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**Case Series**

# The clinical, laboratory, etiological profile and outcome of acute necrotising encephalitis of childhood in tertiary care centre from western India

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## ABSTRACT

Acute necrotising encephalopathy of childhood (ANEC) is an encephalopathy that presents with viral prodrome accompanied by episodes of seizures and rapid alteration of consciousness. Many patients had a previous history of febrile illness before neurological worsening. Though there is no definite genetic cause, few genes are involved in familial forms of the disease. Geographically this disease is seen in East Asian countries involving infantile and childhood age. Radiological evaluation classically shows lesions involving thalami, cerebellum, brainstem, and white matter. We hereby report 4 cases hospitalized at a tertiary health care hospital with classical presentation, hallmark radiographic, and hematological picture. All four patients presented with varied neurological involvement including altered consciousness, status dystonicus, trismus, and status epilepticus following an acute febrile illness. Radiological involvement is classical in all with damage to the thalami, cerebellum, brainstem, and white matter, though the neurological presentation, duration, and outcome of all varied. All these 4 patients were thoroughly investigated and out of them 3 were managed with IVIG and MPS, the rest one with an immunosuppressive state managed symptomatically in a conservative manner, and all four were discharged with varied neurological morbidities. All of them offered symptomatic medical management, and physiotherapy from experts. ANEC is an acute deteriorating neurological disorder with a prior history of febrile illness. Neurological illness has hallmark clinical presentation with classical symmetrical brain involvement including thalami, cerebellum, brainstem, and white matter. Though having a varied clinical spectrum, it has responded well to immunotherapy by anti-inflammatory agents including IVIG and MPS.

**Keywords:** Acute necrotising encephalopathy of childhood, Dystonia, Seizures

## INTRODUCTION

Acute necrotising encephalopathy of childhood (ANEC) is an encephalopathy seen in the pediatric age group mainly seen in the infantile or pediatric age group. More prominence in east Asian countries Japan and Taiwan. however, cases are seen all over the world as well. Etiology and pathophysiology are still a matter of discussion, however, mycoplasma like bacterial infections, influenza virus, herpes simplex virus, and human herpes virus-6 are notoriously involved in the pathophysiology of ANEC.[1] Cytokines, interleukin 1, interleukin 6, and tumor necrotizing factor alpha lighten up the inflammatory process. Presented with seizures, altered sensorium, vomiting, and various degrees of liver dysfunction. MRI findings are characterized by symmetric lesions that must involve the thalami. The prognosis is usually poor, few patients show improvement with IVIG and steroids.[2] We hereby discuss 4 cases of ANEC presented at a tertiary health care center in Gujarat with somewhat similar

clinical presentation and radiological abnormalities with different outcomes in terms of CNS involvement and general condition.

## CASE SERIES

### *Case 1*

A 2-year-old female presented with sudden onset of high-grade fever, followed by status dystonicus and respiratory difficulty with no significant or similar history. Clinical findings suggest hypertonia in all four limbs with dystonia which leads to contractures in bilateral lower limbs.

On investigation, liver enzymes were noted on the higher side along with normal CSF protein with no pleocytosis. EEG done suggestive changes of diffuse encephalopathy with no evidence of non-convulsive status epilepticus.

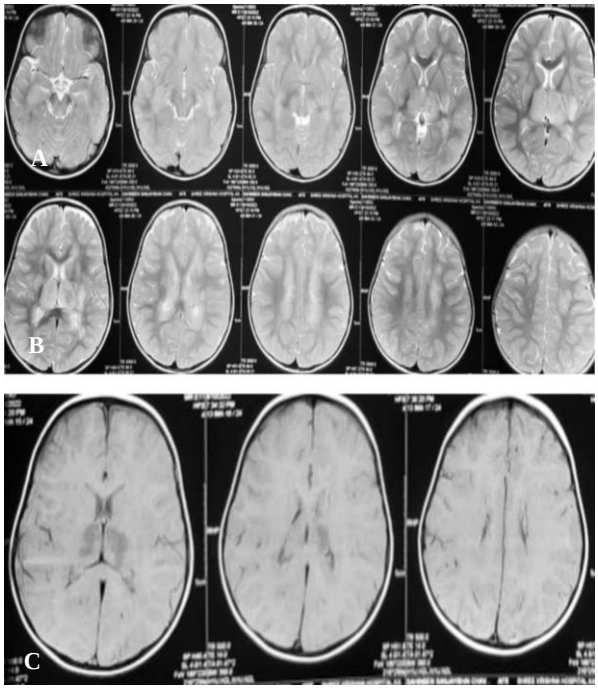


**Figure 1 (A-C): Bilaterally symmetrical abnormal signal hyperintense on T2, barely identified on T1 images, are seen in both thalami, dorsal pons (not shown), bilateral posterior lentiform nuclei, and bilateral centrum semiovale.**

*Management and outcome*

Considering immune therapy IVIG is given at 2 g/kg followed by injection methylprednisolone started at 30 mg/kg and continued for 5 days. The patient managed conservatively with symptomatic treatment, status dystonicus required treatment with anti-dystonia medications clonidine and tetrabenazine. The patient responded well to treatment and was discharged with few morbidities. The patient was followed up on an outpatient basis, CNS involvement improved and complaints resolved.

