

CASE REPORT

Acute Necrotizing Encephalopathy of Childhood: A Severe Case with Fatal Outcome

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ABSTRACT

Acute necrotizing encephalopathy of childhood (ANEC) is a rare condition which is important for clinicians to recognize as it has a high mortality rate and can result in significant neurological morbidities. It presents as acute encephalopathy with radiological findings of symmetrical brain lesions in bilateral thalami, putamen, brain stem tegmentum, internal capsule, periventricular white matter and cerebellar medulla. Intravenous methylprednisolone is the mainstay of treatment. Immunoglobulin therapy and therapeutic hypothermia may be used as adjunctive therapy in cases with severe clinical and neuroradiological presentation. We present a case of severe ANEC and discuss the clinical manifestations, neuroimaging and management options.

Keywords: Acute encephalopathy, Acute necrotizing encephalopathy of childhood, Methylprednisolone

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INTRODUCTION

Acute necrotizing encephalopathy of childhood (ANEC) is a rare neurological disease that predominantly affects children of Oriental origin, with the peak incidence occurring between 6 to 18 months of age (1). This clinical entity was first described by Mizuguchi et al. in previously healthy Japanese children with acute encephalopathy, whom were found to have symmetrical multifocal brain lesions (1). Children with ANEC have devastating neurological sequelae, with mortality rate approaching 30% (1). Unfortunately, there is no specific therapy for this disease, but the prognosis has improved since 1990s with better recognition of this clinical entity (1). Early corticosteroids therapy has been found to improve the neurological and survival outcome in children with ANEC where brain stem lesions are not present (2). We present a severe case of ANEC who was treated early with intravenous methylprednisolone, but yet still succumbed to her illness.

CASE REPORT

A previously healthy 2-year-old girl presented to the emergency ward with one-day history of fever, diarrhea and vomiting. She was less active and more sleepy than usual but still able to respond to her mother when

being called. On the day of presentation, she had 4 episodes of seizures occurring within the duration of 1-hour. Each episode lasted for 5-10min with altered consciousness in between each seizure episode. The seizures were aborted by suppository diazepam followed by intravenous loading dose of phenytoin. At presentation, she was tachycardic with pulse rate of 150/min, hypotensive with the blood pressure of 77/38 mmHg and temperature was 37.7°C. She had a Glasgow Coma Scale (GCS) of 8/15 and her pupils were 2mm and reactive bilaterally. Both upper limbs and lower limbs were hypertonic with brisk reflexes. She had up going plantar reflexes. There was no neck stiffness. Kernig's and Brudzinski's signs were negative. Her GCS declined to 6/15 twelve hours following the last seizure and she was intubated for cerebral protection.

Her first full blood count was normal (Hb 13.3g/dL WCC $9.9 \times 10^9/L$ and platelet $291 \times 10^9/L$). However, at day 6 of admission, investigations revealed leucopenia (WCC $3.6 \times 10^9/L$) and mild thrombocytopenia (platelet $121 \times 10^9/L$). Coagulation profile was normal (PT 15.4s, INR 1.2 and APTT 32.9s). Urea was raised 8 mmol/L (normal 2.1-6.5 mmol/L) but serum creatinine was normal (55 mmol/L). Serum ammonia was 18.2 $\mu\text{mol/L}$ (0-80 $\mu\text{mol/L}$), and serum glucose was 10.5 mmol/L. Her liver function was normal (bilirubin 2.7 $\mu\text{mol/L}$, ALT 46 U/L, ALP 178 U/L). A Computed Tomography of the brain performed on the day of presentation showed bilateral symmetrical thalamic hypodensities. The symmetrical changes were further demonstrated in the caudate, putamen, thalami, brain stem and cerebellum on a

MRI brain performed on the same day (Fig 1A and 1B, 1C). The gradient echo (GRE) axial image also revealed haemorrhagic foci in both thalami and periventricular white matter. (Fig 1D). A diagnosis of ANEC was made and IV methylprednisolone 30mg/kg/day in 3 divided doses was commenced at 17 hours after initial presentation and continued for 5 days. She was also treated with intravenous phenytoin, ceftriaxone and acyclovir. She did not have a recurrence of seizure after admission.

