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ORIGINAL ARTICLE

Acute necrotizing encephalopathy associated with RANBP2 mutation: value of MRI findings for diagnosis and intervention

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Abstract

Introduction Acute necrotizing encephalopathy (ANEC) is a rare entity characterized by encephalopathy following a febrile illness. Most patients are sporadic; however, recurrent and familial cases have been associated with *RAN-binding protein 2* (*RANBP2*) mutation. Well-defined MRI findings can even be life-saving with early diagnosis and treatment.

Methods In this article, nine pediatric cases diagnosed with ANEC1 both clinically and radiologically, and with least one variation in the *RANBP2* gene, are presented.

Results All patients were previously healthy and presented with encephalopathy after an acute febrile infection. The patients of 44% had a similar attack history in their family. Influenza A/B was detected in 7 patients (78%). One patient was admitted at age 32 years old. The first clinical findings of patients were encephalopathy (100%), seizure (44%), vision problems (33%), ataxia (11%), and monoplegia (11%). Recurrent attacks were seen in two (22%) patients. Brain MRI findings including bilateral thalamus, external capsules, and brainstem involvements were highly suggestive for *RANBP2* mutation. Based on MRI findings, genetic analyses were quickly performed and confirmed. All of the patients were treated with empirical encephalitis treatment, oseltamivir, intravenous immunoglobulin (IVIG), high-dose steroid and, if necessary, plasmapheresis, but three (33%) patients died despite treatment.

Conclusion ANEC associated with *RANBP2* mutation may occur early or late-onset and can be recurrent and fatal. Therefore, early diagnosis and treatment have the potential to modify the severity of this encephalopathy. Well-defined MRI findings are highly instructive for early diagnosis.

Keywords ANEC · Acute necrotizing encephalopathy · *RANBP2* · MRI · Treatment

Abbreviations

ANEC	Acute necrotizing encephalopathy of childhood
OD	Autosomal dominant
CSF	Cerebrospinal fluid
FLAIR	Fluid attenuated inversion recovery
GMFCS	Gross motor function classification system
MRA	Magnetic Resonance Angio
RANBP2	RAN-binding protein 2
SWI	Susceptibility Weighted Imaging sequence
URTI	Upper respiratory tract infection

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Introduction

Acute necrotizing encephalopathy of childhood (ANEC) is a rapidly progressing encephalopathy that develops after acute infections in children between 6 and 18 years old [1]. It presents with fever, deteriorating consciousness, personality changes, seizures, focal deficits, and coma [2]. The disease is mostly associated with preceding viral infection, including influenza A/B, parainfluenza, human herpesvirus 6, enterovirus, and varicella. However, it rarely occurs due to bacterial infections, such as *Mycoplasma pneumoniae*, diphtheria, and tetanus. Recently, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease 2019) (COVID-19)-related ANEC cases have also been reported [3]. Inflammatory cytokine storm, which is mediated by Interleukin 6 (IL-6), Interleukin 8 (IL-8), and Tumor Necrosis Factor Alpha (TNF-α), has been hypothesized in the pathogenesis of ANEC [4–6]. Hyper-intense signal changes are observed in symmetrical bilateral thalamus and brain stem, particularly in T2-weighted and fluid-attenuated inversion recovery (FLAIR) weighted magnetic resonance imaging (MRI) [6–8]. Diffusion restrictions that develop secondary to cytotoxic and vasogenic edema in diffusion-weighted series are also helpful in early diagnosis [8, 9].

Most cases of ANEC are sporadic and nonrecurrent. However, *RAN-binding protein 2* (*RANBP2*)-associated type (ANEC1) is the rarer, familial, recurrent and genetic type. In 2003, 11 individuals from the same family were diagnosed with ANEC by Neilson et al. [10]. It was stated that this disease could be inherited as autosomal dominant. In 2009, the *RANBP2* gene mutation was defined for the first time in 10 unrelated patients diagnosed with ANEC [4]. *RANBP2* is a nuclear protein produced in all tissues, with an extensive intracellular function [4]. ANEC1 inherited as autosomal dominant (OD) shows incomplete penetrance. Therefore, the probability of ANEC1 development in a person who has *RANBP2* mutation is 40% in their lifetime [4, 10, 11]. It should be noted that these patients have relatives who were followed up with diagnoses, such as acute disseminated encephalomyelitis (ADEM), Leigh's disease, encephalitis, or aseptic meningitis. *RANBP2* gene has many functions, including mitochondrial, metabolic and nuclear signals, and its mutations lead to different clinical manifestations depending on the underlying mutation type. If mutation disrupts nuclear signal function, impairment in the blood–brain barrier may be seen. Additionally, *RANBP2* mutation leading to mitochondrial dysfunction can cause cell death secondary to energy depletion. Thus, the involvement pattern of the disease resembles the energy depletion diseases, such as Wernicke's encephalopathy and Leigh syndrome [12, 13].

In this article, nine pediatric cases diagnosed with ANEC1 both clinically and radiologically, and with at least one variation in the *RANBP2* gene are presented.

Materials and methods

This is a retrospective study of patients diagnosed with ANEC1 in four tertiary centers in Turkey from 2016 to 2020. These centers were Istanbul Medipol University Faculty of Medicine, Karadeniz Technical University Faculty of Medicine, Republic of Turkey, Ministry of Health Bursa Provincial Health Directorate, University of Health Sciences, Ministry of Health University Adana City Training and Research Hospital. Ethics committee approval was obtained from the Adana City Training and Research Hospital with the decision dated 27/01/2021 and numbered 1301.

Nine ANEC1 patients with *RANBP2* gene variants were included in our study. All neurological examinations of the patients were recorded. Biochemical studies of plasma amino acids, acylcarnitine profile, urinary organic acids, and lactate were performed. Brain magnetic resonance imaging (MRI) was obtained. Diffusion MRI study was the initial technique due to no need for sedation and was later followed by a full sequences study.

Results

The median age of the pediatric patients was 5 years (min: 0.75 max: 10 years); there was one 32-year-old patient. Four of them were female (44%), and 5 of them were male (55%). Four of the patients (44%) had a similar attack history in their family. Seven of them (77%) had their first attack in the winter season. They all had a preceding infection history when the ANEC1 clinical findings occurred, and influenza A/B was detected in 77% of them. All of the patients presented with encephalopathy, four of them (44%) with seizures, three of them (33%) with sudden vision problems, one of them (11%) with monoplegia, and one of them (11%) with ataxia (Table 1). First, diffusion MRI was performed in all patients. Bilateral thalamus involvement was seen on diffusion and brain MRI in all patients, and other areas of involvement, including the external capsule, basal ganglia and cerebellar region, are summarized in Table 2. Spinal cord involvement was seen in 2 patients (22%). The liver function test results were normal in 7 patients (77%), and basal metabolic tests and cerebrospinal fluid (CSF) culture test results were normal. All patients were treated with empirical encephalitis treatment (ceftriaxone, clarithromycin, and acyclovir), oseltamivir, pulse steroid, and intravenous immunoglobulin (IVIG) for 5 days after diffusion MRI was performed.

