# Rehabilitation outcomes in Acute Necrotizing Encephalopathy of Childhood – A Retrospective Study

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## Abstract

**Aims & Objectives:** To assess the outcome of early physiotherapy and rehabilitation in children with Acute Necrotizing Encephalopathy of Childhood (ANEC).

**Methods:** Retrospective review of 10 infants & children with ANEC at Department of Paediatrics, S.N.Medical College & 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 (MRI brain characteristics) findings and response to standard therapy, early physiotherapy and rehabilitation were assessed in all cases. All cases were followed for evaluation of neurodevelopmental outcome.

**Results:** The age ranged from 6 months to 11 years (7 female, 3 male). All cases had precedent viral illnesses and had fever, coryza, diarrhoea. The initial neurological symptoms included altered sensorium (n=3), seizures and status epilepticus (n=7), 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). 9 out of 10 cases survived, responded to standard medical therapy , early physiotherapy and rehabilitation. 6 children had complete recovery with minimal disability in 3 cases.

**Conclusions:** Early detection and appropriate treatment improves outcome in ANEC. Physiotherapy helps in remarkable improvement in the regain of tone, reflexes and movements of limbs

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

## Introduction

Ever since first description by Mizuguchi et al, 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[1-3]. ANEC has occasionally been reported in both Asian and Western countries and is being recognized as reason for longer stay in 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[4], it is now believed that this disease is most likely immune- mediated or metabolic[5].

Patients with ANEC have neither specified symptoms nor typical neurological signs. In addition to

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prodromal symptoms due to different viral infections, which include fever, signs of upper respiratory tract infections ,gastroenteritis, and erythema, patients with ANEC often have signs of Systemic Inflammatory Response Syndrome, shock, multiple organ failure , and disseminated intravascular coagulation[6].With the development of ANEC, brain dysfunctions may present as seizures, disturbance of consciousness and focal neurological deficits[1-3,6]. 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[7, 8]. 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[5-8].

Diagnosis is made mainly by the characteristic findings of computed tomography 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[1-3]. 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 study, we have described 10 children with ANEC to elucidate, the clinical/neuroradiological characteristics, the response to early physiotherapy and rehabilitation.

**Material and Methods :**

This is retrospective analysis of 10 infant and children with ANEC admitted at Department of Pediatrics, S.N.Medical College & 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[3][Table 1].Routine blood tests and 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. After stabilization, these children were initiated on early physiotherapy and rehabilitation. Initially at ICU, breathing exercises , postural drainage and suctioning (as required), passive exercises ,limb elevation, positioning, facilitation techniques like stroking , joint compression , quick stretching were given for all cases . Ankle Foot Orthosis was used to maintain Tendo Achilles length. All the recovered patients were followed-up at our department of Pediatrics OPD and child rehabilitation centre. These cases underwent therapeutic exercises, strength training, stretching, electrical stimulation (for lower limbs and trunk) 5 days a week for 30 minutes. Functional activities in sitting position were given. Each session lasted for 60 minutes and was carried for 6 days a week. All cases were followed for evaluation of neurodevelopmental outcome and response to physiotherapy. Modified Rankin scale [RS] (total 0-6 scale : score 0 - no symptoms ,score 6 - death) was used to assess the response to rehabilitation. The disability (as graded by modified Rankin Scale) in the patient was reduced over time with physiotherapy. 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 neurological outcome are summarized in table 2.

**Clinical features of the subjects**

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

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

**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 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 density on T2-weighted imaging in the bilateral thalami and brain stem in all patients. The findings in all cases were consistent with a unique pattern of ANEC.

**Treatment and Outcome:** All cases were admitted at PICU and received treatment as per standard ICU protocol. Children with seizures and altered sensorium received antiepileptic therapy and raised ICP management respectively. Standard protocols for medical management of ANEC were used in all cases. One child (case no 9) died 6 days after admission due to raised ICP with septicemia and Multiorgan dysfunction syndrome. Remaining cases stabilized and were started on early physiotherapy and rehabilitation. 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. Even though they had initial weakness, spasticity on extremities or memory disturbance, their symptoms improved remarkably with regular physiotherapy.

