imaging (T2WI) showed slightly hyperintense signals in the white matter and basal ganglia of cerebral hemispheres; **(C~D)** patient 2, T2WI (C) and T2-weighted fluid-attenuated inversion recovery (T2-FLAIR) (D)showed abnormal signals in the bilateral basal ganglia; **(E~F)** patient 3, T2-FLAIR showed abnormal signals in bilateral cerebellar hemispheres.

method): weak positive; (3) routine tests, biochemical analysis and bacterial culture of cerebrospinal fluid (CSF): normal; (4) cardiac enzyme tests: creatine kinase (CK) 2064 U/L, CK-MB 122.4 U/L, lactate dehydrogenase (LDH) 476 U/L; (5) electroencephalogram (EEG): diffuse spike-slow wave complex activity; (6) cranial MRI ***(***Fig. 1***A &1B)***: bilateral basal ganglia lesions (an area of softening), white matter lesions (an area of demyelination) around the lateral ventricles, supratentorial ventricular enlargement, groove deepening in the cerebral cortex. After admission, the patient was connected to a mechanical ventilator with a breathing tube placed down her throat, and treated with peramivir (10 mg/kg/d), mannitol (1 g/kg/time, q4h), midazolam (6 ug/kg/min), sufentanil (0.05 ug/kg/h), blood purification therapy, and fluid resuscitation etc. On day 6, she developed involuntary tremors in the limbs, along with an abnormal posture of limb flexion. On day 28, she was weaned from the ventilator but reconnected due to the diaphragmatic weakness. On day 72, the ventilator was removed, but she lost the ability to swallow voluntarily and developed involuntary tremors in the limbs, accompanied by high muscle tone and the knees and hips passively bent. On day 87, whole-exome sequence (WES) identified the compound heterozygous mutations of c.745 T > A and c.76 C>T in the *SLC25A19* gene (Fig. 2). On day 121, the patient was discharged.

Case 2

On February 1, 2019 (day 1), a 30-month-old boy, the elder brother of Case 1 and complaining of fever and lethargy for 3 days and cough for 2 days, was admitted to our hospital. Physical examination: T 38 °C, P 150 beats/min, R 36 breaths/min, BP 95/52 mmHg, lethargy, audible rhonchi over both lungs, no specific abnormalities found in cardiac and abdominal examinations, warm extremities, CRT 2 s. The patient's patellar reflex was hyperactive, but no pathological reflexes were elicited. Diagnostic tests: (1) Influenza A antigen test (throat swabs, colloidal gold method): positive; (2) cardiac enzyme tests: CK 803 U/L, CK-MB 54 U/L, LDH 998 U/L; (3) EEG: diffuse spike-slow wave complex activity; (4) cranial MRI ***(***Fig. 1***C &1D)***: abnormal hyperintense signals in the bilateral basal ganglia and brainstem. After admission, the patient developed frequent convulsions, together with impairment of conscious level in response to defined stimuli (Glasgow Coma Scale: 8 or E2V2M4). His treatment was the same with Case 1. On day 6, he developed involuntary tremors in the limbs, along with an abnormal posture of limb extension. On day 28, he was weaned from the ventilator. His symptoms were similar with those of Case 1, except the passive posture of limb extension. WES identified the same mutation in the *SLC25A19* as Case 1 (Fig. 2). On day 66, he was discharged.

Case 3

On November 2, 2021 (day 1), a 23-month-old girl, suffering from lethargy for 3 days and fever and convulsions for 2 days, was admitted to our hospital for convulsion with a frequency of more than 20 times a day. Though these convulsions could stop on their own, this symptom had been lasting for 2 days before admission. Physical examination: T 37 °C, lethargy, heat rash (miliaria) all over the body, slightly high endurance of deep cervical flexor muscle, no abnormalities in heart, lung, and abdomen, limb muscle strength Grade 3, low muscle tone, Babinski sign positive. Diagnostic tests: (1) CSF routine tests, biochemical analysis and bacterial culture: basically normal except a high white blood cell count of 155 × 10^9/L in CSF; (2) CSF metagenomics next-generation sequencing (mNGS): Human herpesvirus 1 (HHV-1); (3) EEG: slow waves; (4) cranial MRI: abnormal signals in bilateral cerebellar hemispheres ***(***Fig. 1***E & 1F)***. The patient was connected to a mechanical ventilator and treated with acyclovir (10 mg/kg/time, q8h), mannitol (1 g/kg/time, q6h), midazolam (6 ug/kg/min), remifentanil (5 ug/kg/h) and gamma globulin (2 g/kg) therapy. On day 10, the endotracheal tube was replaced with a nasal cannula which worked with an oxygen concentrator. The patient lost the ability to swallow voluntarily, hold her head up or sit up by herself, finding it difficult to regain

