Recurrent Acute Necrotizing Encephalopathy Associated With Family History of Encephalopathy: Clinical Experience And Literature Review

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Case report

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Abstract

Background: Acute necrotizing encephalopathy (ANE) is a rare acute encephalopathy secondary to infection, which is characterized by convulsion and disturbance of consciousness. Besides, recurrent cases with family history are rarer. To the best of our knowledge, only 12 cases reported were recurrent with family history of encephalopathy in the world. The aim of this study is to report a rare case of recurrent ANE with family history of encephalopathy to provide clinical data for future research of ANE.

Case report: A boy had a history of febrile convulsions when he was 1 year old. A few years later, he was hospitalized twice because of convulsions when he was 4 years old and 7 years old. Computed tomography (CT) and magnetic resonance imaging (MRI) were performed on two hospitalizations. Brain CT in the first admission showed low density lesions in bilateral temporal lobes hippocampus and further MRI after 3 days found lesions in bilateral temporal lobe hippocampus, insular lobes, ventrolateral thalamus and pons. Due to the bilateral and symmetrical lesions, metabolic diseases were suspected. When the boy was 7 years old, brain CT was normal while MRI showed multiple lesions in bilateral thalamus, left hippocampus and brainstem. According to the boy's clinical data and MRI findings, pediatrician diagnosed the child as ANE. After 7 days of treatment, he was discharged with slight lameness in the right lower limb.

Conclusion: It reports a Chinese child of recurrent acute necrotizing encephalopathy with family history of encephalopathy and reviewed cases similar to him. Diagnosis should be combined with its clinical symptoms, laboratory and imaging results. Clinicians need to improve their understanding in order to achieve early diagnosis and treatment so as to improve prognosis and reduce the occurrence of sequelae.

Introduction

First reported in 1995，acute necrotizing encephalopathy (ANE) often occurs in children, especially in infants aged 6-18 months [1, 2]. The main performance is as follows: fever, cough, vomit, convulsion, unconsciousness, rash, disseminated intravascular coagulation and liver dysfunction [3, 4, 5]. Although the incidence rate is only 1 in 1000,000, its mortality rate is high because of its rapid process [2]. There are more sporadic cases than recurrent cases reported all over the world. The recurrent cases are so rare that it is difficult to make an accurate diagnosis of ANE. Therefore, it reports a boy of recurrent ANE with a positive family history of encephalopathy. Medical history of the boy is introduced in detail. We found 13 cases in 10 literature were reported similar to this case with 4 features: ANE, ＜18 years old, recurrent encephalopathy, family history of encephalopathy from 3 databases: Pubmed, OVID, Web of Science. We reviewed these literature and summarized clinical features in ***Table 1***.

Table 1
Summary of recurrent cases with positive family history of encephalopathy

Case No.	Author/Year/Country	Age/ Sex	Seizures/ Fever/ Altered consciousness/Vomit/ Decorticate posture	Episodes total	Familial	Gene mutation	CT	MRI	CS
1[16]	Neilson/2003/American	4y/M	-/1/-/-/-	2	nephews (2)	-	-	-	EP
2[16]	Neilson/2003/American	4y8m/M	-	2	aunt (1) brother(1)	-	-	-	EP
3[17]	Marco/2010/American	18m/M	-/-/-/-/1	many times	brother(2)	N	left thalami	-	No
4[18]	Artemis/2010/American	9y/F	-/1/1/1/-	3	mother(1)	C.1880C > T; p.Thr585Met	-	bilateral thalami, pons	-
5[19]	Christian/2014/France	9y/M	1/-/1/-/-	3	sister(1) niece(1)	-	bilateral thalami, brainstem	-	-
6[19]	Christian/2014/France	6y/F	1/-/-/-/-	4	brother(1) daughter(1)	C.1754C > T p.Thr585Met	-	bilateral thalami, bilateral temporal lobes, brainstem	EP
7[20]	Wanigasinghe/2017/Sri Lankan	20m/M	1/1/1/-/-	2	brother(1)	-	external capsule, brainstem	bilateral thalami, external capsule, brainstem	EP
8[21]	Ramos/2018/Spain	10y/M	1/1/-/-/-	4	sibling(1)	C.1754C > T p.Thr585Met	-	bilateral thalami, temporal lobe,occipital lobe, external capsule, brainstem	EP
9[22]	Erin/2019/Australia	5y/F	1/-/-/-/-	4	mother(1), grandmother(1), great-grandmother(1), Cousin(1)	c.1754C > T p.Thr585Met	bilateral external capsules, lateral putamen, temporal and frontal lobes, bilateral thalami, posterior limb of the internal capsules, midbrain, brainstem	-	-
10[6]	Chit/2020/China	22m/F	1/1/-/1/-	2	brother(1)	c.1754C > T(exon 12)	-	thalamus, brainstem, cerebellum	-

