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Case Report

Severe dengue fever presented as acute necrotizing encephalopathy with multiple organ dysfunction syndrome: a case report

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ABSTRACT

Acute necrotizing encephalopathy (ANE) is a para-infectious, pauci-inflammatory disorder predominantly reported among children younger than 5 years of age. The diagnosis is based on the typical clinical presentation, imaging findings, and exclusion of other mimicking conditions. Although the pathophysiology of ANE is not completely understood, it is considered to be immune-mediated after a viral infection. Neurological manifestations of dengue are increasingly being recognized. These include encephalopathy, encephalitis, myelitis, myositis, Guillain-Barre syndrome and mononeuropathies. ANE following dengue fever has been reported earlier but rarely. We present a case of a boy who developed this condition with classical clinico-radiologic findings of ANE secondary to severe dengue infection. He had a stormy hospital course but survived without sequelae. We report this case with the aim to raise awareness about this fatal neurological complication of dengue infection as dengue has become a global health-care problem.

Keywords: Severe dengue fever, ANE, Viral, Sequelae

INTRODUCTION

Dengue is one of the most common arboviral infection in the Southeast Asia. Dengue virus has four related but antigenically distinct serotypes: DENV-1, DENV-2, DENV-3, and DENV-4.[1] Dengue infection has a diverse clinical presentation ranging from asymptomatic subclinical infection to severe multi-organ involvement.[2] Although, vascular plasma leak is the commonest manifestation, dengue can manifest in unusual presentations due to organ dysfunction that can carry high mortality.[2] Although rare, CNS manifestations have been increasingly described in literature, which include dengue encephalopathy, encephalitis, immune complex-mediated syndromes.[3] ANE usually affects younger children and has classical radiological findings of multifocal symmetrical lesions in thalami, brainstem, and cerebellum.[4] Most of the cases of ANE described in literature are reported to be secondary to different viral etiologies, especially respiratory viruses. This is the case of ANE secondary to dengue infection with classical clinic-radiological findings, which is rarely reported.

CASE REPORT

A 9-year-old boy presented to pediatric emergency department, Artemis hospital, Gurugram with history of high-grade fever and loose stools for 2 days. There was

no associated cough, vomiting, body ache or breathing difficulty. He had an episode of generalized, tonic–clonic seizure, lasting for few minutes and aborted by self. His consciousness deteriorated, and he was referred to us. On examination, there was tachycardia and tachypnoea with Glasgow coma scale (GCS) of 8/15. His pupils were constricted bilaterally with downward gaze. There was intact cough and gag reflex and no facial weakness. He had generalized increased tone and brisk reflexes. There was no visceromegaly or rash. Initial impression of meningoencephalitis was made. His laboratory workup showed hemoglobin 11.1 g/dl, total leukocytes count 12200/mm^3 with 89% neutrophils, and thrombocytopenia (platelets 129,000/mm^3). His clotting parameters were within the normal limits.His transaminases were elevated ALT 7261 IU/L, AST 18811 IU/L. His CRP was elevated 6.3 mg/dl (Normal range: 0.0-1.0 mg/dl) and serum ferritin level was 7654 ng/ml.

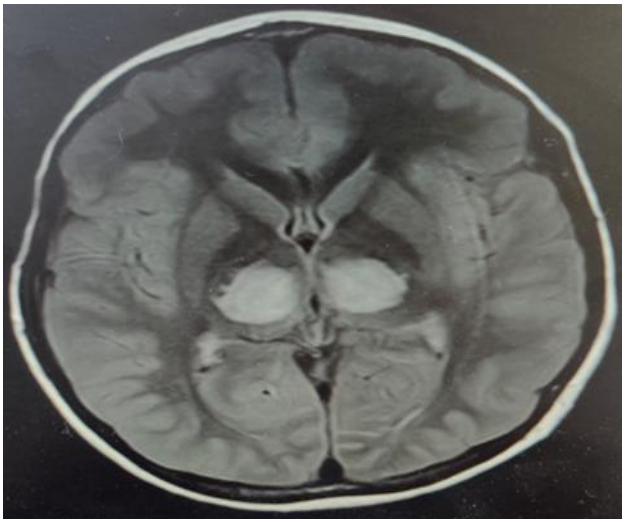

Figure 1: T2W axial image of bilateral thalamic lesion with central necrosis and haemorrhage, cytotoxic edema with surrounding vasogenic edema.

His creatinine and electrolytes were normal. Magnetic resonance imaging (MRI) brain was done which showed bilateral bulky thalami with areas of altered signal intensities involving both thalami, pons, inferior vermis, bilateral cerebellar hemispheres and splenium of corpus callosum with intralesional haemorrhage in thalamic lesions. Findings were suggestive of acute viral necrotizing encephalopathy. His cerebrospinal fluid examination was done which was reported normal. Biofire Meningitis Panel of cerebrospinal fluid was negative. His dengue NS1 Ag ELISA came positive. He was intubated and mechanically ventilated in view of deterioration of sensorium and he was provided neuroprotective mesures. He was managed with IV fluid therapy as per WHO guidelines along with intravenous antibiotics and antiepileptic drugs. With time condition of the child improved and he was extubated. Repeat MRI Brain was done which showed partial resolution of haemorrhagic areas in bilateral thalami. He also developed AKI during the course of treatment which was managed with intermittent hemodialysis. Tracheostomy was done in view of prolong ventilation. Child was discharged with the neurological sequelae after 1 month of hospitalization which improved over a period of next 2 months to complete recovery.