Table 1 Clinical and demographic characteristics of the patients (n: 9)

Case	Years/gender/season	Family history	Preceding illness	Initial presentation	Infection
1	8/male/January	Yes	Yes	Imbalance, headache, somnolence	Influenza B
2	5, 3/male/December	No	Yes	Vomiting, seizure somnolence	Influenza A
3	0, 75/male/February	No	Yes	Acute hemiplegia, encephalopathy	ND
4	1/female/February	Yes	Yes	Diarrhea, vomiting, encephalopathy	ND
5	-/female	Yes	Yes	Fever, vomiting, cough, encephalopathy	ND
1st attack	3, 5/-/June	–	–		
2nd attack	4/-/January	–	–	–	ND
3nd attack	5/-/January	–	–	–	Influenza B
Mother of 5th patient	32 years/female/January	Yes	Yes	Blurred vision, encephalopathy, seizure	Influenza B
6					
1st attack	2/male/January	No	Yes	Encephalopathy, seizure	ND
2nd attack	2, 5/-/June			Encephalopathy, seizure	
7	5/female/April	No	Yes	Encephalopathy, seizure	Influenza A
8	10/female/April	No	Yes	Sudden vision loss, encephalopathy	Influenza A
9	10/male/January	No	Yes	Blurred vision Seizure	Influenza A

ND nondeterminant

Table 2 Neuroimaging features of the patients (n: 9)

	Frequency (n)	Percentage (%)
Brain MRI and diff MRI findings at the first time (one more localization)		
Corpus callosum	1	11
External capsule	8	89
Bilateral thalamus	9	100
Periventricular area	1	11
Basal ganglia	3	33
Cerebellum	2	22
Pons	7	78
Mesencephalon	7	78
Mammillary body	3	33
Temporal lobe	4	44

Diff diffusion

Treatment was continued with 2 mg/kg methylprednisolone for eight weeks. Four patients had plasmapheresis if response to initial therapies was inadequate. One patient (11%) had 3 attacks; 1 patient (11%) had 2 attacks; and 4 patients (44%) were intubated. The 32-year-old mother of the patient who had 3 attacks was also diagnosed with ANEC1 and died. Three patients (33%) improved completely, 3 patients had (33%) paraparesis and 3 patients (33%) died. Two of the patients died at the first attack, one of the patients died at the third attack. At least one pathogenic variant in the *RANBP2* gene was found in all patients (Table 3). Detailed demographic, clinical, and laboratory data of the patients are summarized in the tables.

Patient 1

Eight-year-old male presented with sudden unsteady walking, headache and encephalopathy after a fever and upper respiratory tract infection (URTI) (Table 1). There was a similar attack history among the patient's family. On the first day of admission, MRI showed diffusion restrictions and T2-weighted abnormalities in the thalamus, periventricular white matter, mammillary body, external capsule, corpus callosum splenium, basal ganglia, and temporal regions bilaterally (Figs. 1a–c and 2a and b). Empirical encephalitis treatment, pulse methylprednisolone, and IVIG treatments for five days were followed by plasmapheresis (Table 3). Maintenance treatment was continued with 2 mg/kg methylprednisolone for eight weeks. After one year, repeat MRI was normal, the gross motor function classification system score (GMFCS) was one, he had no sequelae and further attacks.

Patient 2

A five-year-old male was admitted with vomiting, seizures and encephalopathy after fever and URTI for a week. After the seizure, he rapidly became unconscious and comatose, and was intubated (Table 1). Diffusion MRI performed on the first day of admission showed diffusion restrictions in the bilateral thalamus, temporal lobe and pons. On the first

Table 3 Treatment, prognosis and genetic studies of the patients (n: 9)

Case	Treatment	Outcome	Genetic study-*RANBP2*
1	Ceft/acyclovir/clarithromycin/oseltamivir/ 6 *Plx + IVIG + pulse methylprednisolone	Improve mental and motor function, walking without support	c.1966A > G (p.IIe656Val)
2	Ceft/acyclovir/clarithromycin/oseltamivir/ 6 *Plx + IVIG + pulse methylprednisolone	Improve mental and motor function, walking without support, mild dystonia	c.520G > T (p.Val174Leu), c.560A > G (p.His187Arg)
3	Ceft/acyclovir/clarithromycin/oseltamivir/ IVIG + pulse methylprednisolone	Improve mental and motor function	c.7790 T > C (p.Phe2597Ser),
4	Ceft/acyclovir/ clarithromycin/oseltamivir/ 6 *Plx + IVIG + pulse methylprednisolone/Baclofen/Lev	Bedridden, severe dystonia, bad mental status	c.1966A > G (p.IIe656Val)
5			
1st attack	Ceft/acyclovir/oseltamivir/ IVIG + pulse methylprednisolone	Paraplegia	Paraplegia, swallowing dysfunction
2nd attack	Ceft/acyclovir/oseltamivir/ IVIG + pulse methylprednisolone	Paraplegia, swallowing dysfunction	
3nd attack	Ceft/acyclovir/oseltamivir/ IVIG + pulse methylprednisolone	Death	x
Mother of 5th patient	Ceft/acyclovir/oseltamivir/ IVIG + pulse methylprednisolone	Death	–
6	Ceft/acyclovir/oseltamivir/ IVIG + pulse methylprednisolone	Paraplegia and dystonia	c.1754C > T (p.Thr585Met)
7	Ceft/acyclovir/oseltamivir/ IVIG + pulse methylprednisolone	Death	c.1754C > T (p.Thr585Met)
8	Ceft/acyclovir/oseltamivir/ IVIG + pulse methylprednisolone	Paraplegia	c.1754C > T (p.Thr585Met)
9	Ceft/acyclovir/oseltamivir/ 5* plx + IVIG + pulse methylprednisolone	Death	c.2000C > T (p.A667V)

Ceft ceftriaxone, *plx* plasmapheresis, *IVIG* intravenous immunoglobulin, *Lev* levetiracetam

day of admission, empirical encephalitis treatment, pulse steroid, and IVIG were started followed by plasmapheresis and, then, tapering of oral methylprednisolone. Repeat MRI one month later showed atrophy and a nonspecific gliotic lesion (Figs. 1d, e and 2c, d). He had dystonia on discharge with GMFCS of 3. After 1 year, he had no further attacks and an exam with GMFCS of 1 and no dystonia (Table 3).

Patient 3

Nine-month-old boy presented with acute right arm monoplegia and encephalopathy after fever and URTI (Table 1). Diffusion restriction and necrotizing involvement in the left lentiform nucleus were seen on MRI (Figs. 1f, g and 2e, f). Encephalitis treatment, pulse steroid, and IVIG for five days were started (Table 3). Repeat MRI showed a lesion on the basal ganglia. The patient could raise his right arm to head level with 4/5 muscle strength one year later.

