Case Report

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Death due to Dengue Encephalitis: A Rare Case Report

Internal Medicine Section

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ABSTRACT

Dengue is a global public health concern, affecting around 50 million individuals and causing mortality in 20,000 patients per year. It is an arboviral disease caused by a single-stranded Ribonucleic Acid (RNA) virus belonging to the Flavivirus group and is transmitted by mosquitoes, specifically *Aedes aegypti* or *albopictus*. It comprises four serotypes, DENV1 to DENV4, and infection from one serotype only provides lifelong immunity for that subtype. Due to antibody-dependent enhancement, past infection with one serotype increases the prevalence of dengue haemorrhagic fever. The disease spectrum can range from asymptomatic infection to fever, fatal dengue haemorrhagic fever, or dengue shock syndrome. Due to improved disease knowledge, its involvement in the neurological system has been explored. Neurological abnormalities in dengue infection are rare and can be misdiagnosed due to other causes. Present case is of a young 23-year-old male with a history of fever 3-4 days prior, which later manifested with seizures and drowsiness. Despite emergency treatment, encephalitis and viral myocarditis developed, eventually leading to brain death within 24 hours of admission.

Keywords: Brain death, Cerebral oedema, Convulsions, Dengue shock syndrome, Drowsiness, Headache, Viral myocarditis

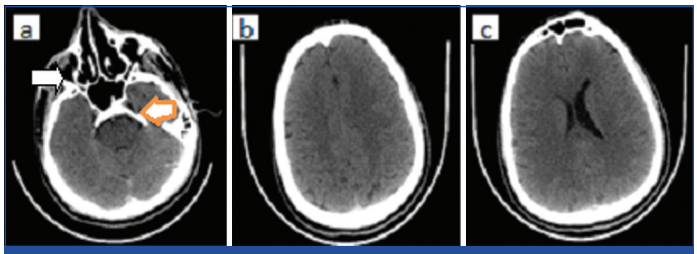
CASE REPORT

A 23-year-old male with no previous co-morbidities presented at the emergency room in a drowsy and confused state, followed by an episode of generalised tonic-clonic convulsion. The patient had a recent travel history to Assam for 15 days; however, while returning, the patient started experiencing intermittent high-grade fever and associated chills and rigor of three to four days' duration, along with a diffuse, dull, aching, continuous headache of three days' duration and three to four episodes of non bilious vomiting prior to the presentation with irritability and body ache. He sought primary treatment from a local practitioner, but his symptoms failed to improve.

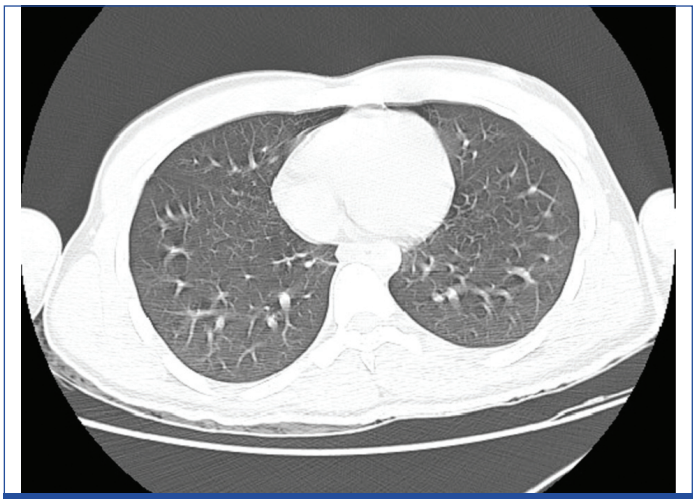
On examination, his body temperature was 102.4°F, heart rate 150 bpm, Blood Pressure (BP) 100/70 mmHg, respiratory rate 40/min, and Oxygen Saturation (SpO_2) 80% on room air. Cardiovascular System (CVS) examination revealed audible heart sounds S1 and S2 with tachycardia, and Respiratory System (RS) examination revealed tachypnoea with bilateral wheezing. The abdomen was soft and non tender. Central Nervous System (CNS) examination showed the patient to be drowsy, sluggish in responding to verbal commands, and moving all four limbs in response to stimuli. The Electrocardiogram (ECG) showed sinus rhythm with tachycardia-related changes.

Due to rapid deterioration in SpO_2 and a Glasgow Coma Scale (GCS) score of 8/15 (eye-opening: 2/4, verbal response: 2/5, motor response: 4/6), and for airway protection, intubation was performed, and the patient was placed on mechanical ventilatory support. Non contrast Computed Tomography (CT) of the brain revealed no significant abnormalities [Table/Fig-1], and High-Resolution Computed Tomography (HRCT) of the chest revealed no significant abnormalities [Table/Fig-2]. Magnetic Resonance Imaging (MRI) and Cerebrospinal Fluid (CSF) examination could not be performed due to the patient's critical condition. The patient was then transferred to the Intensive Care Unit (ICU). The patient's laboratory parameters showed severe alterations indicating severe infection with multisystem involvement [Table/Fig-3].