PC, present case; F, female; M, male; L, left; R, right; CT, computed tomography; MRI, magnetic resonance imaging; CP, cerebral palsy;

–, not recorded; Norm, normal; y, year; m, month; EP, elevated CSF protein; PI, pleocytosis in CSF

Case No.	Author/Year/Country	Age/ Sex	Seizures/ Fever/ Altered consciousness/Vomit/ Decorticate posture	Episodes total	Familial	Gene mutation	CT	MRI	CS
11[9]	Gayatri/2020/India	15m/M	1/1/1/-/-	3	brother(1) sister(1)	-	-	pons, cerebellar dentate nuclei, thalami, posterior putamen, internal and external capsule, hemispheric white matter	No
12[9]	Gayatri/2020/India	13m/F	1/1/1/1/-	2	brothers(2)	-	-	bilateral thalami, external capsule	-
14[a]	PC	4y/M	1/-/1/-/-	the 1st	brothers(1) sister(2) grandpa(1)	-	bilateral temporal lobes	bilateral temporal lobes, insular lobe, bilateral thalami and pons	EP
14[b]	PC	7y/M	1/1/1/1-	the 2nd	brothers(1) sister(2) grandpa(1)	-	Norm	bilateral thalami and external capsule, left hippocampus, brainstem, pons	EP

PC, present case; F, female; M, male; L, left; R, right; CT, computed tomography; MRI, magnetic resonance imaging; CP, cerebral palsy;

–, not recorded; Norm, normal; y, year; m, month; EP, elevated CSF protein; Pl, pleocytosis in CSF

Historical Background

The child was a full-term infant of a G6P6. Parents were healthy with no similar history. His grandpa had a encephalopathy history diagnosed "viral encephalitis" when he was 50 years old. The eldest sister of the boy was 13 years old and failed in school. At the age of 6 months, The eldest brother and the second sister had persistent convulsions and died about 4-6 hours later. The second brother of him was in good health and had no similar attack. When the third sister was 7 years old, she had persistent convulsions and died about 4-6 hours later. According to the boy's family history, we made a genealogical tree of three generations ***(Figure 1)***.

Pathogenesis

The mechanism of ANE can be divided into two aspects: gene and environment.

Genetic factors are mainly reflected in gene mutation of ran-binding protein (RANBP2) gene located on chromosome 2q13 [6]. The dysfunction of nuclear pore components encoded by RANBP2 gene can lead to cytokine storms, blood-brain barrier destruction and mitochondrial dysfunction in neuronal cells . ANE is considered to be an autosomal dominant mutation disease.

Environmental factors refer to ANE caused by pathogens. Pathogens such as mycoplasma, influenza virus, pain influenza virus, herpes simplex virus and human herpesvirus-6 can intensify this disease. Among above pathogens, influenza virus is the most common pathogen [2]. COVID-19-related ANE was first reported in 2020 [7].

Because of positive family history, we suspected that the boy was related to RANBP2 gene mutation. However, his parents refused to do gene examination for high fee. Thus, pathogen was not identified.

Clinical Presentation

THE 1ST ADMISSION

A boy had a history of febrile seizures when he was 1 year old, but his family did not go to hospital because his temperature dropped to normal and seizure relieved. Three years later, on December 15, 2016, when the boy was 4 years and 5 months old, he was admitted to hospital for "two intermittent convulsions in one day". One day ago, the child complained of abdominal pain and cough at the beginning of the disease. Then, he suffered from two convulsions, showing sudden disturbance of consciousness, gaze, cyanosis around the lips and the four limbs ankylosis, which lasted for 1-2 minutes and relieved spontaneously. Vital signs were stable except respiratory rate up to 28bpm. Physical examination were normal except poor spirit and hyperemia in pharynx and occasional slight phlegm sounds in both lungs.