Patient 4

A fourteen-month-old female presented with encephalopathy and vomiting for three days after fever and diarrhea for a week. There was a similar attack history in the patient's family (Table 1). The patient was examined three days after the onset of symptoms, and treatment was started on the third day. MRI was abnormal in the bilateral external capsule, thalamus, and pons (Figs. 1h and 2g, h). Initial therapy was broad-spectrum antibiotics, acyclovir, high-dose glucocorticoid and IVIG followed by plasmapheresis (Table 3) and, then, methylprednisolone 2 mg/kg/day for eight weeks. Repeat MRI was normal. She had no new attacks on 1-year follow-up. The exam showed diffuse dystonia and GMFCS of five.

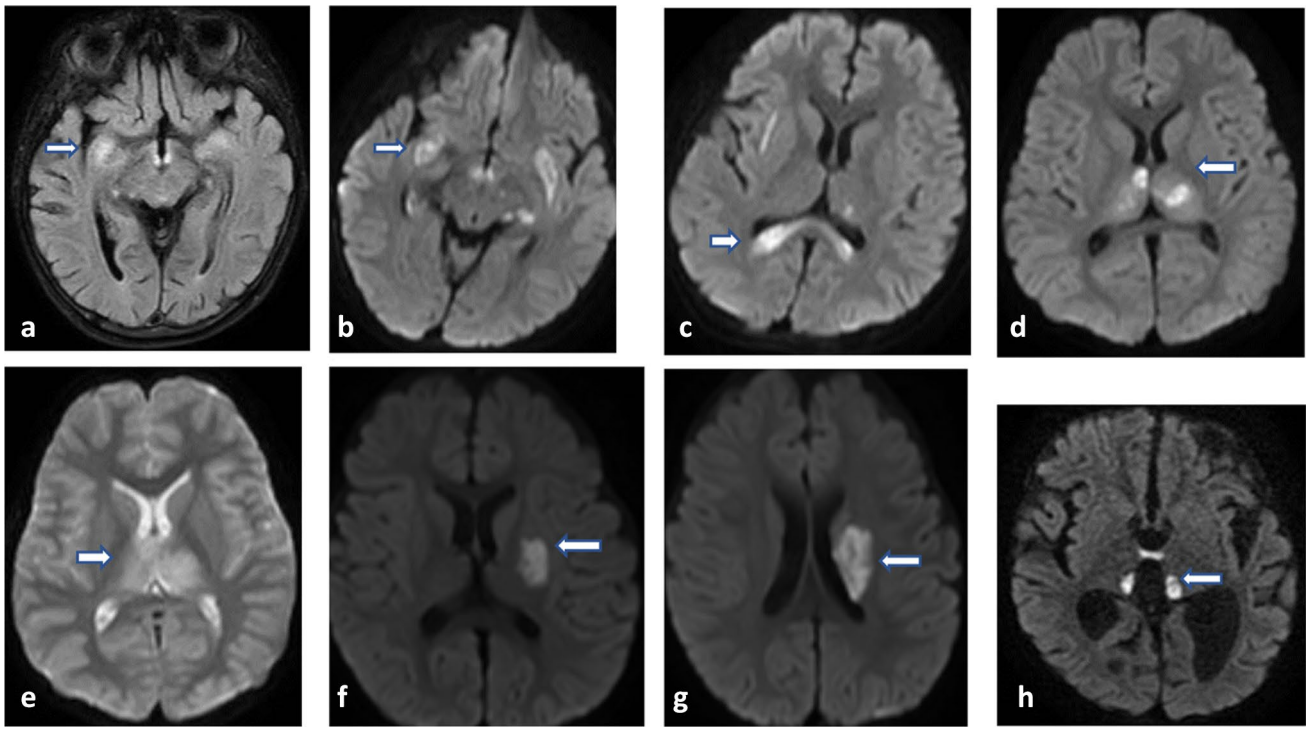

Fig. 1 Diffusion MRI of the patients. Patient 1: **a**–**c**, patient 2: **d**–**e**, patient 3: **f**–**g**, patient 4: **h**. All diffusion MRIs of the patients were taken on the first day of the illness. From a to c, images show extensive involvement to the basal ganglia, mammillary body, splenium of the corpus callosum, and temporal lobes. D and E images show bilateral thalamus involvement. F and G images show a necrotizing diffusion restriction in lentiform nuclei. H image shows involvement in the bilateral thalamus and pons

Patient 5

She had three attacks. During the first attack, she presented with seizures and encephalopathy after fever and URTI. Diffusion restrictions and signal increases without contrast enhancement in the bilateral thalamus, pons, medulla oblongata, and cerebellum were seen on the diffusion and T2-weighted MRI (Fig. 3). Empirical antibiotics, acyclovir, high-dose steroid, and IVIG were started for presumed diagnosis of ADEM and encephalitis. Exam at discharge found GMFCS of four, paraparesis and difficulty in swallowing (Table 3). Six months later, she had a second attack presenting with fever, loss of consciousness and seizures (Table 1) treated with high-dose steroids, IVIG and antibiotics. MRI showed signal increases in the bilateral thalamus, hippocampus, periaqueductal area, and pons (Fig. 4). Exam was abnormal at discharge (Table 3). On the third attack one year later, she presented with fever, URTI and decreased consciousness. There was a high signal intensity in the thalamus, cerebellum and cervical spinal cord on MRI (Fig. 5). She was treated with antibiotics, high-dose steroids, and IVIG, but died during her third hospitalization (Table 3). During this time, her mother was hospitalized due to blurred vision, encephalopathy, and seizures after similar fever and URTI symptoms. MRI showed diffusion restrictions and signal increases in the bilateral thalamus, capsule externa and basal ganglia (Fig. 6). She was treated with broad-spectrum antibiotics, acyclovir, IVIG, and high-dose steroid, but died. *RANBP2* gene mutation testing was not done (Table 3).

Patient 6

He was hospitalized with encephalopathy and coma after URTI and fever. He had two attacks at the age of two and six months old (Table 1). MRI showed diffusion restrictions and T2 signal increases in the bilateral thalamus, external capsule, mesencephalon, pons, and mammillary body (Fig. 7). Antibiotics, high-dose steroids, and IVIG were started. GMFCS was three in follow-up. No new attack occurred (Table 3).

