

## Original Research Article

# Acute necrotizing encephalopathy of childhood: an under-recognized and diverse clinico-radiological syndrome

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## ABSTRACT

**Background:** With advances in neuroimaging, acute necrotizing encephalopathy of childhood (ANEC) is being recognized as an acute encephalopathy with a characteristic rapidly deteriorating neurological course with poor neuro-developmental outcomes with high mortality and morbidity rates. Indian data of ANEC is primitive and hence this study was planned. The objective of the study was to evaluate the clinical, radiological characteristics and its outcomes in children with ANEC.

**Methods:** Retrospective review of 10 infants and children with ANEC at Department of Paediatrics, S.N. Medical College and HSK Hospital, Bagalkot from January 2013 to December 2019. ANEC was suspected based on clinical and radiological characteristics and diagnosis was made based on diagnostic criteria proposed by Mizuguchi et al. Clinical and radiological (Magnetic resonance imaging (MRI) brain characteristics) findings and response to early pulse dose steroid therapy and supportive treatment were assessed in all cases. All cases were followed for evaluation of neurodevelopmental outcome and response to physiotherapy was noted in all the cases.

**Results:** Total 10 cases were analysed (age ranged from 6 months to 11 years). Sex distribution male to female was 3:7. All cases had precedent viral illnesses and had fever, coryza, diarrhoea. The initial neurological symptoms included seizures and status epilepticus (n=7), altered sensorium (n=3), focal neurological signs, gait disturbances (n=2) and diplopia (n=1). MRI brain revealed characteristic thalamus involvement with varied involvement of midbrain, pons, medulla (n=10). Other findings were cavitation (n=5), haemorrhage (n=4), minimal residual lesions (n=4), cerebral atrophy (n=1), normal brain study (n=5) on follow-up. 9 out of 10 cases survived, responded to early physiotherapy and rehabilitation. 6 children had complete recovery with minimal disability in 3 cases.

**Conclusions:** ANEC is a clinico-radiological syndrome. Early detection and appropriate treatment improve outcome in ANEC.

**Keywords:** ANEC, Encephalitis, Rankin scale, Rehabilitation

## INTRODUCTION

Ever since first description by Mizuguchi et al, acute necrotizing encephalopathy of childhood (ANEC) is being recognized as an acute encephalopathy with a characteristic rapidly deteriorating neurological course with poor neurodevelopmental outcomes with high

mortality and morbidity rates.<sup>1-3</sup> ANEC has occasionally been reported in both Asian and Western countries and is being recognized as reason for longer stay in Intensive care unit (ICU) and hospitalization. The etiology and pathogenesis of this disease remain unknown. Although Influenza A virus, mycoplasma, herpes simplex virus, and human herpes virus-6 have been reported as common

causative agents, it is now believed that this disease is most likely immune-mediated or metabolic.<sup>4,5</sup>

Patients with ANEC have neither specified symptoms nor typical neurological signs. In addition to prodromal symptoms due to different viral infections, which include fever, signs of upper respiratory tract infections and gastroenteritis, and erythema, patients with ANEC often have signs of Systemic inflammatory response syndrome, shock, multiple organ failure, and disseminated intravascular coagulation.<sup>6</sup> With the development of ANEC, brain dysfunctions may present as seizures, disturbance of consciousness and focal neurological deficits.<sup>1,2,3,6</sup> Most of the manifestations of ANEC are non-specific and lead to failure of diagnosis of ANEC. Apart from clinical features, laboratory and radiological investigations will be useful in diagnosis.

The clinical course of ANEC is fulminant and diverse, from a mild form with completely recovery or mild sequelae to a severe form with a high mortality.<sup>7,8</sup> Children of ANEC go through three phases during the clinical course including prodromal stage, period of acute encephalopathy, and recovery stage. In the prodromal stage, the common symptoms include cough, vomiting, diarrhea, skin erythema mainly due to various viral infections. Soon after, the dysfunction of the brain gradually appeared during the acute encephalopathy stage, for example, disturbance of consciousness, seizures, and focal deficits. If survived, patients of ANEC would go through the third phase, so-called recovery stage and most patients left with different neurological sequelae while a few could recover completely.<sup>5-8</sup>

Diagnosis is made mainly by the characteristic findings of computed tomography (CT) or magnetic resonance imaging (MRI), which typically shows symmetric lesions in the thalami, with variable involvement of the white matter, basal ganglia, brainstem, and cerebellum.<sup>1-3</sup> With the widespread use of MRI, this unique condition is becoming more familiar. However, the etiology, pathogenesis, guidelines of treatments, or prognostic factors still remain unclear.