Considering the febrile illness with thrombocytopenia and multisystem involvement, the patient was further investigated for malaria, dengue fever, rickettsial fever, enteric fever, and leptospirosis, which all yielded negative results. Dengue NS antigen was reactive, while IgM and IgG were non reactive. The initial diagnosis of dengue fever with thrombocytopenia and multisystem involvement was made, which was confirmed with serological evidence. The patient was started on intravenous ceftriaxone, doxycycline, mannitol, dexamethasone, and potassium correction. After two hours in the ICU, his condition started to deteriorate haemodynamically and neurologically, requiring multiple ionotropic supports (noradrenaline, vasopressin, dobutamine).



[Table/Fig-1]: CT brain axial section images showing: a) mucosal thickening in both maxillary and sphenoid sinuses at level of pons; and b) at centrum semiovale level; and c) lateral ventricle level no other abnormal findings.



[Table/Fig-2]: HRCT chest axial section at level of eighth thoracic vertebrae image showing normal findings.

Parameters	Values	Reference range	Parameter	Values	Reference range
Haemoglobin (Hb) (g/dL)	18.6*	Female: 12-16 Male: 14-18	ESR (mm/hr)	55*	Female: 0-20; Male: 0-15
Haematocrit (HCT) (%)	53.9*	Female- 36-48 Male-40- 54	C Reactive Protein (CRP) (mg/dL)	6.5*	0.00-3.0
Leukocytes (/cumm)	5090	4000-11,000	Procalcitonin (ng/dL)	27.8*	≤0.10
Platelets (/cumm)	82,000*	150,000-450,00	Dengue serology NS1	Reactive*	
Neutrophils (%)	33.7*	40-60	Dengue serology IgM, IgG	Non reactive	
Lymphocytes (%)	46.9*	20-40	INR	1.05	<1.1
Serum sodium (mEq/L)	142	136-145	Prothrombin time (sec)	14.7*	11-13
Serum potassium (mg/dL)	2.23*	3.5-5.0	Malarial rapid antigen test	Negative	
Serum urea (mg/dL)	42*	8-20	Leptospira	Negative	
Creatinine (mg/dL)	2.23*	Female: 0.50-1.10 Male: 0.70-1.30	Weil-Felix for Rickettsia	Negative	
Random blood sugar (mg/dL)	98	70-140	Widal	Negative	
Glutamic-oxaloacetic transaminase (SGOT) (U/L)	565*	5-40	Urine routine and microscopy	Occasional pus cells and RBCs	Pus cells- 2-3 RBCs- 1-2
Glutamic-pyruvic transaminase (SGPT) (U/L)	105*	7-56	Troponin I (pg/dL)	2520*	0-0.4
Alkaline phosphatse (ALP) (U/L)	136*	44-147	Creatinine phosphokinase (CPK-MB) (U/L)	137*	5-25

[Table/Fig-3]: Laboratory investigations on admission.
ESR: Erythrocyte sedimentation rate; IgM: Immunoglobulin M; IgG: Immunoglobulin G; INR: International normalised ratio; *Indicates abnormal values

The echocardiogram showed sinus tachycardia, global Left Ventricular (LV) hypokinesia, mild mitral regurgitation, Grade-III LV diastolic dysfunction, and severe LV dysfunction with Left Ventricular Ejection Fraction (LVEF) of 15%. Troponin-I level was 2520 pg/mL, and Creatinine Phosphokinase (CPK-MB) level was 137 U/L, suggesting viral myocarditis. Intravenous methylprednisolone (1gm stat) was administered. Later, the patient became deeply comatose; the doll's eye reflex was absent; pupils were dilated and non reactive to light, and bilateral absent plantar response. Brainstem reflexes were absent. The Electroencephalogram (EEG) showed no discernable background activity.

Despite continuous ionotropic support, his condition deteriorated over the next few hours. The patient went into bradyarrhythmia and experienced a cardiorespiratory arrest. Cardiopulmonary Resuscitation (CPR) was initiated according to Advanced Cardiovascular Life Support (ACLS) protocols, but the patient could not be revived.