Examination: after admission, the child had a brain computed tomography (CT) ***(Figure 2, A)*** in the emergency department showing low density lesions in bilateral temporal lobes hippocampus. Due to the abnormal results of CT, further examination of magnetic resonance imaging (MRI) was recommended after 3 days. MRI showed lesions in bilateral temporal lobe hippocampus, insular lobes, ventrolateral thalamus and pons ***(Figure2, B~H)***. The child also had a gastrointestinal ultrasonography, electroencephalogram (EEG) and electrocardiogram (ECG). The results were as follows: 1. No abnormality was found in gastrointestinal ultrasonography and ECG. 2. EEG: A large amount of delta slow waves showed in bilateral occipital area and there was no obvious dominant rhythm. In addition, routine examination of blood, urine, stool, blood biochemical (including liver function, renal function, blood glucose and blood ammonia et al) and cerebrospinal fluid (CSF) examination were executed and part of results were listed in ***Table 2***. Blood: c-reactive protein (CRP), creatinine and total bilirubin were lower than normal. AST/ALT, CK-MB and α-HD were higher than normal. CSF: intracranial pressure (ICP), white blood cell count, protein and ammonia were higher than normal, glucose lower than normal and pan test±.

Table 2
Laboratory evaluation of the patient of two episodes.

Variable	Project	1st admission	State	2nd admission	State	Normal Range
Age	-	4y6mo	-	7y	-	-
Routine blood examination	Neutrophils	2.12	N	8.25	↑	1.8–6.3×109/L
	Lymphocyte	1.58	N	2.28	N	1.1–3.2×109/L
	Hemoglobin	120	N	133	N	120-140g/L
	Platelets	160	N	203	N	100–300×109/L
Blood biochemical examination	Lactate	3.43	N	3.87	↑	1.06-2.09mmol/L
	Ammonia	22.9	N	34.4	N	18–72 umol/L
	CRP	0.62	↓	1.00	N	0.068-8.2mg/L
	Homocysteine	9.25	N	NC	N	<15umol/L
	CK-MB	37	↑	24	N	0-24U/L
	Creatine kinase	101	N	222	↑	38–174 U/L
	Crt	31	↓	38	↓	41–109 umol/L
	Total bilirubin	2.5	↓	3.8	↓	5–21 umol/L
	Glu	13	N	13	N	10–60 U/L
	ALT	17	N	14	N	9–50 U/L
	AST	40	N	34	N	15–40 U/L
	α-HD	208	↑	145	N	90–180 U/L
	AST/ALT	2.35	↑	2.43	↑	0.80–1.50
	Glucose	4.68	N	13.85	↑	3.9-6.1mmol/L
CSF	Aspect	transparent	N	transparent	N	transparent
	Pan test	weak positive	(±)	positive	(+ +)	negative(-)
	White blood cell count	20	↑	6	↑	0–15×106/L
	Protein	903	↑	4378	↑	200-400mg/L
	Glucose	2.16	↓	3.94	N	2.5-4.4mmol/L
	Ammonia	124.5	↑	121.7	N	111–123 mmol/L
Hospital stay	-	9d	-	7d	-	-
Outcome	-	fully recovered	-	lameness in the right lower limb	-	-

y, year; m, month; NC, not clear; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; α-HD, α-hydroxybutyrate dehydrogenase;

Crt, Creatine; CRP, C-reactive protein; CK-MB, creatine kinase MB; Glu, Glutamyltransferase

THE 2ND ADMISSION

On December 31, 2019, when the child was 7 years old, the patient was readmitted to hospital because of "fever for 2 days and intermittent convulsions for half a day". Two days ago, he had no obvious trigger of fever, the highest temperature was 40°C. The boy complained of abdominal pain as same as the first admission. After 2 days, he deteriorated and developed 6 convulsions within half a day on the day of admission. During attack, he showed gaze, unresponsive, cyanosis around the lips, four limbs ankylosis, and urinary incontinence. Each convulsion lasted 1 minute and relieved spontaneously. After convulsions, he vomited. Vital signs: temperature: 37.0°C, pulse rate: 120bpm, respiratory rate: 18bpm, blood pressure: 135/84mmHg, Glasgow coma score (GCS) 7. Nervous system physical examination: coma, response to stimulation, stiff-neck three transverse fingers, positive in Knig's sign and Brudzinski's sign.