### *Case 2*

We encountered another 3-year-old male who presented with an abrupt onset of fever, gastrointestinal symptoms, trismus, and encephalopathy. Clinical findings show hypertonia in all four limbs with exaggerated deep tendon reflexes and extensor planter reflexes. Further blood investigations show liver enzymes on the higher side and high CSF protein levels.

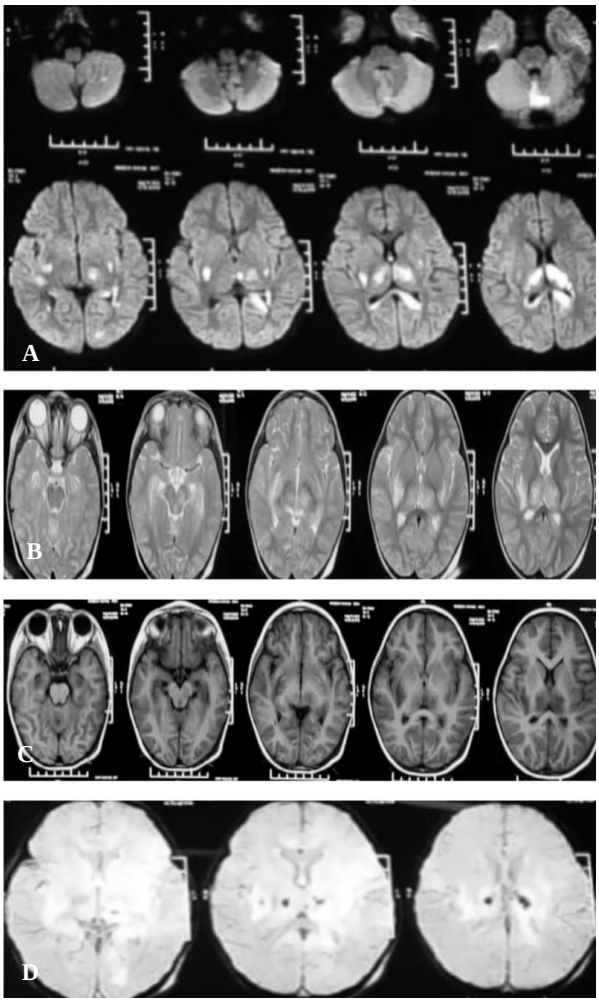


**Figure 2 (A-D): Multiple focal lesions of cytotoxic edema, in bilateral thalami, right posterior lentiform nucleus, bilateral peritrigonal regions, and superior vermis with acute hemorrhagic foci in bilateral thalami and right posterior lentiform nucleus.**

*Management and outcome*

The patient was given methylprednisolone at 30 mg/kg for 5 days following which the patient's sensorium, and general condition improved as well as the trismus resolved, as the patient's CNS involvement improved, and the complaint resolved, the patient was discharged on oral feeds. The patient followed up for neurological response, showed minimal trismus initially, and later turned out to be completely neurologically normal.

***Case 3***

We encountered 3 year 3-year-old female who presented with a sudden onset of fever and encephalopathy. On further examining the patient, planters were extensors and deep tendon reflexes were normal. On investigating the patient's blood reports show altered liver enzymes and CSF protein noted quite on higher side. EEG shows normal sleep EEG, with no evidence of any epileptiform activity.