Indian data on ANEC is still primitive and lacking. In this report, we have described 10 children with ANEC to elucidate, the clinical/neuroradiological characteristics, the response to medical treatment and the response to physiotherapy.

## METHODS

This is retrospective analysis of 10 infant and children with ANEC admitted at Department of Pediatrics, S.N. Medical College and HSK hospital, Bagalkot from January 2013 to December 2019. ANEC was suspected based on clinical and radiological characteristics and diagnosis was made based on diagnostic criteria proposed by Mizuguchi et al (Table 1).<sup>3</sup> Routine blood tests and cerebrospinal fluid (CSF) analysis and brain MRIs were taken in all patients

at the time of initial presentation. MRI imaging characteristics like number of lesions, symmetry, hemorrhage, locations were noted. All patients were managed with standard protocol and other supportive treatment. All subjects received early steroid therapy (intravenous methyl prednisolone) within 24 hours after the diagnosis. After stabilization, these children were initiated on early physiotherapy and rehabilitation. All cases were followed for evaluation of neurodevelopmental outcome and response to physiotherapy was noted in all the cases. Follow up MRI brain scan was done in all surviving cases between 9-12 months after the discharge to assess radiological outcome.

## RESULTS

A total of ten children were enrolled in the study. All cases had normal developmental milestones without any significant past medical and family history. No patients were exposed to any drugs or chemical substances known to cause toxic encephalopathies. The age ranged from 6 months to 11 years (7 female, 3 male). Clinical features, laboratory and radiological findings and outcome are summarized in table 2.



**Figure 1: Gradient axial image shows blooming (hemorrhage due to necrosis).**

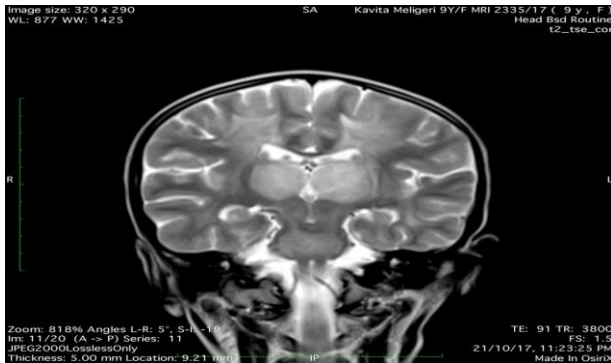


**Figure 2: FLAIR axial image showing bilateral swollen edematous thalami.**

### Clinical features of the subjects

All cases had precedent viral illnesses and had fever, coryza, diarrhea. The initial neurological symptoms

included seizures and status epilepticus (n=7), altered sensorium (n=3), focal neurological signs, gait disturbances (n=2) and diplopia (n=1).



**Figure 3: T2W coronal image showing hyperintense edema involving bilateral thalami and brainstem. Edematous changes noted involving bilateral corona radiata and centrum semiovale.**

**Table 1: Diagnostic criteria of ANEC proposed by Mizuguchi.<sup>2,3</sup>**

S. no.	Diagnostic criteria
1	Acute encephalopathy following viral disease, with seizures and deterioration of consciousness.
2	Absence of CSF pleocytosis, CSF protein is commonly increased.
3	Neuroimaging findings of symmetric, multifocal brain lesions involving the bilateral thalami, upper brain stem tegmentum, periventricular white matter, internal capsule, putamen and cerebellum.
4	Elevation of serum aminotransferase level to a variable degree. No increase in blood ammonia.
5	Exclusion of any resembling disease.
5A	Clinical differential diagnosis; toxic shock syndrome, haemolytic uremic syndrome, Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and heat stroke.
5B	Radiological (or pathological) differential diagnosis; Leigh encephalopathy, glutaric acidemia, methyl malonic aciduria, infantile bilateral strial necrosis, Wernicke encephalopathy, carbon monoxide poisoning, acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis, arterial or venous infarct, severe hypoxic or traumatic injury.

