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Case Series

Paediatrics Section

Clinical, Laboratory, and Radiological Findings in Acute Necrotising Encephalopathy of Childhood: A Case Series

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ABSTRACT

Acute Necrotising Encephalopathy of Childhood (ANEC) is a fatal disease diagnosed on basis of clinical and typical Magnetic Resonance Imaging (MRI) findings. The prognosis of this encephalopathy is generally poor, with fewer than 10% of cases recovering completely. Patients with a favourable outcome had reversible neuroimaging findings. Long-term sequelae commonly include neurologic deficits such as spasticity, epilepsy, and involuntary movements. In this case series, five cases of ANEC were reported. The children included in this series ranged in age from nine months to 16 years. All the children were female, and their presenting symptoms included seizures (n=5), altered sensorium (n=5), features of raised intracranial pressure (n=5), and posturing (n=1). Neuroimaging revealed characteristic lesions in the thalamus with varied involvement of other parts of the brain in all cases (n=5). Cerebrospinal Fluid (CSF) analysis was normal in the majority of children. Four out of five cases survived and responded to early steroids, intravenous immunoglobulin, physiotherapy, and rehabilitation. One child had complete recovery, with three children experiencing disabilities and one child succumbing to the disease.

Keywords: Intravenous immunoglobulin, Spasticity, Thalamic lesions

INTRODUCTION

ANEC is a distinctive form of encephalopathy characterised by bilateral symmetrical lesions in the thalamus and brainstem of infants and children. It has been described as a novel disease with characteristic clinico-pathological and neuroimaging findings [1,2]. The hallmark of ANEC is the presence of symmetric and multifocal thalamic lesions, which may also involve the brainstem, cerebral periventricular white matter, and cerebellum, and can be visualised through neuroimaging [3].

The aetiopathogenesis of ANEC is still not well understood. Clinically, radiologically, and pathologically, it is important to differentiate ANEC from other diseases such as Sandhoff's disease, Leigh syndrome, Wernicke encephalopathy, Reye's syndrome, thalamic tumours, thalamic haemorrhage, and vascular occlusion. The diagnosis of acute necrotising encephalopathy involves excluding these other disease entities [4]. ANEC primarily affects infants and young children, manifesting as an acute encephalopathy following specific viral infections such as human herpesvirus 6, varicella-zoster, influenza A and B, and rarely, even mycoplasma infection [5-7]. The condition was first described by Mizuguchi M et al., in 1997, who also provided the diagnostic criteria for ANEC [1]. Diagnosis of ANEC is mainly based on clinical and typical MRI findings [8].

The prognosis of this condition was very poor in the late 1980s. However, with evolving treatment modalities, the prognosis of ANEC has improved over time. The clinical course of ANEC is distinct and fulminant, ranging from a milder form with complete recovery to a severe form with disability and high mortality [8,9].

CASE SERIES

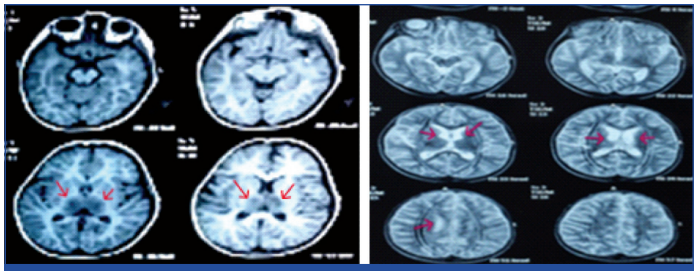
This is a retrospective analysis of five children with ANEC who were admitted to the Department of Paediatrics, ESIMC and PGIMSR, Rajaji Nagar, Bangalore, between August 2019 and September 2022. ANEC was suspected based on clinical and radiological features, and the diagnosis was made using the diagnostic criteria proposed by Mizuguchi M et al., [1]. Routine blood investigations, Cerebrospinal Fluid (CSF) analysis, and MRI brain scans were performed for all patients upon admission. All patients were managed with a standard protocol and received supportive treatment. They were administered steroid/immunoglobulin therapy and neuroprotective measures. After stabilisation, these children were started on early physiotherapy and rehabilitation.