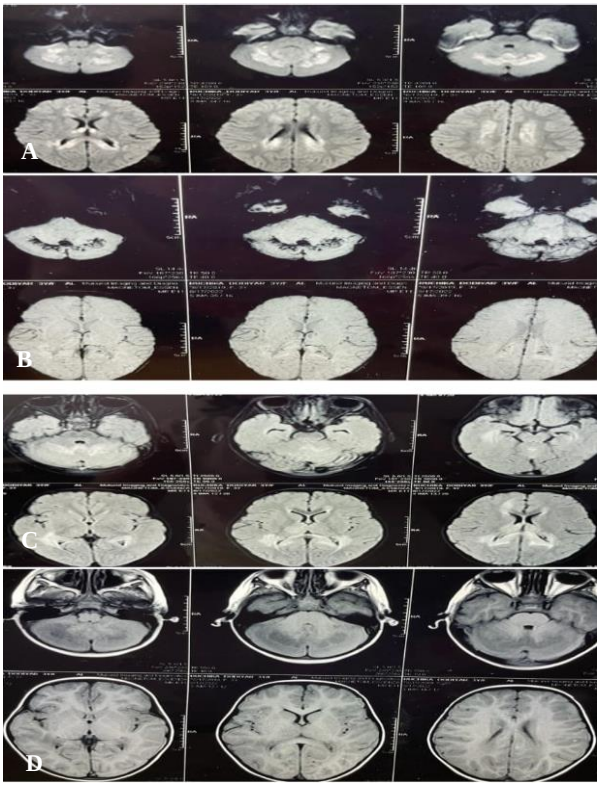


**Figure 3 (A-D): Bilaterally symmetrical multifocal lesions of cytotoxic edema, restricted diffusion on DWI, hyperintense on FLAIR, mildly hypointense on T1W images are seen in bilateral cerebellar white matter, anterior thalami, corpus callosum, and bilateral deep corona radiata. Multiple punctuate foci of blooming on SW images are seen in the lesions of bilateral cerebellar white matter and the posterior body of the corpus callosum represents hemorrhagic foci.**

*Management and outcome*

The patient was given methylprednisolone at 30 mg/kg for 5 days following which state of encephalopathy improved. Simultaneously, the patient required PICU admission. The patient was initially kept on intragastric feeds as sensorium, and general condition improved patient was discharged on oral feeds. The patient followed up for neurological response and showed complete neurological recovery.

***Case 4***

We hereby notify the 4th case, an 8-year-old boy presented to us with an acute gastrointestinal illness with status epilepticus, with a Glasgow coma scale on receiving was E4V1M5. On further evaluation, the patient had extensor planter reflex and exaggerated deep tendon reflexes. Blood investigation shows altered liver function along with serology turns out to be positive for hepatitis B surface antigen with HBV DNA quantitative was $1.0\times10^3$ IU/ml. CSF examination was within normal limits.

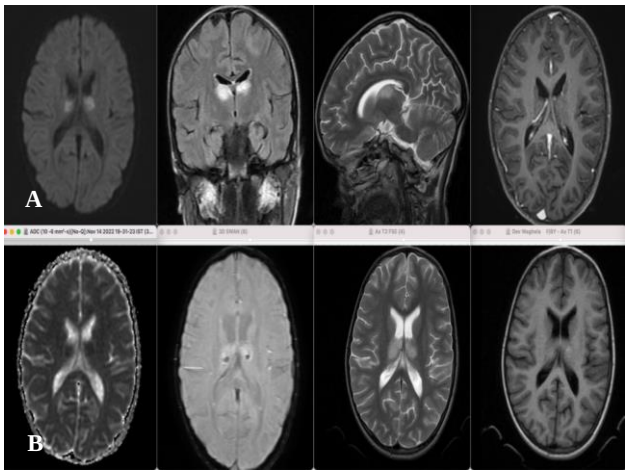


**Figure 4 (A & B): Bilaterally symmetrical lesions of cytotoxic edema, restricted diffusion on DWI, hyperintense on T2W, FLAIR, intermediate on T1W images, in superior thalami with punctate foci of blooming on SW images represent hemorrhagic foci.**

*Management and outcome*

As the patient was already in an immunosuppressive state, immunosuppressive therapy was avoided. The patient required ICU care, managed symptomatically with antiepileptic medications, and routine care. The patient responded well and was discharged with oral feeds. The patient followed up for neurological response and showed complete neurological recovery.

**Table 1: Case description.**

| Cases | Age (years) | Clinical presentation | AST/ALT (U/l) | CSF | | | Radiological findings | Treatment |
|---|---|---|---|---|---|---|---|---|
| | | | | Protein (mg/dl) | Sugar (mg/dl) | Cells (cells/µl) | | |
| **1** | 2 | Fever, respiratory failure, status | 313/128 | 18 | 87 | 5 | Bilaterally symmetrical abnormal signal | IVIG given @2 g/kg followed by |

Continued.

| Cases | Age (years) | Clinical presentation | AST/ALT (U/l) | CSF | | | Radiological findings | Treatment |
|---|---|---|---|---|---|---|---|---|
| | | | | Protein (mg/dl) | Sugar (mg/dl) | Cells (cells/µl) | | |
| | | dystonicus, altered sensorium | | | | | hyperintense on T2, barely identified on T1 images, are seen in both thalami, dorsal pons (not shown), bilateral posterior lentiform nuclei and bilateral centrum semiovale. | MPS @30 mg/kg given for 5 days |
| **2** | 3 | Acute gastrointestinal illness, fever, trismus, altered sensorium | 180/532 | 27 | 61 | 10 | Multiple focal lesions of cytotoxic edema, in bilateral thalami, right posterior lentiform nucleus, bilateral peritrigonal regions and superior vermis with acute hemorrhagic foci in bilateral thalami and right posterior lentiform nucleus. | MPS @30 mg/kg given for 5 days |
| **3** | 3 | Fever, altered sensorium | 60/199 | 75 | 65 | 5 | Bilaterally symmetrical multifocal lesions of cytotoxic edema, restricted diffusion on DWI, hyperintense on FLAIR, mildly hypointense on T1W images are seen in bilateral cerebellar white matter, anterior thalami, corpus callosum and bilateral deep corona radiata. Multiple punctuate foci of blooming on SW images are seen in the lesions of bilateral cerebellar white matter and the posterior body of the corpus | MPSS @30 mg/kg given for 5 days |