#### Laboratory findings

All cases had mildly elevated hepatic transaminases (less than 3 times the normal level) may indicate hepatic dysfunction, but their levels varied highly from case to case. In addition, serum ammonia levels were normal in all cases. CSF analysis was within normal limits in 7 cases.

Isolated mildly elevated protein level was seen in 3 cases. ABG lactate and CSF lactate was also normal in all cases. Serological test of one showed positive immunoglobulin G (IgG) for dengue virus, viral panel for neurotropic virus was done in only two cases, which was negative.

#### Radiological findings

Brain MRI revealed increased signal intensity on T2-weighted imaging in the bilateral thalami and brain stem in almost all patients. Gradient blooming hemorrhagic areas noted in most of patients. The findings in all cases were consistent with a unique pattern of ANEC (Figures 1-3). The radiological features at the time of diagnosis and follow-up are listed in Table 3.

#### Treatment and outcome

All cases were admitted at Pediatric intensive care unit (PICU) and received treatment as per standard ICU protocol. Children with seizures and altered sensorium received antiepileptic therapy and raised ICP management respectively. Intravenous methylprednisolone pulse therapy was started in all patients (30 mg/kg/day of methyl prednisolone for 5 days) within 24 hours of diagnosis of ANEC. One child (case number 9) died 6 days after admission due to raised ICP with septicemia and multiorgan dysfunction syndrome. Rest of the cases stabilized and were started on early rehabilitation. With regular physiotherapy 6 cases showed excellent outcomes without any neurological deficits at 6 months after the illness. The other three patients showed a relatively good to fair outcome.

#### DISCUSSION

ANEC was proposed as a novel disease entity by Mizuguchi et al extensively affecting infants and young children worldwide including sporadic cases in Indian scenario.<sup>2,3</sup> Most of the patients in India remain unreported and there is lack of comprehensive data in Indian children. However, we were able to recognize and manage 10 cases of ANEC over period of 5 years at our institution. Here with we present data of cases of ANEC with respect to clinical, radiological features, response to medical treatment, and role of physiotherapy in neurorehabilitation.

Patients with ANEC manifest fulminating neurologic deterioration with preceding non-specific febrile illness and frequently undergo intractable convulsions. In our study, all cases met diagnostic criteria for ANEC (Table 1) proposed by Mizuguchi and had varied presentation at the time of admission.<sup>2,3</sup> Cases were worked up and the diagnosis of ANEC was reached. Despite proposed the diagnostic criteria of ANEC, atypical and milder cases have been reported.<sup>9</sup> None of our cases had atypical presentations. All our cases were previously healthy, in whom diseases initiated with fever and other viral like prodromes, seizures and neurologic disturbances.

**Table 2: Summary of clinical, laboratory findings and outcome.<sup>21</sup>**

Age/sex	Presenting illness	CNS presentation	SGOT /ALP (IU/L)	CSF profile	GCS on admission	GCS on discharge	Modified ranking scale at discharge	Modified ranking scale at 3 months follow-up	Modified ranking scale at 9 months Follow-up	Outcome
<b>5 year 6 months, F</b>	Non-specific febrile illness	Altered sensorium	78/46	Normal	6	10	4	3	1	Fully recovered
<b>6 months, F</b>	URTI	Seizures, irritability	85/54	Normal	8	12	5	3	2	Spasticity
<b>2 years, F</b>	Non-specific Febrile illness	Status Epilepticus	54/42	CSF protein 62 mg/dl	6	11	5	3	2	Spasticity and speech disorder
<b>5 year 10 months, M</b>	URTI	Status epilepticus	124/78	Normal	5	13	5	3	1	Fully recovered
<b>4 years, F</b>	Non-specific febrile illness	diplopia, gait disturbance, altered sensorium	102/85	CSF protein 58 mg/dl	6	12	5	3	2	Fully recovered
<b>2 years, 10 month, F</b>	URTI and AGE	Gait disturbance, altered sensorium	75/65	Normal	6	13	5	5	5	Spastic quadriparesis, speech disorder
<b>3 years 6 month, M</b>	AGE	Status epilepticus	93/45	Normal	7	13	5	2	1	Fully recovered
<b>11 months, F</b>	AGE	Altered sensorium	118/98	Normal	7	14	4	2	1	Fully recovered
<b>1 year 4 months, M</b>	URTI and AGE	Status epilepticus	210/146	CSF Protein 142 mg/dl	6	-	-	-	-	Expired
<b>9 years, F</b>	Non-Specific febrile illness	Status epilepticus	46/120	Normal	7	14	5	2	1	Fully recovered