Case 1

A 14-year-old female child with a normal birth and developmental history and no significant past illness presented with a history of fever, loose stools, and vomiting for three days. Following this, the child developed convulsions and altered sensorium. Upon admission, GCS of 12/15 and exhibited features of raised intracranial tension such as severe headache and irritability. The child was started on antiepileptic medications and received neuroprotective measures including hypertonic saline, head end elevation, euglycaemia, and euthermia. Investigations revealed elevated liver transaminases-SGOT/SGPT: 111/72.5, and serum Japanese Encephalitis (JE) IgM antibodies tested positive. CSF analysis was normal, and MRI brain showed lesions typically affecting the bilateral thalamus, hippocampus, and midbrain [Table/Fig-1]. Although JE antibodies were positive, based on the clinical and radiological findings of acute encephalopathy following a nonspecific febrile illness, a diagnosis of ANEC was made. The child recovered completely without any neurological complications.

Case 2

A five-year-old female child presented with a chief complaint of fever, cold, and cough lasting for two days. Subsequently, the child experienced convulsions (status epilepticus) and altered sensorium, displaying symptoms of raised intracranial pressure such as headaches, seizures, and depressed sensorium. Upon admission, the child had a Glasgow Coma Scale (GCS) of 9/15. Antiepileptic medications and neuroprotective measures, including hypertonic saline, head end elevation, euglycaemia, and euthermia, were initiated. An MRI of the brain revealed bilateral symmetrical thalamic involvement [Table/Fig-2]. CSF analysis yielded normal results, and the CSF viral panel was negative. The clinical and radiological

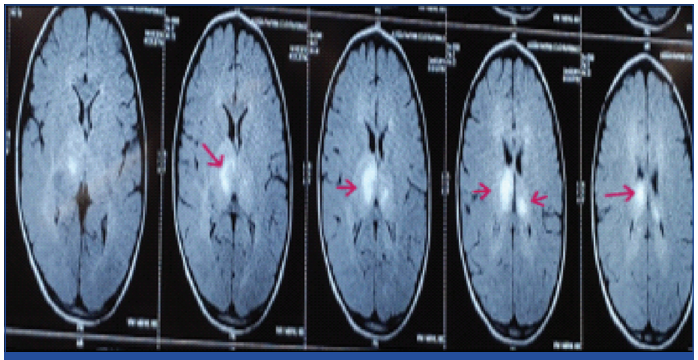


[Table/Fig-1]: (Case 1)- Bilateral thalamic, hippocampus, midbrain, cerebellar hemisphere and vermis lesions. **[Table/Fig-2]:** (Case 2)- Bilateral symmetrical hypointensities in thalamic region. (Images from left to right)

findings were similar to ANEC. Hence, child was treated as ANEC with intravenous immunoglobulin, antiepileptic medications, and early physiotherapy. Consequently, the child developed neurological sequelae in the form of spasticity and seizures. The child is currently receiving antiepileptic medications and undergoing physiotherapy.

Case 3

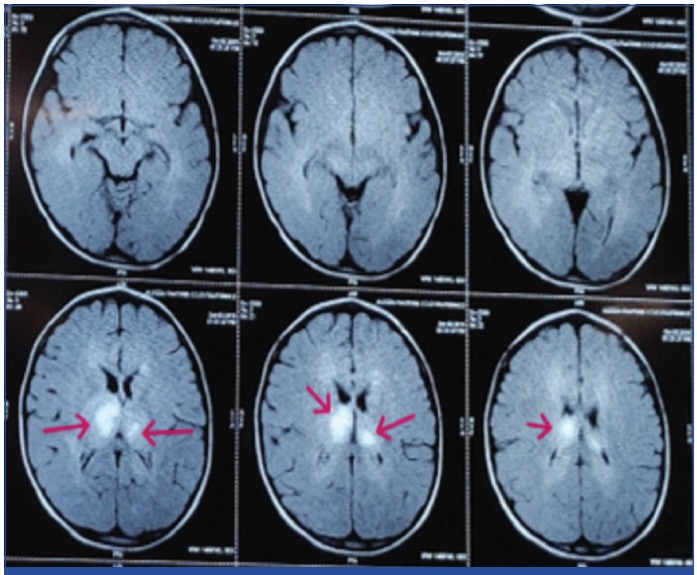
A three-year-old female child with no significant past illnesses presented with a history of fever and cold lasting three days. The child experienced convulsions and altered sensorium, along with symptoms of raised intracranial pressure such as seizures and irritability upon admission. The child's GCS score was 7 out of 15, and mechanical ventilation was initiated. Antiepileptic medications, as well as neuroprotective measures like hypertonic saline, head end elevation, euglycaemia, and euthermia, were administered. Investigations revealed elevated liver transaminases (SGOT/SGPT: 146/140), CSF analysis showed increased protein levels (89 mg/dL). CSF viral panel results were negative. MRI brain scans revealed bilateral symmetrical thalamic and temporal lobe involvement, as shown in [Table/Fig-3]. Based on the clinical and radiological findings, a diagnosis of ANEC was made. The child received treatment with steroids, intravenous immunoglobulin, antiepileptic medications, and early physiotherapy. However, the child developed spasticity and epilepsy and currently receives regular physiotherapy and antiepileptic medications.