Examination: after admission, the child underwent imaging examinations: brain CT was normal ***(Figure 3, A)***. MRI showed multiple lesions in bilateral thalamus, left hippocampus and brainstem ***(Figure 3, B~F)***. Laboratory tests was the same as the first admission and results were listed in ***Table 2***. Blood: neutrophils, lactate, creatine kinase, AST/ALT and glucose were higher than normal. Creatinine and total bilirubin were lower than normal. CSF: ICP, white blood cell count, protein and ammonia were higher than normal.

The clinical process can be divided into three stages: prodromal stage, acute encephalopathy stage and convalescent stage. The first stage lasted about 3 days and children had respiratory, gastrointestinal symptoms such as fever, cough and vomit [8]. After a short prodromal period, rapid alteration of consciousness and convulsions occurred. About 30% children may die in acute encephalopathy stage. Among patients who were lucky enough to get through the second period, less than 10% of them recovered completely in the third period [3]. This child admitted to hospital twice for seizures, the first time his prodromal period was so short that the boundary between prodromal and acute encephalopathy stage was not clear. The child showed abdominal pain without any other common prodromal symptoms. At the 2nd admission, he fevered for 2 days and the highest temperature up to 41℃. In acute encephalopathy stage, the child showed 6 seizures and alteration of consciousness.

Most ANE cases are sporadic and will not recur. But the neurological function of a few ANE patients with recurrent encephalopathy deteriorated [9, 10]. For this little boy, he left the right lower limb slightly lameness at the 2nd discharge even though the treatment was similar to the first admission which leaded to fully recovery. A study in Japan, it was pointed out that the independent factors related to the death of ANE included AST > 500U/L, blood glucose > 150U/dl, hematuria/ albuminuria. For this boy, he was not satisfied with any of the independent factors.

In radiological research, the identification of ANE is the most important factor in determining the outcome [11]. Imaging shows multiple and symmetrical lesions located mostly in bilateral thalamus, brain stem, periventricular white matter, cerebellar medulla etc[12]. Thalamus is the most frequently involved area, which can be seen in most ANE patients. The typical signs are “concentric/laminar structure” or “tricolor pattern” in appearance. At the first of admission, the child had a brain CT showing low density lesions in bilateral temporal lobe hippocampus. After 3 days, MRI showed bilateral and symmetrical long T1 signal and long T2 signal in bilateral thalami, insular lobes. Axial fluid attenuated inversion recovery (FLAIR) showed abnormal, high signal of the bilateral thalami, insular lobes, temporal lobes hippocampus and the pons. Apparent diffusion coefficient (ADC) map showed “concentric/laminar structure” in bilateral insular lobes, large areas of restriction of diffusion in bilateral insular lobes and temporal lobes hippocampus. Diffusion-weighted imaging (DWI) showed high signal in the bilateral thalami, insular lobes. The 2st time, brain CT showed normal. But MRI showed long T1 and long T2 signal in bilateral thalamus, left hippocampus and brain stem. FLAIR, ADC, DWI showed high signal. According to the literature, hemorrhagic transformation may occur in the focus. Compared with MRI on the first admission, lesions on the second time were reduced and absorbed. Therefore, the performance was consistent with literature.

Laboratory examination showed that thrombocytopenia, liver enzyme increased but blood ammonia decreased in hematological and increased protein without pleocytosis in CSF [13]. Due to cytokine storms, cytokines may cause damage to multiple organs and lead to the above abnormality. It may show platelets reduced or liver enzymes increased in blood examinations. However, the results of platelet count and liver function were unremarkable during two hospitalizations. CSF protein increased obviously while no pleocytosis is one of the characteristics of ANE. Although the mechanism is unclear, it can help distinguish ANE from other encephalitis such as acute diffuse encephalomyelitis (ADE). CSF showed no pleocytosis and protein results of two admission were 903mg/L, 4378mg/L respectively, which distinguished ANE from ADE. In addition, CSF protein is one of the indexes to predict the prognosis of ANE. Higher CSF protein is associated with worse prognosis. 94% of the seriously ill patients had CSF protein > 0.45g/l [9]. For this boy, CSF protein was much higher than the first one. And he recovered completely the first time but left a sequelae the second time the second time.