Patient 7

Five-year-old girl presented with loss of consciousness and seizure after fever and URTI (Table 1). After the seizure, she rapidly became unconscious and comatose and was intubated. MRI showed diffusion restrictions and signal increases in the bilateral thalamus, mesencephalon, pons, external capsule, mammillary body, and temporal lobes (Fig. 8). Encephalitis treatment, IVIG, and high-dose steroid

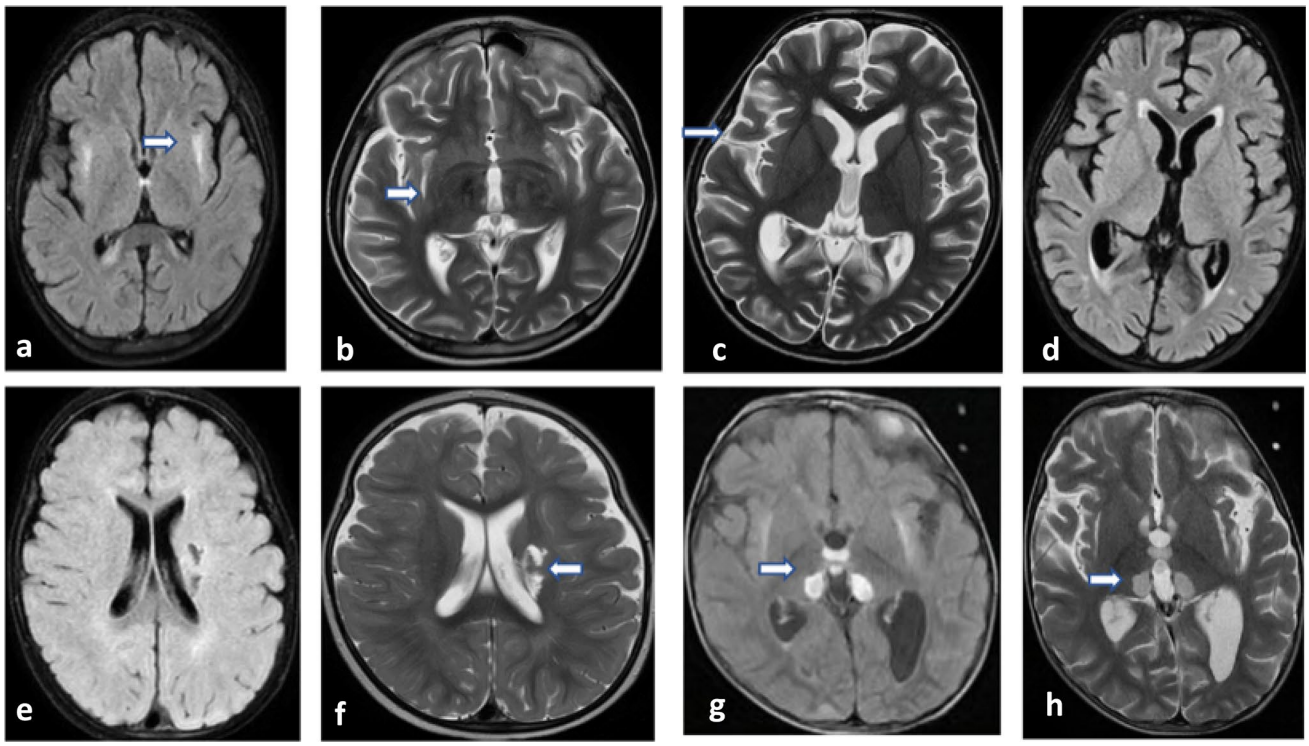

Fig. 2 Brain MRI of the patients. **a** and **b** show the flair and coronal T2-weighted images of patient 1. There is extensive involvement in the bilateral thalamus, basal ganglia, mammillary body, and splenium of the corpus callosum. **c** and **d** show the flair and T2-weighted images of patient 2, and it was taken after the first month of the illness. There are some atrophy and nonspecific gliotic lesion. **e** and **f** show the flair and T2-weighted images of patient 3. There is a necrotizing lesion in the lentiform nuclei. **g** and **h** show the flair and T2-weighted images of the patient 4. There is extensive involvement in the bilateral thalamus, mammillary body, basal ganglia, and pons

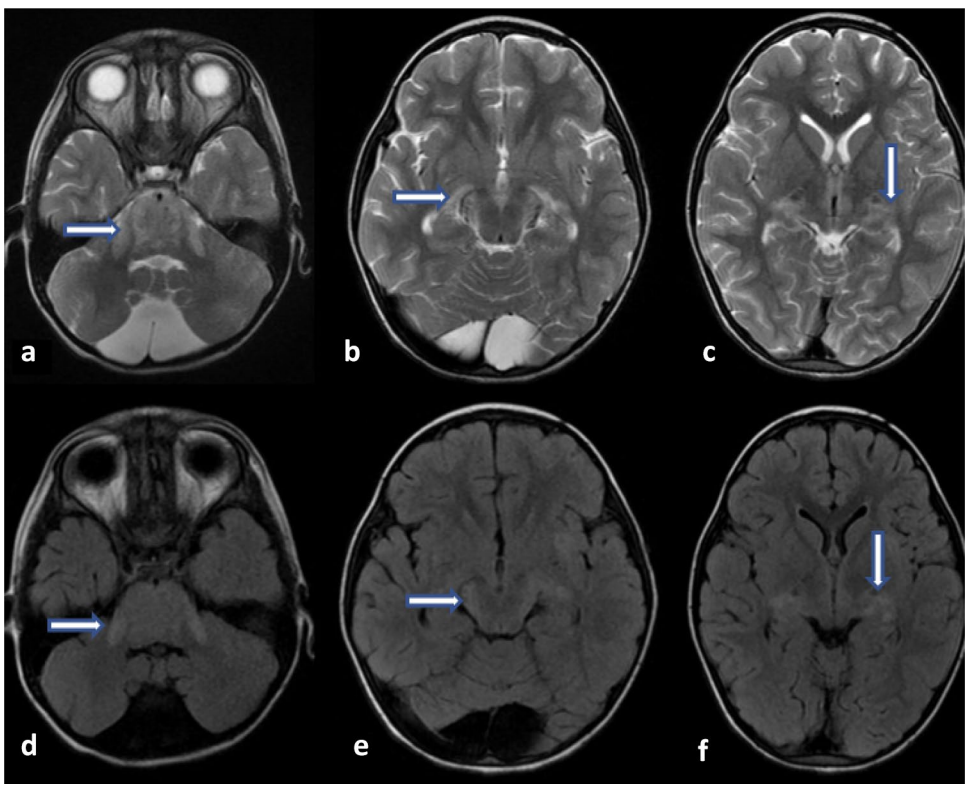

Fig. 3 MRI findings in the 1st attack of patient 5. There is extensive involvement in the bilateral thalamus, pons, medulla oblongata, and cerebellar peduncle