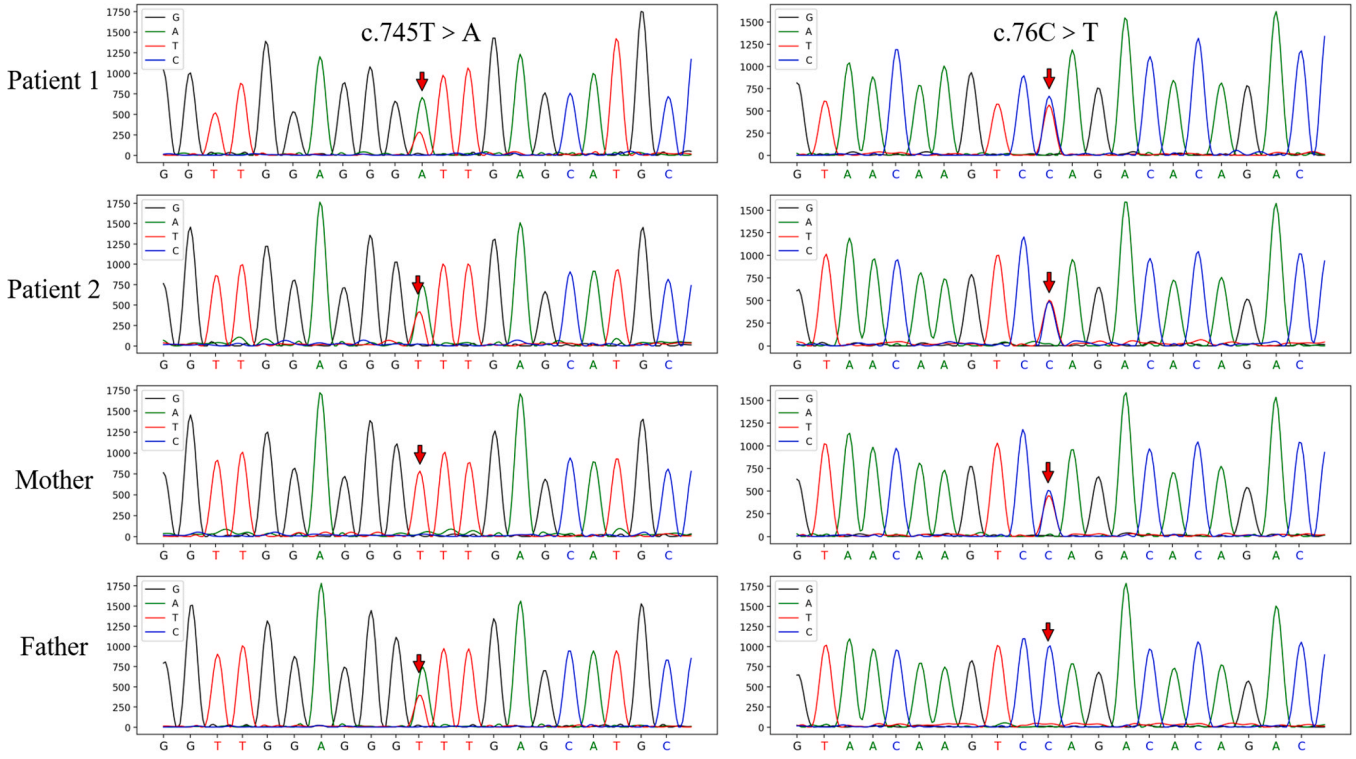

Fig. 2. c.745T>A and c.76C>T compound heterozygous mutations of *SLC25A19* in patient 1 and patient 2. Patient 1, patient 2 and their father has heterozygous mutations at c.745T>A of *SLC25A19*, while their mother is wild type. Patients 1, patient 2 and their mother has heterozygous mutations at c.76 C>T of *SLC25A19*, while their father is wild type.

muscle strength and muscle tone. Meanwhile, she could neither talk nor show any responses to sound and light stimuli. These symptoms were improved on day 18. On day 29, she could sit up by herself and even stand with the help of another person. She was discharged on day 31. WES identified a c.583 C>G variant of uncertain significance in the *TICAM1* gene (Fig. 3).