We believe that it is necessary to test RANBP2 gene in ANE patients because one of the risk factors of ANE is RANBP2 gene mutation. It is associated with familial ANE and recurrent ANE. In addition, 40% of children carrying RANBP2 mutations are likely to develop ANE and there is a 50% chance of recurring ANE [6]. Moreover, infection-induced acute encephalopathy (IIAE) is a group of neurological diseases caused by infection. IIAE has many subtypes. ANE is one of the subtypes which is known as IIAE3 [9]. As for this family, the boy presented with IIAE3. His grandfather had “viral encephalitis”. His three siblings also showed acute encephalopathy although the cause was unknown. It was a pity that even though we highly suspected that his families carried RANBP2 gene mutation, the little boy and his families did not test RANBP2 gene. Nevertheless, we still believe that it is very important to establish a diagnosis of gene-related ANE [9, 10]. Because genetic test of ANE patient may be a benefit to family members. It provides opportunities for preventive vaccination, early intervention and prenatal detection of ANE. Some experts suggest that children more than 6 months old could be vaccinated against influenza every year, which is meaningful for ANE survivors and caregivers.

Diagnosis

Diagnostic criteria: 1. Convulsions and deterioration of consciousness after viral infection. 2. CSF Protein increases with no pleocytosis. 3. Multiple, symmetrical lesions involving bilateral thalamic, frontal lobes, parietal lobes, temporal lobes, brainstem, internal capsule and cerebellum. Bilateral thalamic are imaging markers. 4. Liver dysfunction as hepatic transaminase increased in various degree while blood ammonia did not increase. 5. Exclude resembling disease.

Differential diagnosis mainly from two aspects [8]: Clinically, ANE needs to be differentiated from viral encephalitis, fulminant hepatitis, heatstroke and hemolytic uremic syndrome. In imaging, ANE should be differentiated from carbon monoxide toxic encephalopathy, Reyes syndrome and ADE. Among these three diseases, ADE and Reyes syndrome are the focus of differential diagnosis. Brain lesions of ANE are symmetrical, while ADE are asymmetrical. CSF protein is normal in ADE, while increased in ANE. Reyes syndrome is characterized by liver dysfunction, high serum ammonia and hypoglycemia [14]. But ANE showed liver dysfunction but normal serum ammonia. Brain lesions of this patient were bilateral, symmetrical, and blood examination was normal, so it can be distinguished from ADE and Reyes syndrome.

MANAGEMENT AND PROGNOSIS

General treatment includes intensive care management, detection and treatment of elevated ICP and therapeutic hypothermia. Antiviral drugs and early use of immunosuppressive therapy such as hormone and immunoglobulin or plasma exchange can improve prognosis [15]. Although the exactly mechanism is unclear, it is well-known that timely diagnosis and treatment may lead to successful effection. The child was treated with intensive care, mannitol to reduce ICP, improving brain metabolism, nourishing brain cells, resolving phlegm and maintaining internal environment stability. Dexamethasone and oseltamivir were also treated. Hospitalization time was 9 days, 7 days respectively. Although the treatment were similar, the boy's neurological function deteriorated and left the right lower limb slightly lameness at the second admission.

Literature Review

Acute necrotizing encephalopathy is very rare. We searched the Pubmed, Web of Science and Ovid databases for English-language literature and case series of encephalopathy by key words: acute and encephalopathy. We screened the literature published between January 1, 1995 and February 28, 2021. A total of 13 cases involved in 10 articles were contained with 4 features: ANE, ≤18 years old, recurrent encephalopathy, family history of encephalopathy. For each case, publication year, the first author and country were documented, along with the patient's age, sex, symptoms, imaging characteristics, gene test, episode time, encephalopathy history of relatives and follow-up results ***(Table 1)***.