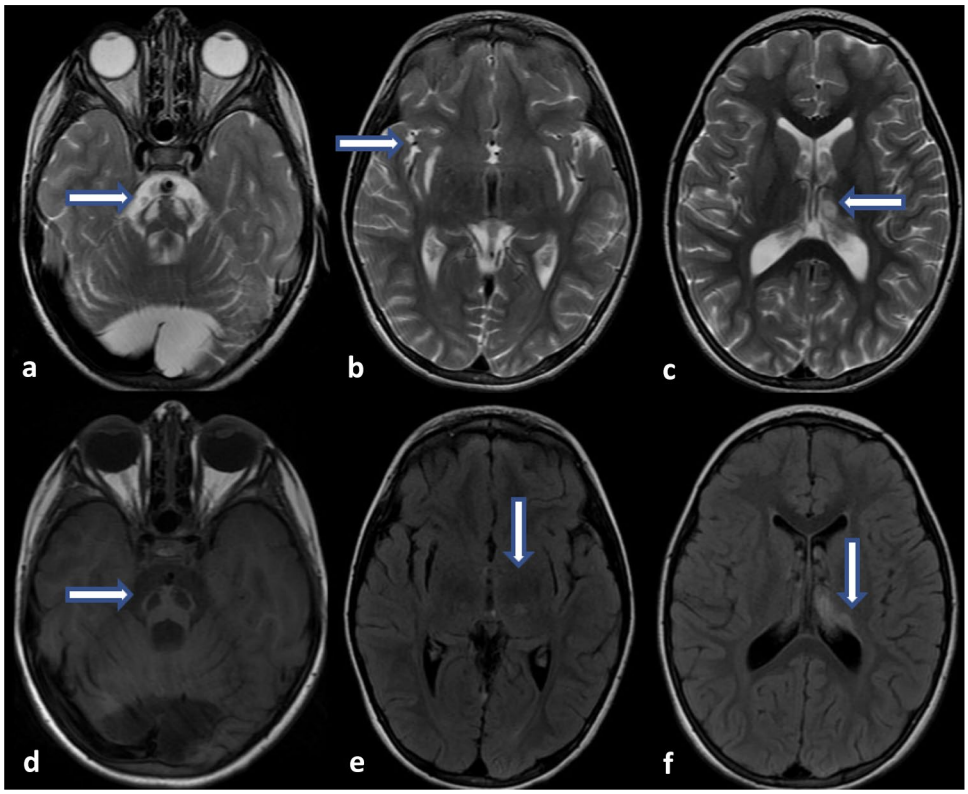

Fig. 4 MRI findings in the 2nd attack of patient 5. There is extensive involvement in the pons and bilateral thalamus, also a cystic appearance on the pons

were started, followed by a tapered dose of prednisolone for eight weeks (Table 3), but she died.

Patient 8

Ten-year-old girl presented with sudden vision loss after a fever (Table 1). Bilateral thalamus, external capsule, and pons signal increases and diffusion restrictions were seen on MRI (Fig. 9). She was treated with encephalitis treatment, IVIG, and high-dose steroid followed by a tapered dose of deltacortil (Table 3). Follow-up MRI showed abnormal signal in the left external capsule. She had no further attacks and GMFCS of three.

Patient 9

Ten-year-old boy presented with seizures and blurred vision after fever and URTI (Table 1). He received encephalitis treatment, IVIG and high-dose steroid followed by deltacortil. His general status gradually deteriorated so was intubated and treated with plasmapheresis. On MRI, there was a signal increase and diffusion restriction in the bilateral thalamus, external capsule, mesencephalon, pons, and temporal lobe (Fig. 10). Increased signal intensity and diffuse bleeding were shown on spinal MRI. The patient died (Table 3).

Discussion

ANEC1 is an extremely rare disease that requires rapid diagnosis and treatment. Experiences with therapeutic interventions and follow-up of patients with ANEC1 are limited and usually consist of case series. Early treatment with steroids might be correlated with a favorable prognosis, presumably secondary to interrupting elevated cytokines and decreasing inflammation [14]. High-dose steroids can also limit the edema associated with neuroinflammation [13]. The outcome of ANEC1 varies from complete recovery to persistent sequelae or death. The mortality rate of ANEC1 is 30%.

Studies have reported that the prognosis varies according to the duration and number of seizures, the time of diagnosis and treatment initiation, the number of recurrences and the areas of involvement in the brain [15, 16]. Sell et al. [17] reported 2 cases with poor prognosis who had seizures, more than one attack and typical involvement pattern on MRI. Lee et al. [14] also reported that two patients had seizures and a fatal prognosis despite aggressive immunosuppressive therapy and IVIG on the first day. In our study, we found that the prognosis of cases who had more than one attack, (patient 5 and patient 6) were intubated after seizures (patient 7 and patient 9), or started treatment late (patient 4), was quite poor. The only exception was the second case. He was admitted with a seizure and was intubated, but he could walk independently

