

# Dengue encephalitis: why we need to identify this entity in a dengue-prone region

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## ABSTRACT

**Classical dengue fever is commonly seen in children and young adults. It commonly presents with fever, severe headache, body ache and retro-orbital pain. Unlike other arboviral infections, dengue virus does not usually cause neurological manifestations. We report a 13-year-old boy with dengue encephalitis. Dengue encephalitis should be considered in the differential diagnosis of acute viral encephalitis especially in countries like India where dengue has assumed epidemic proportions. These undiagnosed cases are at risk of developing complications of dengue haemorrhagic fever.**

**Keywords:** dengue encephalitis, dengue fever, encephalitis

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## INTRODUCTION

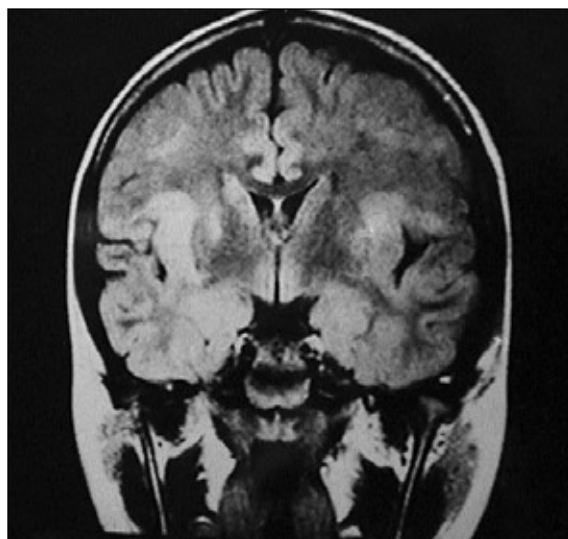
Dengue virus is a single-stranded RNA arbovirus belonging to the family *Flaviviridae*. Infection with any of the four types of dengue virus can cause dengue fever, dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS). Classical dengue fever is commonly seen in children and young adults. It commonly presents with fever, severe headache, body ache and retro-orbital pain; hence the term break-bone fever. Unlike other arboviral infections, dengue virus does not usually cause neurological manifestations. We present a case of dengue encephalitis, which may be the only case of true encephalitis reported from New Delhi, India.

## CASE REPORT

A 13-year-old boy presented to the emergency department of Lok Nayak Hospital with continuous, high-grade fever for 12 days with severe headache and body ache. One day earlier, he developed difficulty in walking, with falling to one side while standing, and drowsiness. There was no

significant past or family history. On examination, the patient was febrile and drowsy. His pulse, blood pressure and respiratory rate were within normal limits. General physical examination was normal. Neurological examination revealed left ptosis with sluggish pupillary reaction to light in that eye. There was gait ataxia with tendency to fall sideways. Other systems were normal.

His metabolic profile was normal except for a decreased platelet count. Standard ELISA kits (Standard Diagnostics, Suwon City, South Korea) were used to detect IgM and IgG antibodies against the four known strains of dengue virus in the serum of the patient. IgM antibodies against dengue virus were positive. Magnetic resonance (MR) imaging of the brain showed altered signal intensity in both temporal and periventricular areas, which was suggestive of viral encephalitis (Fig. 1). Cerebrospinal fluid (CSF) examination showed ten cells/ $\mu$ L, all lymphocytes, protein 11 mg/dL (normal range 15-50 mg/dL), and glucose 60 mg/dL (normal range 40-70 mg/dL). IgM and IgG antibody against *Herpes simplex virus 1* (HSV1) and HSV2 (both by enzyme immunoassay)



**Fig. 1** Coronal MR image of the brain shows bilateral symmetric gyral oedema and altered signal intensity involving bilateral temporal, perisylvian regions and cingulate gyri.

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in CSF was negative. IgM antibodies against dengue virus were positive in the CSF. Therefore, a diagnosis of dengue encephalitis was made.

Repeat dengue serology after ten days was positive. The patient was managed conservatively with fluid support and continuous monitoring. His ataxia improved after two days, and he became afebrile. He was discharged after two weeks. On follow-up, the patient was healthy and had no neurological deficits. Dengue serology performed after two weeks showed presence of IgG antibodies against the virus in the serum of the patient.