Conclusion

We report a Chinese child of recurrent ANE with a positive family history of encephalopathy, providing clinical data for future research of ANE. Doctors need to improve their understanding of ANE because diagnosis is difficult. It should combine with clinical symptoms, laboratory examination and gene detection of suspicious patients. In order to improve the prognosis and reduce the occurrence of sequelae, we should try our best to achieve early diagnosis and treatment.

Declarations

Author contributions

Yu Yin and Jingjing Zhang collect the patient data. Yang Yang and Cheng He analyzed data. Yanli Yang and Yu Yin made pictures. Yanli Yang was a major contributor in writing the manuscript. Heng Liu modified the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The case report was approved and supervised by the ethics committee of the Affiliated Hospital of Zunyi Medical University.

Consent for publication

Written informed consent for publication of patients' clinical details and clinical images was obtained.

Competing interests

The authors declare that they have no competing interests.

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Figures

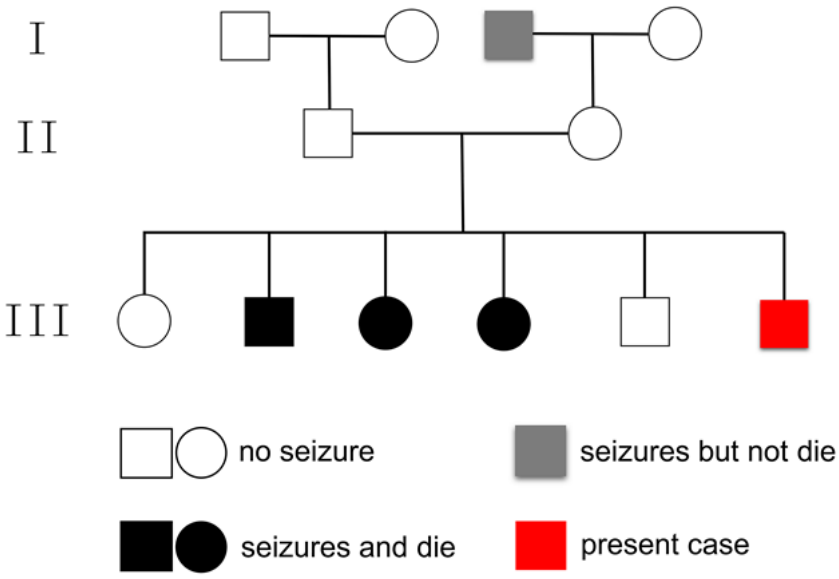

Figure 1

Genealogical tree. I, His grandpa had a history of similar attacks diagnosed "viral encephalitis" when he was 56 years old. II, Parents were healthy and had no similar attack. III, The eldest sister of the child was 13 years old and failed in school. At the age of 6 months, the eldest brother and sister had persistent convulsions and died about 4-6 hours later due to fever and vomiting. The second brother of the child was in good health and had no similar attack. When the second sister was 7 years old, she had persistent convulsions and died about 4-6 hours later due to vomiting after a cold.