DISCUSSION

Dengue infections pose a significant healthcare concern, with approximately 390 million reported cases, both symptomatic and asymptomatic, particularly in Southeast Asian regions [1]. The high prevalence of dengue can be attributed to poor environmental sanitation and increased mosquito infestation [2]. The Dengue virus is an arbovirus with a single-stranded RNA, and it presents four serological variants. The clinical presentation of dengue can range from mild symptoms such as headache, myalgia, fever, rash, and abdominal pain to more severe conditions like dengue haemorrhagic fever, dengue shock syndrome, gastrointestinal bleeding, ascites, pleural effusion, fulminant hepatitis, and cardiomyopathy. About 10% of dengue cases exhibit neurological disorders such as encephalitis, encephalopathy, myelitis, Guillain-Barre Syndrome, and meningitis. Neurological manifestations are primarily observed in cases with severe dengue infections [3]. These neurological complications can resemble encephalitis and may delay treatment, leading to cerebral oedema or brain death [4]. Therefore, it is crucial to consider dengue-associated encephalitis in patients presenting with neurological symptoms in endemic areas. Early diagnosis is essential, and confirming the infection through testing for NS1 antigen in CSF is recommended [5]. In 2009, the World Health Organisation (WHO) included neurological manifestations as a criterion for assessing the severity of dengue infection [3]. Although dengue encephalitis is a rare presentation with limited literature available [6,7], in the case presented above, the infection progressed rapidly, and the patient's condition deteriorated despite receiving optimal rescue treatment. Initially, CNS involvement was believed to be secondary to dengue haemorrhagic fever, causing cerebral oedema, sodium imbalance, and hepatic and renal failure. Hepatic encephalopathy, cerebral hypoperfusion, cerebral oedema resulting from vascular leakage, and coagulopathy leading to intracranial bleeding can all contribute to dengue encephalopathy and encephalitis [8]. The exact pathophysiology of CNS involvement in dengue is not clear; however, it is believed that the impairment of the Blood-Brain Barrier (BBB) due to hyperactivity of TNF-α and IL-6 allows the entry of the virus [9]. Brain autopsies have revealed dengue-specific IgM antibodies and positive Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) results in the CSF, indicating CNS invasion of the dengue virus during acute infection [10].

Autopsy findings in dengue patients with CNS involvement have revealed significant cerebral oedema, which obliterates the sulci and causes flattening of the gyrus. Haemorrhagic spots throughout the brain have also been observed, and there is one reported case of brain herniation in the literature [11]. Certain laboratory parameters, such as increased mean haematocrit or elevated serum transaminase levels, show an association with severe dengue infection and high body temperature, independently predicting the occurrence of encephalitis [12]. Two studies have indicated higher mortality rates in cases of dengue encephalitis, with rates of 32% and 33.33% [13,14]. The cases of encephalitis caused by dengue are more commonly reported in young adult males, as seen in the case presented above [14]. Cases with dengue-positive CSF are associated with an increased mortality rate, suggesting severe infection [14].

Encephalitis is the most common CNS manifestation of dengue, characterised by symptoms such as headaches, seizures, and altered consciousness, which can also be present in other cerebral diseases. Many patients with encephalitis also exhibit typical dengue symptoms such as fever, myalgia, rash, or bleeding [15]. Confirming the diagnosis of neurological dengue infection can be done by detecting the presence of dengue IgM, virus RNA, or antigens, along with CSF analysis, CT, or MRI of the brain [16]. In the present case, MRI of the brain and CSF analysis could not be performed due to the patient's haemodynamic instability. In a study by Solomon T et al., out of nine patients with confirmed dengue infection and encephalitis, the virus or antibody could only be

isolated in two patients [15]. The pathogenesis of a severe dengue infection depends on secondary infections, the virulence of the virus, and the susceptibility of the host [17]. Secondary dengue infection enhances the virulence through antibody-dependent enhancement, leading to increased severity of the disease [13].

The patient presented in this case had a travel history from Assam, an endemic region for dengue infection [18]. In addition to fever, vomiting, and headache, the patient developed drowsiness and experienced one episode of tonic-clonic convulsion. Upon admission, systemic examinations and vital parameter assessments revealed encephalitis with a deteriorating condition, ultimately resulting in brain death. Laboratory findings confirmed dengue infection and indicated a poor prognosis. Despite treatment with ionotropic medications and supportive care, the patient could not be saved. The role of antiviral drugs and treatment strategies in critical cases like these needs to be defined to reduce mortality. Currently, there is no FDA-approved antiviral drug for dengue fever. Therefore, dengue-associated neurological manifestations, such as encephalitis and encephalopathy, although rare, must be considered in cases of fever, especially during a dengue epidemic, as they can be life-threatening and require immediate intervention.

CONCLUSION(S)

Acute dengue infection was previously considered non encephalitic. However, due to increasing viral neurotropism, neurological manifestations in dengue infection are on the rise. Although encephalitis in dengue patients is generally thought to be benign, it can be fatal in some cases. In the present case, despite receiving emergency treatment, the patient developed encephalitis and viral myocarditis, ultimately leading to brain death within 24 hours of admission. Therefore, physicians should be aware and vigilant in the early diagnosis of neurological manifestations, altered sensorium, and severely abnormal laboratory and imaging findings, as they could potentially indicate dengue encephalitis and allow for earlier intervention, thus reducing mortality and morbidity. In suspected cases, early neuroimaging, preferably MRI, is recommended.

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