Received: 8 March 2023 | Revised: 5 April 2023 | Accepted: 10 April 2023

DOI: 10.1002/ccr3.7253

CASE REPORT

Clinical Case Reports Open Access WILEY

Risk factors for mortality in fulminant acute necrotizing encephalopathy following influenza A in an adolescent boy

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Key clinical Message

Acknowledging the risk factors of mortality and morbidity of each disease is effective for its final outcome. Recognizing these cases can have the value of preventing the occurrence of unfortunate events, such as not recommending the use diclofenac in an influenza epidemic.

KEYWORDS

ANEC, children, encephalopathy, influenza

1 | INTRODUCTION

Acute necrotizing encephalopathy of childhood (ANEC) as a rare fulminant neurological disorder is accompanied with rapid progressive encephalopathy, seizures, altered mental status, raised intracranial pressure (ICP), impaired liver function, poor outcome, and high mortality.[1,2] ANEC was first reported in Japan in 1995.[3] It mostly affects healthy East Asian children with ages ranging from 6 months to 11 years with the highest incidence between 6 and 18 months.[4] Radiological findings of ANEC are multifocal and symmetrical involvement of the thalamus, brain stem, supratentorial region, putamen, internal capsule, white matter, and cerebellum which are diagnostic.[1,2,5] Viruses that can cause ANEC are Influenza A and B, human herpesvirus 6 (HHV-6) and 7 (HHV-7), parainfluenza, varicella, enterovirus, novel reovirus strain, rotavirus, herpes simplex virus, rubella, Coxsackie A9, measles,[4,6,7] and COVID-19.[8,9] According to studies, influenza is the most common cause of this disease.[10]

Here we describe the clinical and neuroimaging findings of ANEC in a 13-year-old boy with influenza infection along with some risk factors for death.

2 | CASE PRESENTATION

A 13-year-old boy was referred to Bahrami Children's Hospital, Tehran, Iran with lethargy since the day before admission. This picture was accompanied with

high-grade fever and chills, severe diarrhea, hallucinations, and decreased level of consciousness. Immediately after admission he presented an episode of generalized tonic-colonic seizure with upward gaze and jaw locking. The patient had mild flu-like symptoms (rhinorrhea and productive cough) during the previous week. He had normal development with no history of seizures and/or head trauma. He had not received influenza vaccination. Diclofenac suppositories were used to control his fever. His parents were not related and there was no family history of neurological disorder, even though his mother was diabetic. After the seizure, he was not conscious and had no proper verbal and eye response to even painful stimuli [Glasgow Coma Scale (GCS) was five: motor3, verbal responses1, eye-opening1]. His vital signs were as follows: Blood pressure: 100/65 mm Hg, pulse rate: 100/min, RR: 30 breaths/min, T: 38.5 degrees Celsius, Spo2: 98%. His pupils were miotic with appropriate response to light, without Babinski's sign, or focal neurologic findings. There were no abnormal findings in the examination of other organs.

The laboratory tests are summarized in Table 1. Other biochemistry tests including arterial blood gas (ABG), ammonia, lactate, urinary culture, and blood culture were normal. The virological tests showed negative PCR for COVID-19 and positive PCR for influenza A.

TABLE 1 Paraclinical findings of the patient with acute necrotizing encephalopathy.

Blood tests (unit)	Admission	Third day	Last day	Normal range
Glucose (mg/dL)	173	179	379	60-100
BUN (mg/dL)	40	45	75	15–45
Creatinine (mg/dL)	1.3	1.5	1.9	0.31–0.88
Sodium (meq/L)	136	138	167	135–145
Potassium (meq/L)	3.3	3.6	3.5	3.5–5
Calcium (mg/dL)	9.6	9.1	9.2	9–11.2
Phosphorus (mg/dL)	2.1	3.5	1.8	3.2–5.7
Uric acid (mg/dL)	7.4		8.1	3.2–7.4
ALT (U/L)	69		877	10–40
AST (U/L)	70		469	25–40
Alkaline phosphatase (U/L)	647		360	180–1200
PT (s)-INR	14.9–1.3		12.8–1.1	(12–15) (0.9–1.1)
PTT (s)	42		41	25–45
WBC (×103/μL)	8200	7600	7300	8000–1540
Neutrophils (%)	78	83	84	40–75
Lymphocytes (%)	14	13	10	20–45
Monocytes (%)	4	3	3	2–10
Eosinophiles (%)	2	3	3	1–6
Hgb (g/dL)	13	10.7	16.1	13.3–16.9
HCT (%)	36.3	30.2	48.9	30.8–37.8
Platelets ($\times 10^3/\mu L$)	225	120	90	177–381
Urinalyses				
Hematuria	0–1	8–9	2–3	
Blood	-	+	Trace	
Proteinuria	-	+	+	
Glucose	+	-	++	
CPK	19,710	14,680	12,080	24–195
LDH	1910	1910	2180	˂746

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CPK, Creatine phosphokinase; HCT, hematocrit; Hgb, hemoglobin; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood count.