On the second day of presentation, her condition continued to deteriorate. She became hypotensive and required inotropic support. Both her pupils became fixed and dilated, 7 mm bilaterally. On the 8th day of ICU admission, she became polyuric due to central diabetes insipidus and unfortunately succumbed to death. Blood culture taken on admission had no growth. Post mortem cerebrospinal fluid (CSF) studies revealed no cells, raised protein 757 mg/L (normal range 50-400 mg/L) and a normal glucose of 4.66 mmol/L. CSF PCR for influenza A and influenza B virus, herpes simplex virus, coxsackie virus A, B and 16, enterovirus 71 and 70, echovirus and poliovirus were negative. Gram stain and CSF culture did not reveal any organism. Postmortem histopathological examination of the brain was not done.

DISCUSSION

The diagnostic criteria for ANEC include acute encephalopathy in previously well children with symmetrical multifocal brain lesions within both thalami, putamen, internal capsule, brain stem tegmentum, periventricular white matter and cerebellar medulla with the exclusion of other neurological conditions (1). In patients with ANEC, altered conscious state is typically preceded by coryza symptoms but vomiting and diarrhoea are also recognized features, as seen in our patient (1). The commonest viruses identified in these individuals are influenza A or B, human herpes virus 6 and 7 (HHV-6 and HHV-7), suggesting an immune mediated inflammatory response to the viral illness as a possible explanation for the pathogenesis of ANEC (1). The breakdown of blood-brain barrier due to vasoactive substances and cytokines is evident by the histopathologic findings of edema and necrosis at the regions of the multifocal brain lesions (1).

The laboratory abnormalities associated with ANEC are thrombocytopenia, hematologic changes of disseminated intravascular coagulation and elevated serum aspartate transaminase and alanine transaminase without hyperammonaemia and hypoglycemia (1).