## DISCUSSION

Infection by dengue virus is commonly associated with dengue fever, DHF and DSS. However, in recent years, it has been recognised that this virus can also cause neurological manifestations<sup>(1-13)</sup>. Many neurological manifestations of dengue infection have been described to include headache, seizure, depressed sensorium, behavioural disorders, neck stiffness, delirium, paralysis, cranial nerve palsies and coma. Previously, reports of neurological manifestations in dengue infection had been referred to as encephalopathy rather than encephalitis because attempts to demonstrate direct invasion of the central nervous system (CNS) by dengue virus had failed<sup>(1)</sup>. Therefore, the pathophysiology of these neurological manifestations was thought to be secondary to prolonged DHF/DSS as opposed to encephalitis, which is defined as a localised invasion of the CNS<sup>(2-5)</sup>. Various physiological events were thought to lead to encephalopathy such as cerebral oedema<sup>(2)</sup>, cerebral haemorrhage, hyponatraemia, fulminant hepatic failure<sup>(6)</sup>, cerebral anoxia, micro-capillary haemorrhage and release of toxic products<sup>(7)</sup>.

Recent reports, however, have demonstrated a possible neurotropic effect of the virus. Animal studies done in mice showed that the virus could break down the blood brain barrier leading to CNS invasion. Virus-mediated cytokines were responsible<sup>(8)</sup>. In a study of six cases of dengue encephalitis, the virus was isolated from CSF in four cases by mosquito inoculation. In one patient, virus was detected in CSF by polymerase chain reaction, and IgM antibodies against dengue were present in the CSF in the sixth case<sup>(9)</sup>. In another study of nine cases of encephalitis in patients with dengue, four patients had presence of either the virus or IgM antibodies in CSF<sup>(10)</sup>, suggesting that the virus can cross the blood-brain barrier directly and invade the brain. In five fatal cases of dengue

infection, dengue virus antigen was demonstrated in CNS biopsies by immunohistochemistry<sup>(11)</sup>. These findings strongly support the hypothesis of direct neuro-virulence of the dengue virus.

Our patient had presented to us with drowsiness, which is consistent with reports of dengue encephalitis in literature. In a meta-analysis of 355 cases of dengue encephalitis, 47% of patients were drowsy while 21% had seizures<sup>(12)</sup>. Our patient had no feature suggestive of DHF; neither the haematocrit was raised, nor did the patient have any haemorrhagic manifestations. MR images of the brain showed encephalitis-like changes. As IgM and IgG antibodies against dengue virus were positive in the CSF, and IgM and IgG antibodies against HSV1 and 2 were negative, a diagnosis of dengue encephalitis was the only logical conclusion. CNS imaging studies in cases of dengue encephalitis have shown that cerebral oedema is the predominant finding in the majority of patients<sup>(9,13)</sup>, although a few cases do show encephalitis-like changes. One case of isolated hippocampus involvement has also been reported<sup>(14)</sup>. Therefore, given the clinical diagnosis of dengue fever along with MR imaging findings of encephalitis and a positive CSF serology, it can be said that this case represents a true case of dengue encephalitis.

Dengue encephalitis should be considered in the differential diagnosis of acute viral encephalitis, especially in countries like India where dengue has assumed epidemic proportions. Most case series on dengue encephalitis suggest that patients with the disease have a higher tendency to develop DHF/DSS. In one study of six patients, it was shown that all patients developed thrombocytopenia and five developed characteristic clinical features of DHF/DSS<sup>(9)</sup>. In another study of eight patients, seven progressed to DHF<sup>(15)</sup>. Although the neurological recovery was complete in most of the patients, they had increased incidence of DHF/DSS.

In one of the largest meta-analyses of 178 cases of dengue-related encephalopathy<sup>(16)</sup>, it was shown that their outcome was often very severe (with up to 50% mortality). However, most of the deaths were related to DHF/DSS. The mortality in cases of dengue encephalitis is increased, not due to the encephalitis per se, which usually has a benign course, but due to the increased incidence of DHF/DSS. These undiagnosed cases are at risk of developing complications of DHF/DSS. It is therefore very important for the clinician to be aware of the possibility of dengue infection as a cause of encephalitis.

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