Continued.

| Cases | Age (years) | Clinical presentation | AST/ALT (U/l) | CSF | | | Radiological findings | Treatment |
|---|---|---|---|---|---|---|---|---|
| | | | | Protein (mg/dl) | Sugar (mg/dl) | Cells (cells/µl) | | |
| | | | | | | | callosum represents hemorrhagic foci. | |
| **4** | 8 | Acute gastrointestinal illness, fever, status epilepticus, altered sensorium | 125/117 | 41 | 77 | 5 | Bilaterally symmetrical lesions of cytotoxic edema, restricted diffusion on DWI, hyperintense on T2W, FLAIR, intermediate on T1W images, in superior thalami with punctate foci of blooming on SW images represents hemorrhagic foci. | Conservative |

## DISCUSSION

Acute necrotizing encephalopathy of childhood is a rare severe encephalopathy seen in previously well children. It is thought to be triggered by a viral illness and bacterial illness including influenza, HHV-6, mycoplasma, etc.[1,3] Many patients had a previous history of gastrointestinal and respiratory symptoms. No clear evidence of genetic basis however a familial or recurrent form is associated with mutations in the RANBP2 gene and is designated ANE1.[2]

As we encountered four cases, clinical presentation varied in the form of seizures, dystonia, altered sensorium, vision loss, and trismus along with a wide spectrum of clinical outcomes from complete recovery to persistent dystonia even on discharge as well. According to previous studies, no significant relationship exists between the extent of brain damage and disease outcome.[5] As in our case series neurological outcomes were different in all four cases with almost similar brain involvement observed in all 4 patients.

### *Diagnostic criteria*

Acute encephalopathy following (1-3 days) a febrile illness. The rapid deterioration in level of consciousness and seizures. Cerebrospinal fluid shows an increase in cerebrospinal fluid protein with no pleocytosis. CT or MRI evidence of symmetric, multifocal brain lesions, involvement of the bilateral thalami, cerebral periventricular white matter, internal capsule, putamen, upper brainstem tegmentum, and cerebellar medulla.[1,2] Elevation of serum aminotransferases of variable degrees with no increase in blood ammonia levels.

### *Exclusion of other diseases*

From clinical viewpoints overwhelming bacterial and viral infections, Fulminant hepatitis, toxic shock syndrome, Reye's syndrome, hemorrhagic shock and encephalopathy syndrome, and heat stroke.

From radiological viewpoints Leigh encephalopathy and related mitochondrial cytopathies, glutaric academia, methylmalonic academia, Wernicke's encephalopathy, acute disseminated encephalomyelitis, and acute hemorrhagic leukoencephalitis.[4,5]

Management includes supportive care including hydration, electrolyte balancing, prevention of infection and seizure, and spasm control. Treatment with levodopa has also been part of management. For sepsis control broad spectrum antibiotics are advised. L-dopa, trihexyphenidyl, and IVIG also play important roles in management.[8-10] Mortality and morbidity of these patients are high with less than 10% complete recovery. Most patients face intense neurologic decline. Focal cystic degeneration and cortical atrophy were more seen on convalescent imaging of the patients who showed full clinical improvement. However, a poor prognosis was seen in children who had petechial hemorrhage and cavity lesions in their MRIs.[6,7]

## CONCLUSION

ANEC is a sudden deteriorating neurological disorder with a prior history of acute febrile illness involving respiratory or gastrointestinal symptoms. Neurological illness has hallmark clinical presentation with classical symmetrical brain involvement including thalami, cerebellum,

brainstem, and white matter with hemorrhagic foci. Though having a varied clinical spectrum with unique clinical symptoms and morbidities, it has responded uniformly well to immunotherapy by anti-inflammatory agents including IVIG and MPS. Paediatricians and neurologists should consider ANEC as one of the differential diagnoses of acute deteriorating neurological illness that occurs following a febrile illness. Acute neurological event with classical radiographic findings of hemorrhagic foci in bilateral thalami, cerebellum, brainstem, and white matter with raised liver enzymes and CSF proteins level, should raise suspicion of ANEC. The patients with ANEC respond differently to IVIG and MPS in terms of neurological recovery and prolonged morbidities.

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