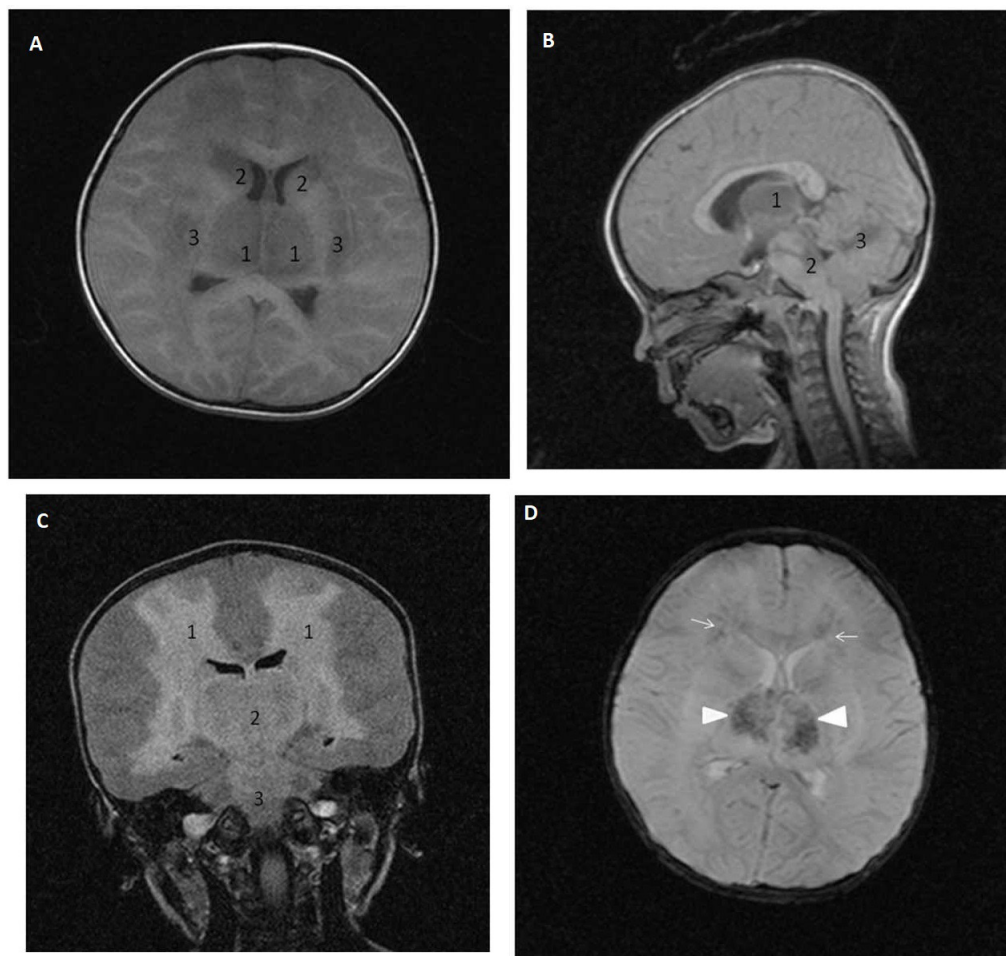


Figure 1: (A) T1W Axial image showing bilateral low intensity changes within the thalami (1), head of the caudate nuclei (2) and putamina (3). (B) T1W Sagittal image showing low signal intensities within the thalamus (1), brainstem (2) and cerebellum (3). (C) FLAIR coronal image showing extensive bilateral symmetrical high intensity changes within the white matter extending to the grey white matter junction (1), both thalami (2) and the brain stem (3). (D) GRE axial image showing blooming artifact within the thalami (arrow heads) and the periventricular white matter (white arrows) suggesting haemorrhagic foci.

Creatinine kinase and serum urea can sometimes be raised if there is muscle or kidney involvement. CSF studies usually reveal no pleocytosis, but an increase in protein is commonly observed due to plasma protein extravasation and disintegrating neural tissue protein at the sites of periventricular necrotic brain lesions (1). The symmetrical distribution and characteristic affected sites from MRI as well as typical clinical presentation in our patient fitted the diagnosis of ANEC. Viral encephalitis and acute disseminated encephalomyelitis (ADEM) are unlikely as the brain lesions in these two conditions are asymmetrical and pleocytosis would be expected in the CSF studies. Reyes syndrome is also unlikely in the absence of liver dysfunction, hyperammonaemia and hypoglycemia.

Our patient showed rapid deterioration in conscious level with coma ensuing within 24 hours despite intravenous methylprednisolone being started at 17 hours of admission. The poor prognostic factors associated with her were young age of less than 4 years, brain stem involvement, raised CSF protein and extensive cerebral and cerebellar involvement with thalami haemorrhage. A study conducted by Wong AM et al. showed that clinical outcome of the patient corresponded with the MR imaging score, which is a composite score derived from the presence of haemorrhage or cavitation and extent of brain stem and white matter (cerebral and cerebellar) involvement (2).

There is no definitive recommended therapy for ANEC. Intensive care, symptomatic treatment, therapeutic hypothermia, antiviral therapy and immunomodulator therapy have been used in ANEC with steroids being the mainstay of treatment. Steroids decreases vascular permeability by suppressing the release of cytokines in the acute inflammatory stage. Our patient however showed poor response to steroids as her neurological status continued to deteriorate rapidly even though she was treated early with methylprednisolone. The use of IV methylprednisolone as monotherapy in our patient might not be adequate as she had extensive brain lesions including brain stem involvement. Okumura et al also reported that intravenous methylprednisolone administration within 24 hours of presentation only improved the outcome in cases where brain stem lesions were not present (3). Patients with severe clinical and neuroradiological presentation might benefit from other treatment modalities in addition to steroids therapy. Early combined therapy of both steroid and immunoglobulins had been found to be useful in avoiding a fatal outcome in few reported cases of severe ANEC although these patients developed significant neurodevelopmental

morbidities later on (4). Early therapeutic hypothermia used in combination with steroids has also been shown to have favourable outcome in severe ANEC and is another treatment option to be considered (5). Therapeutic hypothermia has been postulated to reduce pro-inflammatory cytokines and hence reduce brain injury. The use of therapeutic hypothermia combined with steroid therapy has shown promising results in Japan where ANEC cases are more prevalent.

CONCLUSION

Early diagnosis of ANEC is not too difficult with better recognition of this neurological entity and characteristic radiological findings demonstrable in the early stage of the disease. Patients with extensive white matter lesions with haemorrhage and brain stem involvement have poor prognosis even though they are treated early with intravenous methylprednisolone. The MRI changes of a patient with ANEC should be used to prognosticate the disease progression. Other adjunct treatment modalities besides corticosteroids should be considered in the case of severe ANEC. Due to the rarity of this condition, firm evidence on treatment guidelines are unfortunately still lacking. Randomised controlled trials on different treatment modalities are needed to provide clear evidence to guide clinicians on the most appropriate treatment regimen for this condition.

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