[Table/Fig-3]: (Case 3)- B/L Thalamic hyperintensity and in left temporal lobe and pons.

Case 4

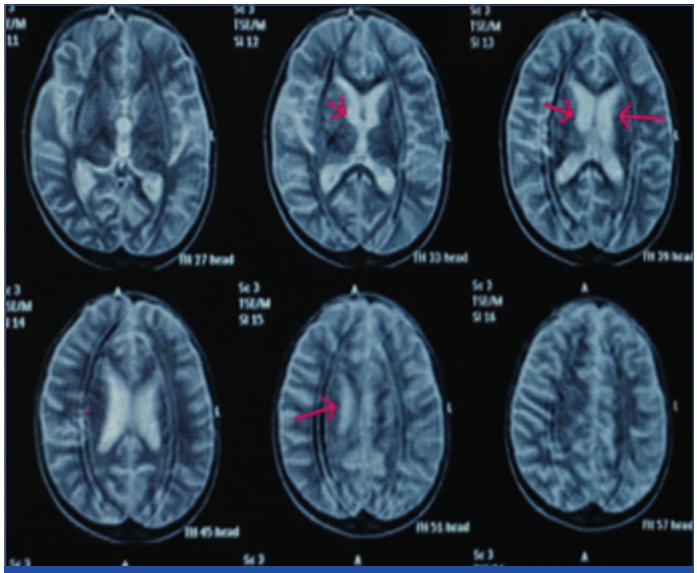
Nine-month-old female child with a normal birth and developmental history, and no significant past illness, presented with a four-day history of fever, cold, and coryza. Following this, the child experienced convulsions (status epilepticus), posturing, and altered sensorium, with features of raised intracranial pressure such as seizures, posturing, and depressed sensorium observed upon admission. The child had a GCS score of 9/15 and required mechanical ventilation due to status epilepticus. Antiepileptic medications and neuroprotective measures including hypertonic saline, head end elevation, euglycaemia, and euthermia were initiated. Investigations revealed elevated liver transaminases (SGOT/SGPT: 156/112). CSF analysis showed elevated protein levels (79 mg/dL), while the CSF viral panel was negative. MRI brain showed bilateral symmetrical thalamic involvement and occipital lobe necrosis. The clinical and radiological findings were suggestive of ANEC [Table/Fig-4]. Therefore, the child was diagnosed and treated as ANEC. Steroids, intravenous immunoglobulin, antiepileptic medications, and early physiotherapy were administered. The child subsequently developed quadriplegia, epilepsy with cortical visual loss, and is currently receiving regular physiotherapy and antiepileptic medications.



[Table/Fig-4]: (Case 4) B/L thalamic hyperintensities and occipital lobe, areas of necrosis +.

Case 5

Three-year-old female child presented with a history of fever and loose stools for a duration of two days. Following this, she developed convulsions and altered sensorium, exhibiting features of raised intracranial pressure such as seizures and depressed sensorium upon admission, with a GCS of 10/15. The child was mechanically ventilated and started on anti-epileptic medications and neuroprotective treatment. Liver transaminases SGOT/SGPT were elevated at 564/320, CSF analysis was normal, and dengue serology (NS1 antigen) was positive. MRI brain revealed bilateral symmetrical thalamic and pons involvement [Table/Fig-5]. Although dengue serology (NS1 antigen) was positive, the clinical and radiological findings were similar to ANEC. Hence, a diagnosis of ANEC was made, and the child received both steroids and immunoglobulins. Unfortunately, the child developed multiorgan dysfunction and passed away. The findings of all the cases have been summarised in [Table/Fig-6,7].



[Table/Fig-5]: (Case 5)- showed abnormal, symmetrical signals in the thalamus. Necrotic area also identified in the right thalamus.