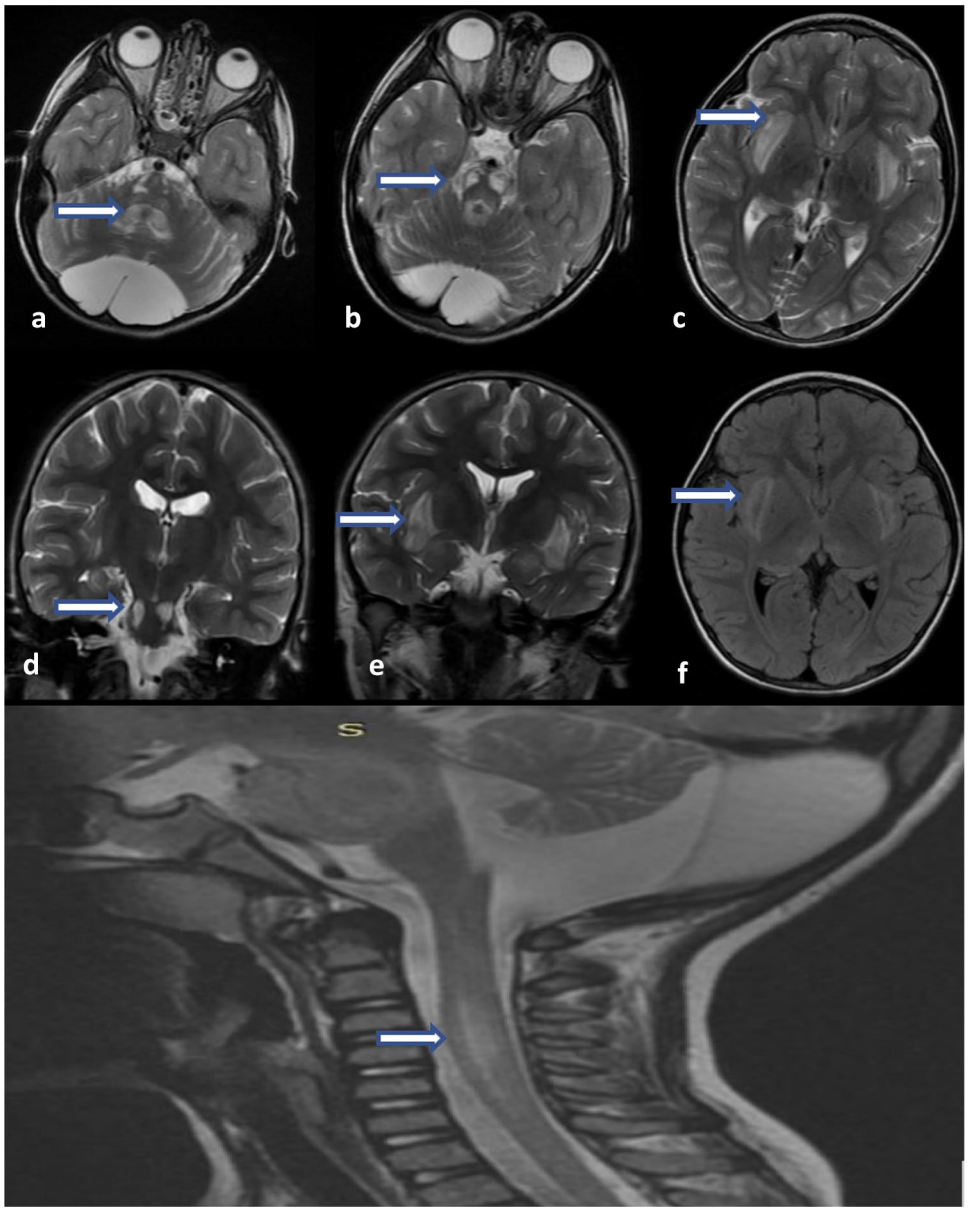

Fig. 5 MRI findings in the 3rd attack of patient 5. There is extensive involvement in the bilateral thalamus, pons, medulla oblongata, basal ganglia, and cervical region

after one year, possibly due to the fact that he had a single attack and was treated with plasmapheresis and pulse steroid followed by prednisolone taper. Patients 9 and patient 5 died, suggesting that spinal involvement may be also associated with a poor prognosis.

Cases with more than 2 attacks have not been reported in the literature. Patient 5 had three attacks and died during the third attack. Also, her mother had an attack and died. On the other hand, presentation with acute hemiplegia and acute visual loss is infrequent in the literature. Sell et al. [17] reported a patient presented with encephalopathy and acute hemiplegia, and Chew et al. [18] reported a patient whose first complaint was acute vision loss. Three of our patients presented with acute vision loss, likely related to involvement of the bilateral thalamus and lateral geniculate nucleus.

For our population, diffusion MRI was critical in the evaluation of ANE or ANEC1 because it was not easy to perform conventional MRI due to the technical and patient challenges. Albayram et al. [19] also reported that diffusion MRI could be performed in ANE cases and that diffusion restrictions might be observed due to vasogenic edema and necrosis. In our study, diffusion MRI was performed after emergency department presentation since conventional MRI would be technically challenging (need for anesthesia). When the typical involvement areas were observed (bilateral thalamus, external capsule, cerebellum, and basal ganglia), steroid and IVIG treatments were started quickly.

As previously reported, 100% of the patients had bilateral thalamus, 89% of them had external capsule, and 78% of them had brain stem and mesencephalon involvement.

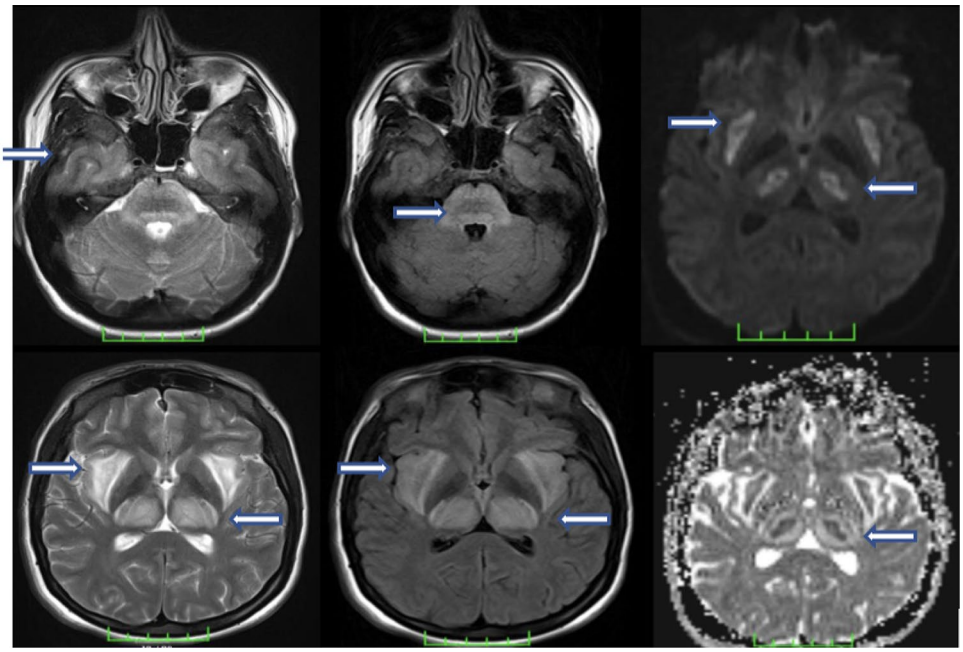

Fig. 6 Mother's MRI and diffusion MRI findings. There is extensive involvement in the bilateral thalamus, pons, basal ganglia, external capsule, and temporal lobes