**Table 1 : Diagnostic criteria of ANEC proposed by Mizuguchi**

| | |
|---|---|
| 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. |
| | A. Clinical differential diagnosis; toxic shock syndrome, haemolytic uremic syndrome, Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and heat stroke. |
| | B. Radiological (or pathological) differential diagnosis; Leigh encephalopathy, glutaric acidemia, methyl malronic aciduria, infantile bilateral strial necrosis, Wernicke encephalopathy, carbon monoxide poisoning, acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis, arterial or venous infarct, severer hypoxic or traumatic injury. |

Table 2: Summary of clinical, and neurological outcome

| | Age/sex | Presenting illness | CNS presentation | GCS at admission | GCS at discharge | Modified Rankin Scale score at discharge | Modified Rankin Scale score at 3months Follow-up | Modified Rankin Scale score at 9month Follow-up | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 5yr 6mon, F | Non specific Febrile illness | Altered sensorium | 6 | 10 | 4 | 3 | 1 | Fully recovered |
| 2 | 6month, F | URTI | Seizures, irritability | 8 | 12 | 5 | 3 | 2 | Spasticity |
| 3 | 2yr, F | Non specific Febrile illness | Status Epilepticus | 6 | 11 | 5 | 3 | 2 | Spasticity & Speech disorder |
| 4 | 5yr 10 month, M | URTI | Status Epilepticus | 5 | 13 | 5 | 3 | 1 | Fully recovered |
| 5 | 4yr, F | Non specific febrile illness | diplopia, gait disturbance, altered sensorium | 6 | 12 | 5 | 3 | 2 | Fully recovered |
| 6 | 2yr 10mon, F | URTI & AGE | Gait disturbance, Altered sensorium | 6 | 13 | 5 | 5 | 5 | Spastic quadriparesis, Speech disorder |
| 7 | 3yr 6mon, M | AGE | Status Epilepticus | 7 | 13 | 5 | 2 | 1 | Fully recovered |
| 8 | 11months, F | AGE | Altered sensorium | 7 | 14 | 4 | 2 | 1 | Fully recovered |
| 9 | 1yr 4 month, M | URTI & AGE | Status Epilepticus | 6 | - | - | - | - | Expired |
| 10 | 9yrs, F | Non Specific febrile illness | Status Epilepticus | 7 | 14 | 5 | 2 | 1 | Fully recovered |

## Discussion

ANEC was proposed as a novel disease entity by Mizuguchi et al[2], extensively affecting infants and young children worldwide including sporadic cases in Indian scenario. 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 physiotherapy and neuro-rehabilitation.

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 Mizuguzichi[2,3] and had varied presentation at the time of admission. 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[9]. None of our cases had atypical presentations. All our cases were previously healthy, in whom diseases initiated with fever and other viral like prodrome, seizures and neurologic disturbances.

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%[1,2,6-9]. In our study,9 out 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 due to raised ICP with septicemia and multiorgan dysfunction syndrome. One surviving child left with severe sequelae (table 2). Kim JH et al reviewed 14 Korean cases over 10 year study period and suggested no mortality. 57% patients completely recovered or left with mild deficits[10]. 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[11-15]. 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[9,15-19]. Radiological findings 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 AM 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[19].

In so far published cases of ANEC, there is limited data on role of physiotherapy and rehabilitation. Importance of physiotherapy is brought out in our study. We were able to assess only short term and intermediate term outcome of neuro-rehabilitation these children with ANEC and comparative studies are lacking in this aspect.

**Limitations of the study:**

This study is a relatively small number of the patients and a retrospective design with only short term outcome. Prospective trials with a large number of the patients with long-term outcome are desirable.

## Conclusion

Early detection and appropriate treatment may lead to better outcome. Physiotherapy helps in remarkable improvement in the regain of tone, reflexes and functional activities in cases with ANEC.

**Ethical Clearance:** taken from S.N.Medical College Institutional Ethics Committee on Human Subject Research, Bagalkot (Approval reference number – SNMC/IECHSR/2017-2018/A-53/1.0)

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