Case No.	Age/Sex	Presenting illness	CNS presentation	Features of raised ICP	GCS at admission	GCS at discharge	SGOT/ SGPT	CSF profile	Other investigations	Outcome
1	14 years/ female	Acute gastroenteritis 3 days duration	Altered sensorium, seizures	+	12	15	111/72.5	Normal	JE IgM antibodies-positive	Recovered completely
2	5 years/ female	URTI 2 days duration	Status epilepticus, alteredsensoriunm	+	9	13	30/8	Normal	CSF viral panal-neg	Spasticity
3	3 years/ female	URTI 3 days duration	Seizures, altered sensorium	+	7	13	146/140	CSF Protein-89 mg/dL	CSF viral panel-neg	Spasticity, epilepsy
4	9 month/ female	URTI 4 days	Status epilepticus, posturing, altered sensorium	+	9	14	156/112	CSF Protein-79 mg/dL	CSF viral panel-neg	Spastic quadriparesis with cortical visual loss, epilepsy
5	3 years/ female	Acute gastroenteritis 2 days duration	Seizures, altered sensorium	+	10	14	564/320	Normal	Dengue serology-NS1 positive	Expired

[Table/Fig-6]: Clinical profile and laboratory findings.
URTI: Upper respiratory tract infection

Case No.	Location of lesion	Haemorrhage/Necrosis	Details
1	Thalamus, midbrain, hippocampus	+	Bilateral thalamic, hippocampus, midbrain, cerebellar hemisphere and vermis showing restricted diffusion with areas of blooming suggestive of haemorrhagic encephalitis
2	Thalamus	-	Bilateral symmetrical hypointensities in thalamic region
3	Thalamus, pons, temporal lobe	-	B/L Thalamic hyperintensity and in left temporal lobe and pons
4	Thalamus, occipital lobe	+	B/L thalamic hyperintensities and occipital lobe, areas of necrosis +
5	Thalamus, pons	+	showed abnormal, symmetrical signals in the thalamus. Necrotic areas were also identified in the right thalamus and both sides of the pons showing peripheral enhancement and diffusion restriction

[Table/Fig-7]: MRI findings.

DISCUSSION

ANEC is a fatal neurological condition, and its diagnosis is based on clinical features and typical MRI findings. In India, a significant number of ANEC cases remain undiagnosed and unreported, leading to a lack of concise knowledge and data on ANEC in Indian children. In this series, the authors present cases of ANEC, focusing on clinical, laboratory, and radiological features.

Children with ANEC experience rapid and progressive neurologic deterioration following a preceding non-specific febrile illness. All cases in this series meet the diagnostic criteria for ANEC proposed by Mizuguchi M et al., [8], and none of them exhibited atypical presentations. One child had a milder form of ANEC and achieved complete recovery. All children were previously healthy but developed febrile illness, seizures, and neurologic deficits.

The prognosis of ANEC is generally poor, although recent improvements have been observed. Severe neurological deficits like decorticate or decerebrate posturing, as well as long tract signs, may appear [9,10]. In this case series, four children developed neurological sequelae in the form of spasticity, and one child experienced cortical visual loss. The mortality rate of ANEC is considered to be as high as 30% [10].

In this study, four out of five cases survived, and out of the four cases that survived, one case (25%) showed complete recovery. One out of five children died (mortality rate of 20%) due to multiorgan dysfunction. The remaining three children who survived were left with severe sequelae, with one experiencing cortical blindness [Table/Fig-6].

Kim JH et al., reviewed 14 Korean cases over 10 years and suggested no mortality. They reported that 57% of patients completely recovered or were left with mild deficits [11]. However, the present study had a mortality rate of 20% (n=1). The authors observed poor outcomes, although several other reported cases in the literature showed good outcomes [2,12-15].

ANEC is known to be a neurological complication of certain viral infections. A viral panel with CSF for neurotropic viruses was conducted in three cases, but the results were negative. Serological tests showed that one case had NS1 antigen positive for dengue virus and another case had JE virus IgM Antibody positive. Infants with high serum transaminase levels, high levels of proteins in CSF, and lesions in other parts of the brain had poorer outcomes in terms of disabilities, as described in the literature as poor prognostic factors in ANEC [2,16-19].

Radiological findings [Table/Fig-7] were in accordance with the diagnostic criteria of ANEC. The present study showed that incomplete neurological recovery with disability was observed in children with MRI brain findings, such as extensive lesions, presence of haemorrhage, and necrosis. Vanaki RN et al., in a retrospective analysis of 10 cases of ANEC, also reported similar results [20].

The patients received supportive care, including physiotherapy, speech therapy, and rehabilitation. One case had an excellent outcome without any neurological deficits, while the other three cases had neurological deficits, and one child succumbed.

CONCLUSION(S)

ANEC is a rare and rapidly progressing disease with a poor outcome. Early diagnosis and management may lead to better outcomes. This case series emphasises the significance of MRI brain in the early diagnosis and, hence, the early initiation of immunomodulators (steroids, intravenous immunoglobulin).

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