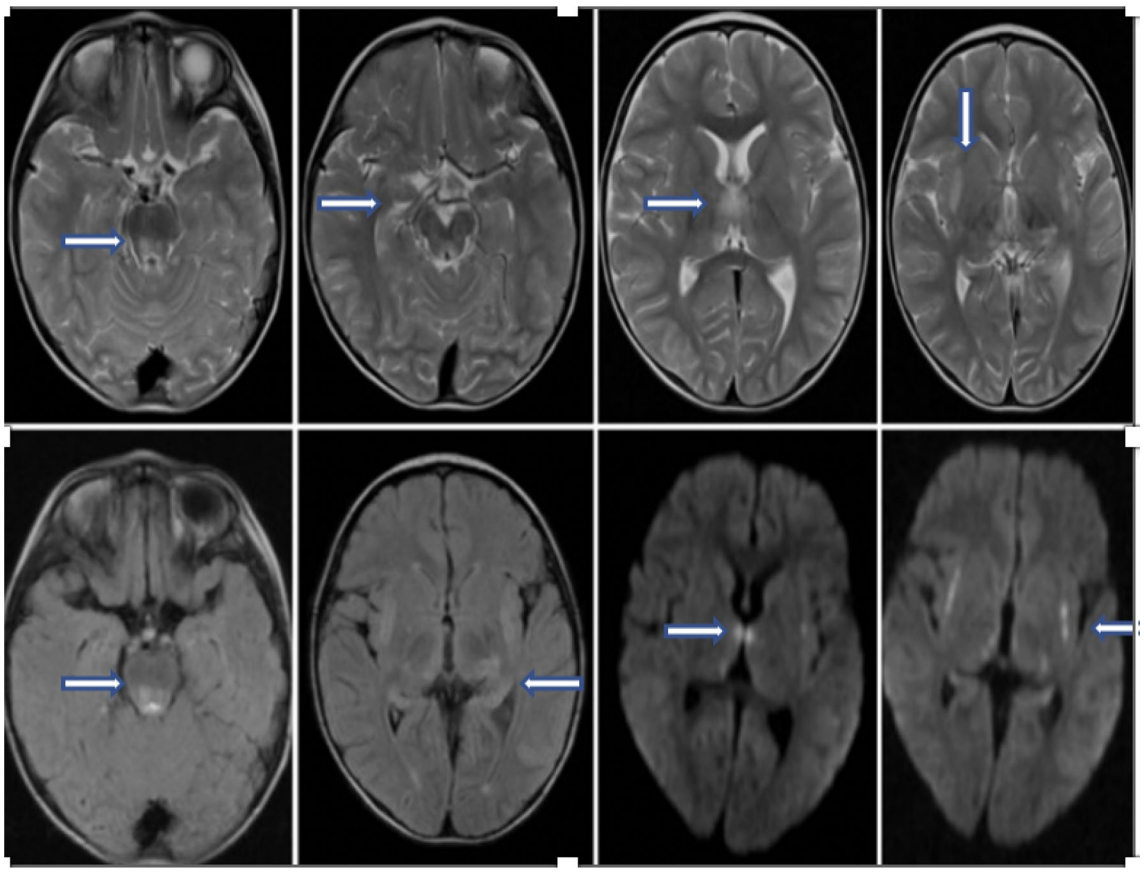

Fig. 7 T2- and Flair-weighted images and diffusion MRI of the patient 6. There are extensive signal increases and diffusion restriction in the bilateral thalamus, external capsule, mesencephalon, pons, and mammillary body

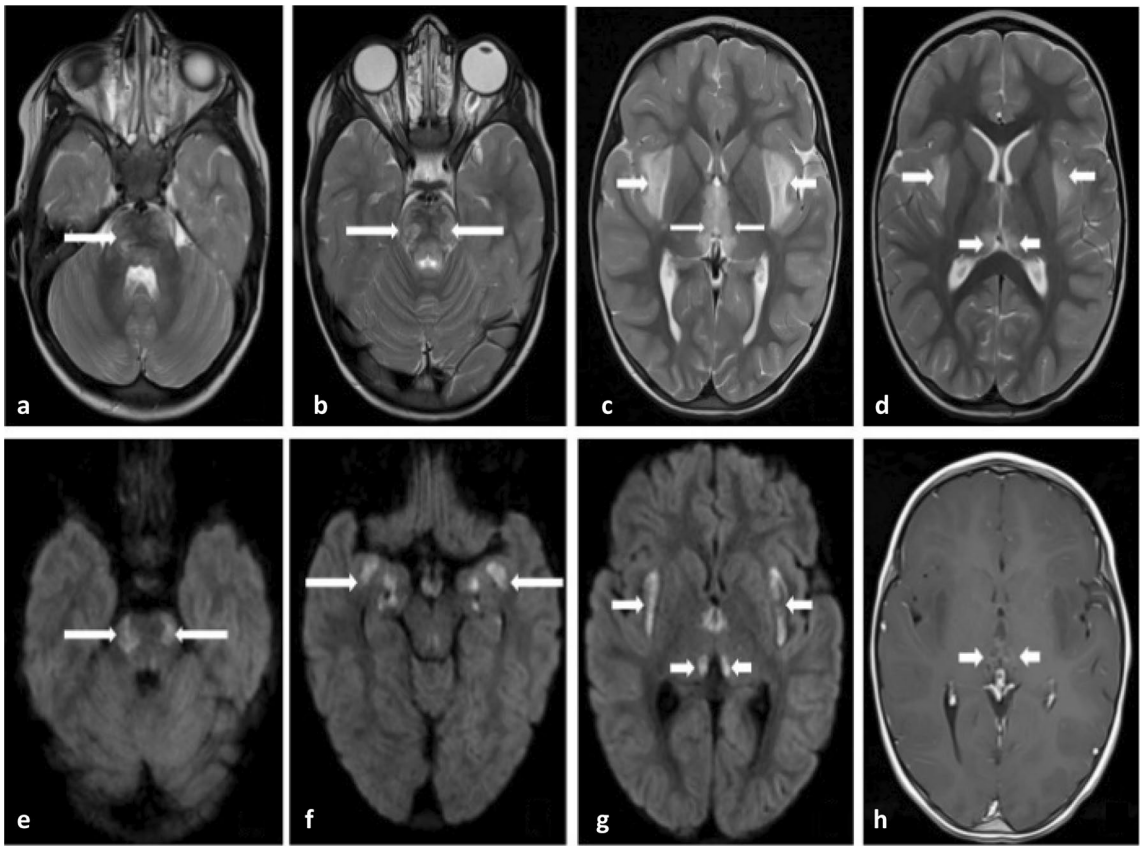

Fig. 8 T2- and Flair-weighted images and diffusion MRI of the patient 7. There are extensive signal increases in the bilateral thalamus, external capsule, mesencephalon, pons, and mammillary body. Also, diffusion restrictions are observed in the temporal lobe, thalamus, external capsule, and pons

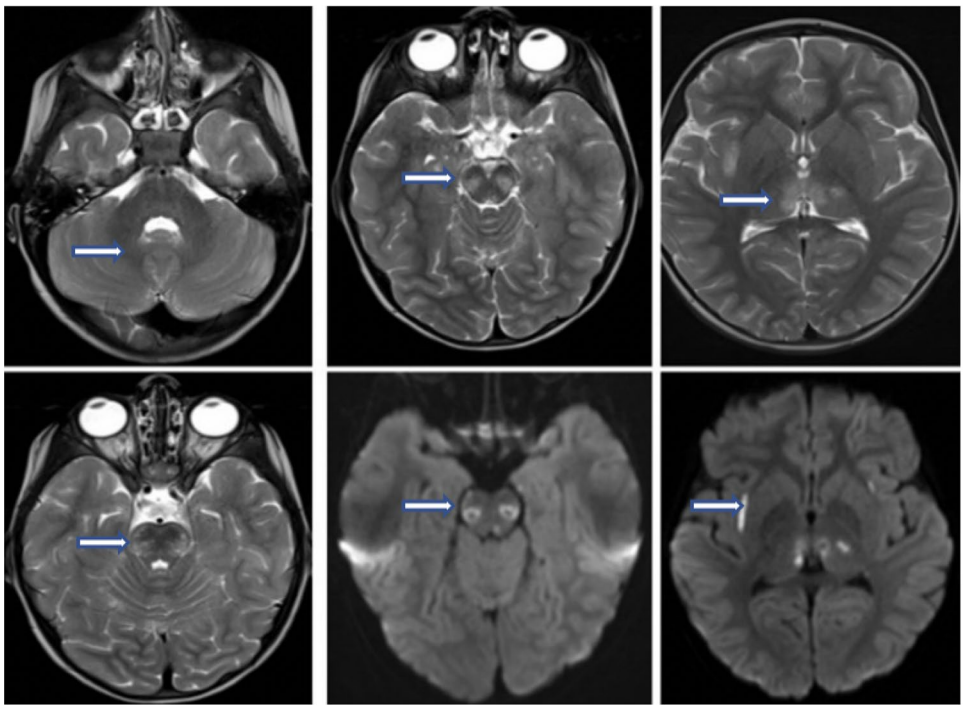

Fig. 9 T2-weighted and diffusion MRI of the patient 8. There are bilateral signal increases in the mesencephalon, thalamus, and pons. And there are diffusion restrictions in the pons, external capsule, and bilateral thalamus