Discussion

Infection-associated acute encephalopathy usually presents as headache and fever [3]. The uncommon clinical manifestations of infection-associated AE may include severe and long-lasting impairment of consciousness, accompanied by convulsions or seizures, and increased intracranial pressure [4]. In our study, all cases were admitted to the PICU for recurrent fever with concurrent manifestations of neurologic compromise, including recurrent convulsions and lethargy. They were all treated with endotracheal intubation with ventilator-assisted ventilation. During their hospitalization, the treatment was not satisfactory, as evidenced by difficulty in body temperature control, impairment of consciousness, frequent convulsions, and frequent seizures.

Before admission, patient 1 and patient 2 developed AE symptoms at the same time after contact with their grandparents who had flu-like symptoms. These symptoms progressed simultaneously during the course of the disease, as evidenced by development of abnormal muscle tone, passive postures, and limb tremors almost on the same day. The two patients are siblings of the same parents, with a compound heterozygous mutation (an autosomal recessive disorder) in the *SLC25A19* gene (Fig. 2). *SLC25A19* (NCBI Gene ID: 60386) encodes a mitochondrial protein, a member of the solute carrier family which functions as a mitochondrial thiamine pyrophosphate carrier by transporting thiamine pyrophosphates into mitochondria. Mutations in this gene cause Amish lethal microcephaly, a metabolic disease that results in severe congenital microcephaly, severe 2-ketoglutaric aciduria, and early death within the first year. These two cases were also reported in another study, individuals carrying *SLC25A19* variants tends to suffer from thiamine metabolism dysfunction syndrome-4, characterized by episodes of encephalopathy in childhood that are frequently triggered by febrile illness. They often present with muscular weakness and lose deep tendon reflexes. Cranial MRI reveals abnormal signals in the bilateral basal ganglia, and some patients show high levels of lactic acid in CSF or serum. In some cases, patients may develop mild distal muscle weakness or cognitive delay after recovery, which elucidated protein function from the perspective of SLC25A19 protein function as a causative factor in acute necrotizing encephalopathy [5]. For patient 1 and patient 2, they were also able to perform activities of daily living with normal limb function until they got infected by influenza virus. Suddenly, these patients developed acute necrotizing encephalopathy, which severely compromised their limb function, put them in passive postures and deprived them of the ability to take care of themselves even after treatment. Though *RANBP2* and *CPT II* are the two major susceptibility genes for influenza-associated encephalopathy [6–10], it remains unclear whether there are other susceptibility genes involved in the pathogenesis of influenza-associated encephalopathy. During the follow-up period, patient 1 was admitted to the hospital twice within one year for aspiration pneumonia caused by swallowing issues. She had a painful expression on her face when subjected to external sound stimuli, but still could not talk and lost the ability to track a moving target with her eyes. In contrast, patient 2 did not have any major issues in swallowing function, and had been receiving limb rehabilitation therapy. Unfortunately, no significant improvements were observed in both cases with regard to the muscle strength and muscle tone, and long-term care was required.

In patient 3, the clinical manifestations included impaired consciousness, frequent convulsions, low muscle strength,low muscle tone, and swallowing issues. It took 2 weeks for the patient to gradually regain limb function following ventilator removed. Cranial MRI provided a