**Table 3: MRI brain findings at the time of diagnosis and follow-up.**

Case no	Location of lesion	Haemorrhage	Cavitation	Residual lesions on follow-up scan
1	Thalamus, thalamotegmentum	-	-	No residual lesions
2	Thalamus	+	+	Small hypodensities in thalamus
3	Basal ganglion, thalamus	+	+	Small hypodensities in thalamus
4	Thalamus	-	-	No residual lesions
5	Thalamus	-	-	No residual lesions
6	Thalamus	+	+	Cerebral atrophy
7	Thalamus	-	-	No residual lesions
8	Thalamus, midbrain, pons, medulla	-	-	No residual lesions
9	Thalamus, midbrain, pons, medulla	+	+	N/A (Expired)
10	Thalamus, midbrain, pons, medulla	-	+	Small hypodensities in thalamus

The outcome of ANEC is generally grave, although the prognosis has improved recently. Serious neurological signs such as decorticate, decerebrate posturing or long tract signs may appear. Its mortality is considered to reach as high as 30%.<sup>1,2,6-9</sup> In our study, 9 out of 10 cases survived and out of 9 cases who survived, 8 cases (88.9%) showed complete recovery or left with minimal deficits. 1 out of 10 children died (mortality rate of 10%) due to raised ICP with septicemia and multiorgan dysfunction syndrome. One surviving child left with severe sequelae (table 2). Kim et al reviewed 14 Korean cases over 10 years study period and suggested no mortality. 57% patients completely recovered or left with mild deficits.<sup>10</sup> This study showed better outcome, compared to previous published data of around 65% of patients with death or were left with severe neurological sequelae. Our study suggested better outcomes similar to several other reported cases with good outcomes in literatures.<sup>11-15</sup>

Laboratory evaluations in our study were non-specific and included elevated hepatic transaminases and increased CSF protein levels (Table 2). ANEC is known to be neurological complications of viral infections and in our study evaluation for possible viral etiology was done in only 3 cases. Serological test of one showed positive IgG for dengue virus, viral panel for neurotropic virus was done in only two cases, which was negative. Patients less than 24 months age, those with high serum transaminases level, high level of proteins in CSF and those with brain stem lesions had poorer outcome in terms of disability etc. Similar factors have been described in literature as poor prognostic factors in ANEC.<sup>9,15-19</sup> Radiological findings (Table 3) were specific and consistent with the diagnostic criteria of ANEC. In our study children with MRI brain findings like extensive involvement of lesions, presence of hemorrhage and cavitation had incomplete neurological recovery and disability and poor outcome. Wong et al in a retrospective analysis of MRI brain in 12 cases of ANEC reported a significant and positive co-relation between

clinical outcome and MRI brain findings like presence of hemorrhage, cavitation and extensive location of lesions.<sup>20</sup>

Although the optimal regimen of steroid use for treatment of ANEC is still inconclusive in majority of studies. In our study, all cases received early steroid therapy (less than 24 hours of diagnosis) and had excellent outcome after the steroid therapy and other supportive therapy including physiotherapy. Okumura et al strongly suggested the efficacy of early steroid treatment for children with ANE without brainstem lesions. However, no beneficial effects were observed in those with brainstem lesions.<sup>20</sup>

The patients underwent supportive care including physiotherapy, speech therapy and supportive therapy. 6 cases showed excellent outcomes without any neurological deficits at 6 months after the illness. The other three patients showed a relatively good to fair outcome.

#### Limitations of the study

This study is a relatively small number of the patients and a retrospective design with only short term and medium-term outcome. CSF analysis for viral markers in evaluation of etiology was not done in all cases. Randomized control trials with a large number of the patients with long-term outcome are desirable.

#### CONCLUSION

Diagnosis and management of ANEC is based on clinical and radiological features. Early detection and appropriate treatment may lead to better outcome. Early steroid treatment can be considered important treatment option once the diagnosis is made.

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