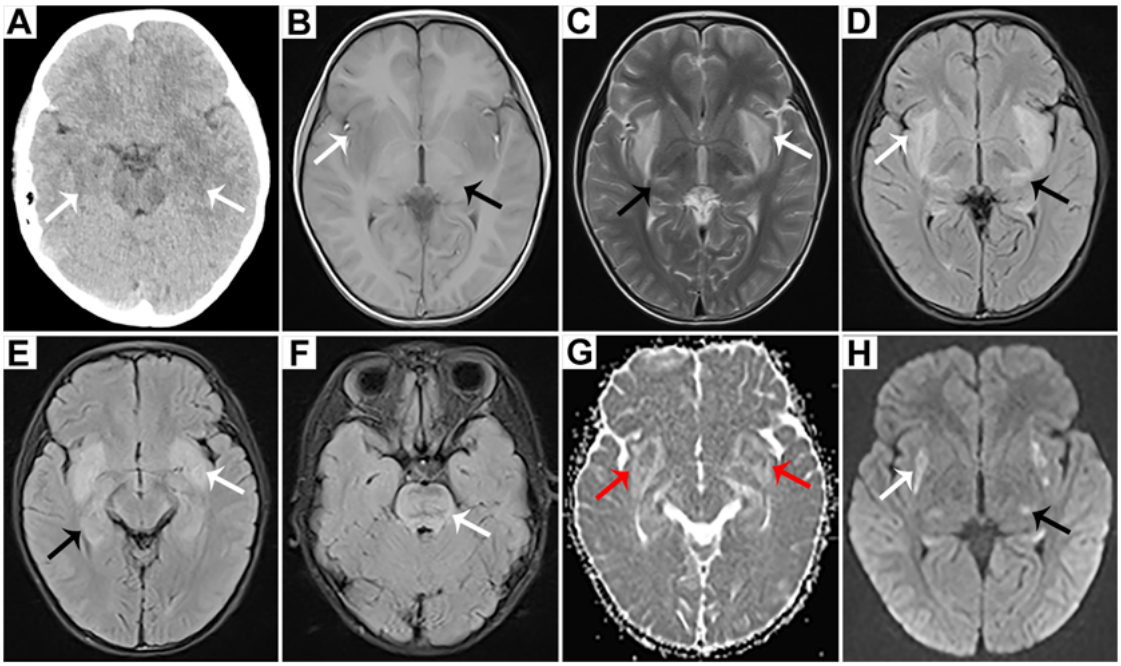

Figure 2

Images of the first episode at 4 years old (A~H). A, CT scan on admission showing low density lesions in bilateral temporal lobes hippocampus (white arrow). B, C. T1WI and T2WI of 3 days after admission showing long T1 signal and long T2 signal of bilateral thalami (black arrow), insular lobes (white arrow). D~F, T2-FLAIR showing abnormal, high signal of the bilateral thalami (D, black arrow), insular lobes (D, E, white arrow), temporal lobes hippocampus (E, black arrow) and pons (F, white arrow). G, ADC map showing large areas of restriction of diffusion in bilateral insular lobes (red arrow) and temporal lobes hippocampus. H, DWI showing high signal in the bilateral thalami (black arrow), insular lobes (white arrow).

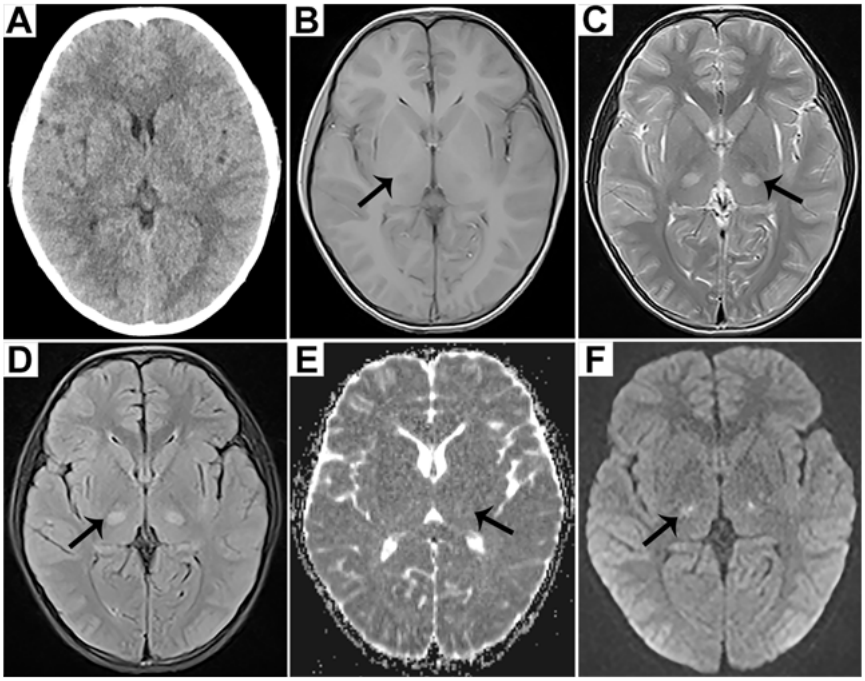

Figure 3

Images of the second episode at 7 years old (A~F). A, CT scan on admission showing no abnormality. B~F, T1WI, T2WI, T2-FLAIR, ADC map of 17 hours after admission showing abnormal, signal of bilateral thalami (black arrow).