This child presented with acute onset fever, loose stools and seizure and was initially suspected of having a CNS infection. He had signs of raised intracranial pressure. MRI showed classical radiological findings of ANE. Thrombocytopenia with raised liver enzymes levels during dengue season prompted us to send the dengue serology, which came positive. We observed the typical course of rapid progression of neurological deterioration of ANE in our patient. However, the development of multi organ failure has not been described in acute necrotizing encephalitis patients earlier, which could be due to severe dengue infection.

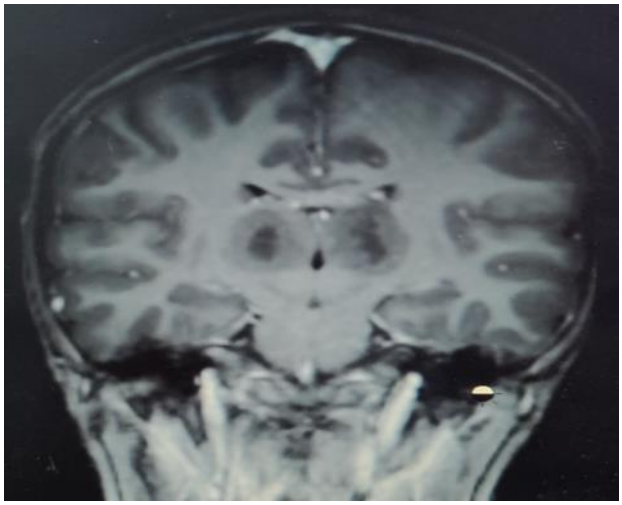

Figure 2 : T1W coronal image showing trilaminar target sign in basal ganglia region.

Table 1: Investigations.

Test	Day 1	Day 3	Day 7	Day 11
Hb	11.1 gm/dl	6.8 gm/dl	8.5 gm/dl	9.4 gm/dl
TLC	12200 (N89%, L10%)	8400 (N68%, L22%)	11000 (N80%, L13%)	12800 (N67%, L21%)
Platelets	129000/ cumm	64000/ cumm	120000/ cumm	316000/ cumm
S. creatinine	2.54 mg/dl	4.42 mg/dl	5.5 mg/dl	0.85 mg/dl
AST/ALT	18811/ 7261 IU/L	11036/ 4113 IU/L	1730/ 2537 IU/L	45/ 205 IU/L
CRP	6.3 mg/dl	1.1 mg/dl	3.7 mg/dl	0.9 mg/dl

DISCUSSION

ANE is a rare subtype of acute infectious encephalopathy, first described by Mizuguchi, a Japanese pediatric neurologist, in 1995. The clinical characteristics of ANE include febrile illness followed by altered consciousness and seizures. The pathologic features of the disease are necrosis and multiple petechiae in both the thalamus and tegmentum of the pons, as well as myelin pallor in the cerebral and cerebellar deep white matter.

ANE typically develops in children younger than 5 years of age; only case reports have been published thus far in adults. Although viral infections play an important role in triggering ANE, genetic predisposition is noted especially in familial and recurrent cases.

Dengue, as an inciting trigger has not been described commonly in previous studies. In the pediatric population, ANE has been described with viral infections such as influenza, parainfluenza, herpesvirus 6 and 7, herpes simplex virus, measles, rubella, varicella, coxsackie A9, rotavirus, reovirus, and dengue. Most of the data published on ANE are from the east Asian regions such as Japan, Korea, and Taiwan, where dengue infection is uncommon. The exact pathogenesis of ANE is still not clear. The most prevalent hypothesis is the increased cytokine levels causing "cytokine storm" resulting in brain injury by altering vessel wall permeability without vessel wall disruption or inflammation; shock, liver dysfunction, acute renal failure, and disseminated intravascular coagulation.[5] ANE is not considered inflammatory encephalitis due to the minimal inflammation in histopathological studies compared to marked necrosis and also the absence of CSF pleocytosis in most cases. Genetic predisposition has been noted especially in familial and recurrent cases. Ran binding protein-2 (RANBP2) is one such gene, missense mutations predispose to ANE in autosomal dominant pattern with incomplete penetrance with some cases occurring without infectious trigger.[6]

Bilateral, symmetrical brain lesions involving thalamus, brainstem, cerebrum, and cerebellum affecting both grey and white matter with necrosis and hemorrhage is the characteristic feature of ANE.[7,8] Thalamus is involved in most of the cases along with involvement of brainstem, cerebral, and cerebellar white matter. The pattern of thalamic involvement is the hallmark of ANE aiding in clinching the diagnosis.[9,10] The trilaminar pattern is the hallmark pattern of involvement which is best seen in apparent diffusion coefficient image with higher-than-normal ADC values at the center of lesion due to hemorrhage, surrounded by low ADC values at the peripheral portion of central lesions suggesting cytotoxic edema with very high ADC value at the outermost region suggesting vasogenic edema.

Management of ANE is mainly supportive with antiepileptic drugs and neuroprotective measures. Some studies have shown the beneficial role of antiviral agents such as amantadine and oseltamivir along with methylprednisolone pulse doses and intravenous Ig.[3] The outlook of ANE is very poor with 30% patients dying during the acute illness and those who survive have a significant neurological impairment. ANE carries significant morbidity and mortality with long-term sequelae usually observed in children less than 4 years/ when they present with shock, thrombocytopenia, brainstem lesions, hemorrhage, and cavitation.

CONCLUSION

This is one of the few reports of ANEC secondary to dengue infection with a very fulminant course. With the passage of time and more awareness, the outcome of ANEC is improving but it still remains a deadly disease. The availability of dengue vaccination could be the only way to prevent these deadly complications of dengue infection. High index of suspicion is required to diagnose these types of rare complications in pediatric patients. Supportive care and symptomatic management are the key to manage these types of patients. To the best of our knowledge, this is the report of ANEC secondary to dengue infection with a very fulminant course. With the passage of time and more awareness, outcome of ANEC is improving.

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