Abdomen and pelvic ultrasound were normal. Echocardiography and electrocardiography (ECG) findings were normal as well. Brain CT scan showed: Brain swelling accompanied by bilateral symmetric periventricular low attenuation areas in white matter and thalami (shown in Figures 1,2). Findings were in favor of leukoencephalitis. ANEC could be considered in the differential diagnosis. On the other hand, due to the unstable condition of the patient, it was not possible to perform MRI.

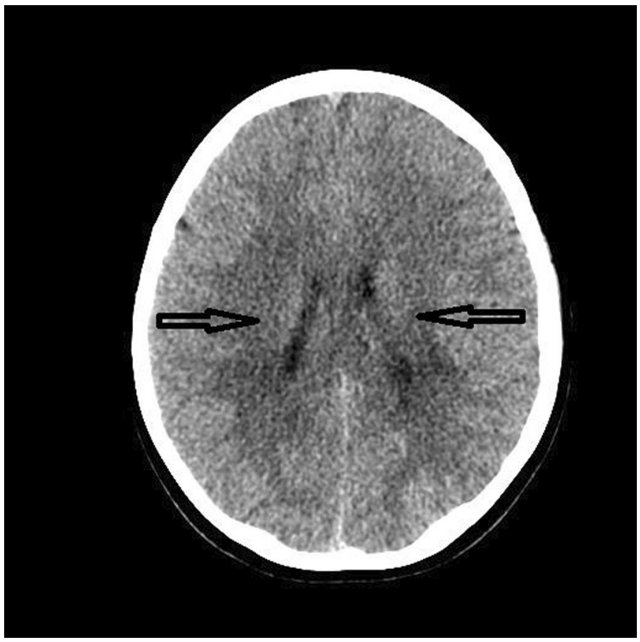

FIGURE 1 Bilateral symmetric periventricular low attenuation area in white matter.

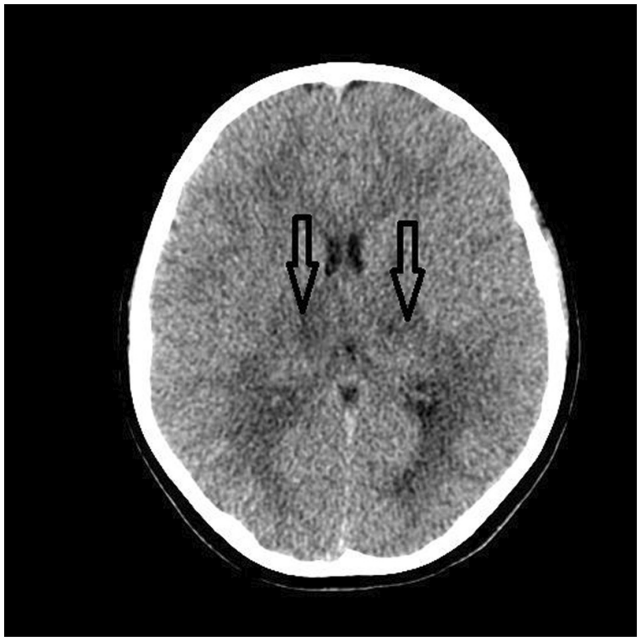

FIGURE 2 Bilateral involvement of thalami.