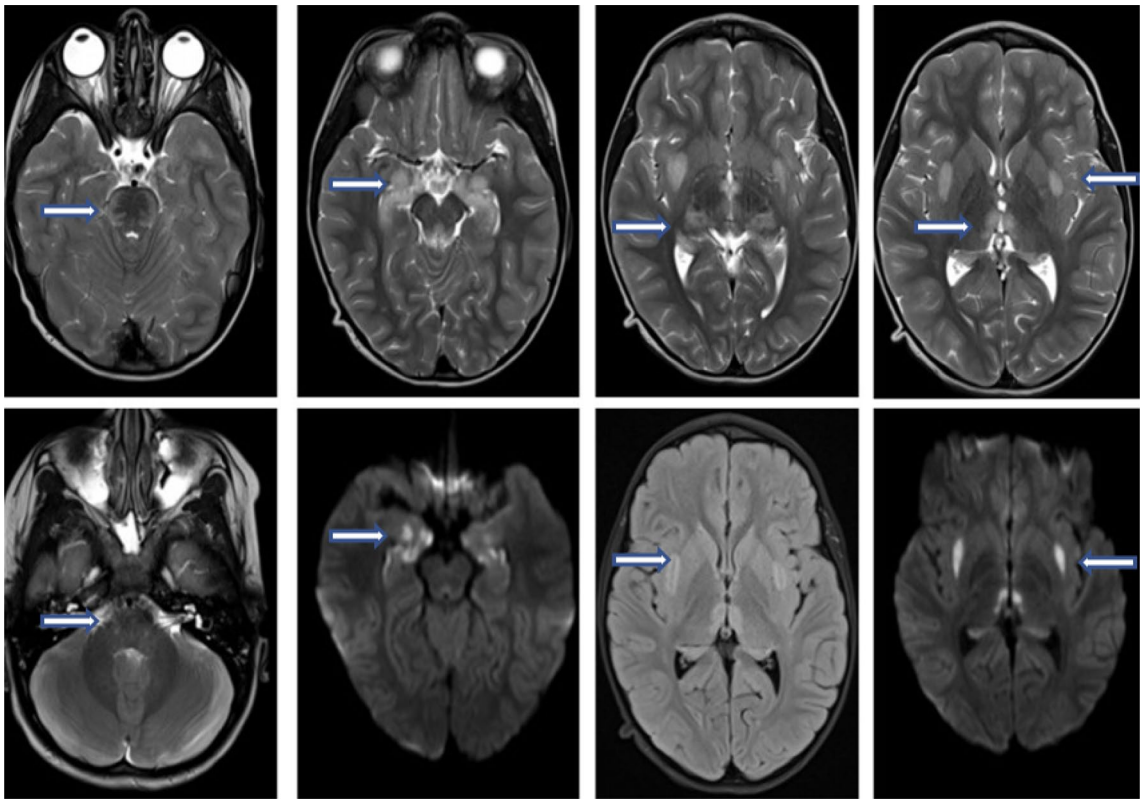

Fig. 10 T2- and Flair-weighted images and diffusion MRI of the patient 9. There are extensive signal increases in the bilateral thalamus, external capsule, mesencephalon, temporal lobe, and pons. Besides, diffusion restrictions are observed in the thalamus, external capsule, pons, and temporal lobe

Patient 1 had corpus callosum involvement, which was not previously reported. Levine et al. [3] and Okumara et al. [15] reported that oseltamivir, IVIG, and plasmapheresis were ineffective in ANEC1 patients. However, we had favorable results in our patients who received pulse steroid, IVIG, and plasmapheresis early in the course of their illness. In our study, we performed plasmapheresis for patients 1, 2, 4, and 9. Only patient 9, who started plasmapheresis after clinical deterioration, died. Plasmapheresis might be helpful because of possible immune dysregulation due to genetic mutation.

The coexistence of ANEC and influenza is common. Therefore, influenza vaccines are recommended for patients with a history of ANEC and their relatives for further infections and possible recurrences [20, 21]. In our study, we suggested that patients should be monitored closely during the influenza season, and encouraged annual influenza vaccination.

The function of the *RANBP2* gene is still unclear and clinical difference in patients may be due to the differences in mutations. Very few cases have been reported in the literature. The *RANBP2* gene (601,181) is localized on chromosome *2q12. T*he *missense p.Thr585Met* mutation is most frequently observed. The *RANBP2* gene is both Ran GTPase-dependent and -independent. Ran GTPase-dependent *RANBP2* gene is responsible for the nuclear and pro-inflammatory function, whereas Ran GTPase-independent *RANBP2* gene is responsible for mitochondrial function. Depending on the gene mutation, cell destruction, cytokine dysregulation, blood–brain barrier destruction, oxidative stress, and energy metabolism disorder can be seen [18]. Ohashi et al. [22] reported a pediatric case with concomitant *RANBP2* and *carnitine palmitoyltransferase 2 (CPT2)* gene mutation, and stated that *CPT2 gene* mutation might also cause the onset of acute encephalopathy. Shibata et al. reported that the mutated *RANBP2* gene had an attenuated binding ability to COX11. Therefore, this change might lead to a decrease in ATP production and energy deficiency, followed by the onset of encephalopathy [23]. Thus, reporting of all mutations is important for clarifying the function and clinic heterogeneity of the gene.

Conclusion

ANEC associated with *RANBP2* gene mutation may occur early or late-onset and can be recurrent and fatal. If a previously healthy person has seizures, encephalopathy or sudden loss of consciousness after fever and URTI, and specific

region involvement on brain MRI or diffusion MRI, the *RANBP2* gene is indicated. We also recommend high-dose steroids and IVIG; if there is no clinical improvement, plasmapheresis can be performed. Influenza vaccination and close monitoring during influenza season can reduce the risk of possible recurrence. Early diagnosis, including brain MRI with characteristic findings, and treatment, have the potential to modify the severity of this encephalopathy.

Limitations

This was the retrospective and multicenter study. The number of patients with ANEC1 is not enough, so the experiences of therapeutic interventions and follow-up of patients with ANEC1 are limited and usually consist of case series. As more cases are gathered and multicenter studies are designed, we will conduct more detailed analyses and more comprehensive follow-ups.

Declarations

Conflict of interest The authors declare that they have no conflict of interest to disclose. There is no funding support available for this study.

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