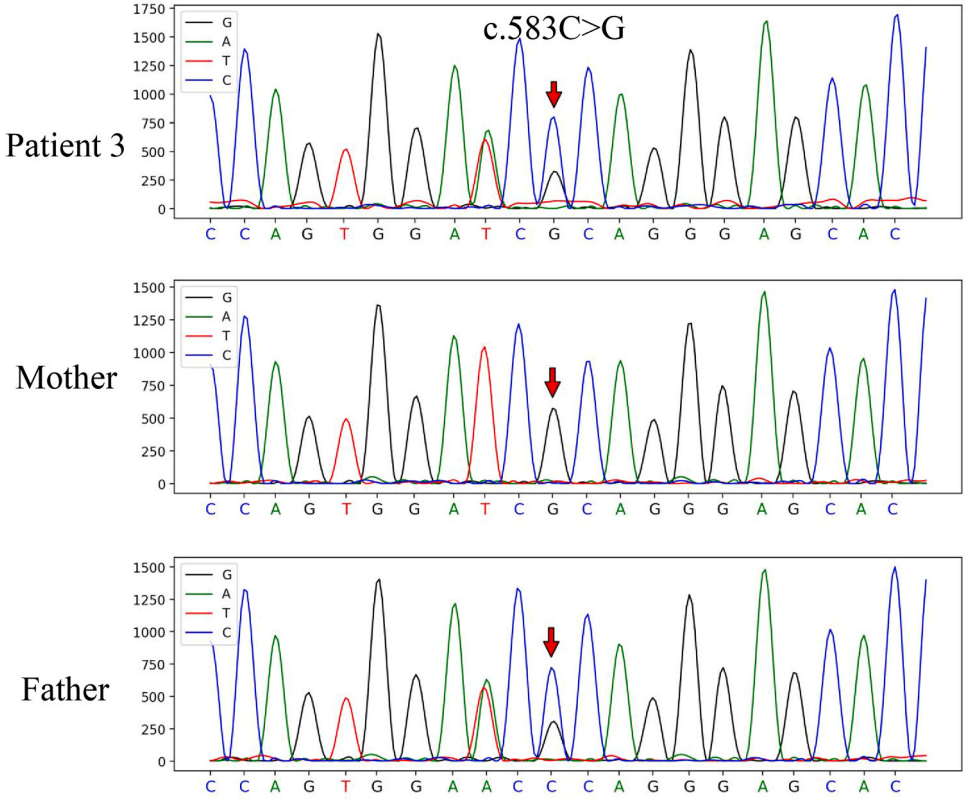

Fig. 3. c.583C>G heterozygous mutations of *TICAM1* in patient 3. Patient 3 and her father have a heterozygous mutation at c.583 C>G of *TICAM1*, while her mother turn to be wild-type.

plausible cause for the state of low muscle tone by revealing infectious lesions in the cerebellum, a region different from those commonly involved by HSV encephalitis, such as the temporal lobe, frontal lobe and limbic system [10]. On the other hand, WES identified a variant of uncertain significance in the *TICAM1* gene (Fig. 3). *TICAM1* (NCBI Gene ID: 148022) encodes an adaptor protein containing a Toll/interleukin-1 receptor (TIR) homology domain, which is involved in native immunity against invading pathogens. Thus, mutations in this gene have a great chance of increasing an individual's susceptibility to HSV encephalitis. After discharge, the patient was transferred to the Department of Brain Rehabilitation for functional training. These exercises substantially improved limb function but did not seem to make any difference to speech and language development. She could neither communicate verbally nor express her needs, and still required rehabilitation therapy for a full recovery.

Generally, WES of all these patients revealed mutations in the exons of susceptibility genes for infection-associated encephalitis, but those mutations did not seem to be much of a problem to the growth and development of the children, or their parents who also carry these genetic variants. Nonetheless, after acute infection, they all presented with clinical manifestations related to and/or similar to the phenotypes of these genetic variants. The disease progressed rapidly during the treatment process, leading to a variety of complications which demanded a longer time and a higher cost to deal with. These patients also ended up with a poor prognosis as evidenced by varying degrees of neurological sequelae found at follow-up visits.

However, for the case reports in a single center, we could not explain the causal relationship between pathogens, genetic variants, and encephalopathy. A large cohort need be recruited to observe the pathogens infections and genetic variants relationships in multiple centers. Last but more important, it should be furthered validated in the animal model to explored mechanisms between the virus infection, genetic variants, and the acute encephalopathy.

Conclusion

Overall, sudden onset of encephalopathy may be caused by infection, and potentially aggravated by mutations in the exons of susceptibility genes, especially in cases where clinical manifestations differ from common ones. To explore the possible causes for this condition, etiological testing should be combined with WES to identify causative pathogens, as well as genetic variants that increase one's susceptibility to this condition, providing convincing evidence for a precise diagnosis and an appropriate treatment.

Ethics approval and consent to participate

Written informed consent for publication of the case details included accompanying images was obtained from the patient.

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CRediT authorship contribution statement

JW N was responsible for manuscript preparation and manuscript review. KN F and SJ L reviewed the manuscript, and takes responsibility for the integrity and accuracy of the cases. H X reviewed the test results, YH L provided the image pictures. All authors read and approved the final manuscript.

Declaration of Competing Interest

All authors must disclose any financial and personal relationships with other people or organisations, that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include, employment, consultancies, stock ownership, honoraria, paid expert testimony, patent, applications/registrations, and grants or other funding.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

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Consent for publication

Written informed consent was obtained from the patient's parent for publication of this Case Report and accompanying material. A copy of the written consent is available for review by the Editor of this journal.

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