At the ward he had five episodes of focal seizures of the left upper limb, GI bleeding, and respiratory distress (RR: 30 breaths/min and Spo2: 88%). Then he was transferred to the pediatric intensive care unit (PICU). Intubation and mechanical ventilation were initiated. Transfusion of fresh frozen plasma (FFP), pantoprazole, and octerotide drip was started because of GI bleeding. During the second day of admission, the blood pressure raised (139/73 mm Hg), so he was treated for hypertension under suspicion of Cushing's triad. As the patient's ICP was elevated, lumbar puncture (LP) was impossible. He was loaded and maintained with phenytoin for seizures. Intravenous immunoglobulin (IVIG) (2 gr/day) and methylprednisolone (20 mg/kg/day for 3 days) were prescribed from the second day of admission. In addition, he was treated with oseltamivir for 5 days and, since LP was not done, acyclovir was added because the probability of herpes encephalitis. Antibiotics (vancomycin 40 mg/kg/day divided in 4 dose plus meropenem 120 mg/kg/day divided in 3 dose) were prescribed to cover meningitis. On the other hand, mannitol and hypertonic sodium were indicated to control cerebral edema. During the third day, his neurological examination revealed a GCS of M1V1E1, double midriatic pupils with no response to light, and no gag neither deep tendon reflexes. Unfortunately, he died on the seventh day of hospitalization.

3 | DISCUSSION

ANEC is an acute neurological disorder with nonspecific symptoms. It usually occurs in healthy children with no past serious medical history, as in our case.[4] The pathogenesis of ANEC involves cytokine dysregulation, leading to systemic inflammation, multiorgan damage, vascular leakage, brain cell apoptosis, and brain edema.[11]

The diagnosis is based on clinical manifestations and MRI findings. Multiple symmetrical brain lesions of bilateral thalami, upper brain stem tegmentum, the cerebellar white matter, and the cerebellar medulla, showing a concentric structure on CT or MR images, characterize ANEC.[12] Our patient had similar CT scan findings (bilateral symmetric low attenuation areas in white matter and thalami).

Neurological complications are seen in 3%–9.7% of patients with influenza, most of whom are under 5 years of age.[10,13] These neurological complications include febrile seizures, seizures, encephalopathy, Guillain–Barre syndrome, myositis, postinfectious cerebellitis, and ANEC.[1,14] Among these complications, seizures are the most common.[13,15] These complications increase the mortality rate caused by influenza to more than 30%.[14]

ANEC is accompanied with high mortality and poor outcome. Survivors use to be in vegetative state or have moderate-to-severe disability at the time of discharge from hospital.[9] The poor prognostic factors for death in ANEC include: young age (<4 years), underling disorders (pulmonary, cardiovascular, immunological, neurological, neuromuscular, metabolic, renal, etc.), thrombocytopenia, elevated aspartate aminotransferase, hyperglycemia, hematuria or proteinuria, increased CSF protein, and consumption of diclofenac sodium.[13,15,16] Multiple organ involvement, brain stem involvement, low GCS score, high MR imaging score and presence of hemorrhage, and cavities on MRI are associated with poor outcome as well.[17,18] Among these mortality risk factors, our patient had thrombocytopenia, elevated aspartate aminotransferase, hyperglycemia, hematuria, proteinuria, and consumption of diclofenac sodium.

There are no definitive guidelines for the treatment of ANEC but having a high index of suspicion according to seasonal prevalence of influenza and its neurological complications is very important. Aggressive intensive care, management of elevated ICP, using methylprednisolone, and gamma globulins within 24 h of onset can improve the outcome.[17]

4 | CONCLUSION

ANEC is an uncommonly complication of influenza infection. CT scan or MR images can help in diagnosis. We describe a case of ANEC from influenza infection, which unfortunately expired in spite of using methylprednisolone, IVIG, and antivirals. We found some risk factors for death that have prognostic value.

AUTHOR CONTRIBUTIONS

Nahid Khosroshahi: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – original draft; writing – review and editing. **Darya Rezaee:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; project administration; resources; software; supervision; validation; visualization; writing – original draft; writing – review and editing. **Farnoosh Emami:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – original draft; writing – review and editing. **Kambiz Eftekhari:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – original draft; writing – review and editing.

FUNDING INFORMATION

No external funding was secured for this study.

CONFLICT OF INTEREST STATEMENT

The authors had no conflict of interest.

DATA AVAILABILITY STATEMENT

The dataset presented in the study is available on request from the corresponding author during submission or after publication. The data are not publicly available due to ethics.

ETHICS STATEMENT

The written informed consent was taken from child parents to publish his case in the journal.

CONSENT STATEMENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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How to cite this article: Khosroshahi N, Rezaei D, Emami F, Eftekhari K. Risk factors for mortality in fulminant acute necrotizing encephalopathy following influenza A in an adolescent boy. *Clin Case Rep*. 2023;11:e7253. doi:10.1002/ccr3.7253