CASE REPORT

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Atypical Manifestation of Dengue Fever: A Tale of 2 Cases

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Abstract

Dengue fever is a common tropical illness with varying severity often causing thrombocytopenia and haemorrhagic manifestations. We describe 2 cases with central nervous system manifestations in dengue fever. First is the case of a 20-year-old female who presented with high grade fever, headache, altered sensorium, and seizures. Clinical findings were suggestive of meningoencephalitis. Initial blood investigations of the patient showed thrombocytopenia. The magnetic resonance imaging of the brain showed bilateral thalamic, internal capsule, and occipital lobe hyper-intensities. Based on the preliminary examination and investigations, a diagnosis of acute febrile illness with meningoencephalitis was made. Further investigations showed Dengue NS1 antigen positivity in serum and a raise in anti-dengue IgM antibodies. Following symptomatic treatment and antiepileptic drug usage, the patient made a complete recovery. In another case, a 32-year-old gentleman with a short duration of fever and altered sensorium was diagnosed with dengue fever based on NS1 antigen positivity and IgM antibody positivity. He had poor GCS and MRI brain revealed bilateral thalamic and cerebellar hyper-intensities suggestive of encephalitis. He succumbed to the illness. These 2 cases highlight the importance of knowing the atypical manifestation of dengue fever.

Key words: Dengue fever, meningoencephalitis, seizure.

Introduction

Dengue virus is a RNA virus belonging to flavivirus genus. Rapid raise in urban population and poor public health infrastructures have led to significant increase in the number of dengue cases. A recent approximation indicates 390 million dengue infections per year, out of which around 96 per cent show clinical features[1]. Dengue virus infection can lead to a wide array of clinical symptoms. In its milder form, patients maybe asymptomatic or have undifferentiated viral illness. In severe cases it can lead to haemorrhage, circulatory collapse, and profound shock. Unlike other arboviral diseases, neurological complications due to dengue infection are rare. However, in recent years there has been a surge in neurological manifestation of the infection[2]. We describe two cases of dengue encephalitis to describe this rare presentation of a common disease.

Case report

Case 1

A 20-year-old student presented with high-grade fever and generalised headache of 5 days duration. One day before presentation to the hospital, the patient had an episode of generalised tonic-clonic seizure which lasted for 5 minutes. Since the episode of seizure, the patient had altered sensorium with reduced speech output. She also had diffuse arthralgia involving multiple joints. There was no history of seizures in the past. On examination, she was febrile (101° F), pulse rate of 66 beats per minute, and blood pressure 130/70 mm of Hg. Skin rash, oedema, abdominal distension, and icterus were absent. There was no evidence of cutaneous or mucosal bleeding. On CNS examination, neck stiffness was present and Brudzinski's sign was positive. She was conscious but confused and obeyed simple verbal commands. Speech output was reduced. There were no features suggestive of focal neurological loss. Rest of the systemic examination was unremarkable.

The patient's full blood count showed a low platelet count (69 x 10^9/l) with a haemoglobin of 13.6 g/dl and lymphopenia (WBC count of 2 x 10^9/l). Liver function tests were deranged, which showed elevated alanine aminotransferase (444 IU/L) and aspartate aminotransferase (263 IU/L). Renal function tests showed no abnormalities. Dengue NS1 antigen and anti-dengue IgM antibodies were positive in the serum. Peripheral

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smear and QBC for malaria were negative. Being endemic diseases and with similar presentation, leptospirosis and scrub typhus were ruled-out through appropriate tests. Blood cultures were sterile. MRI brain demonstrated symmetrical hyper-intensities involving bilateral thalami, bilateral posterior limb of internal capsules and periventricular white matter of bilateral occipital lobes with associated micro-haemorrhages within the bilateral thalamic lesions. It also showed subtle enhancement of leptomeningeal enhancement involving bilateral parietal lobes (Fig. 1, Fig. 2). Electroencephalogram done showed diffuse electrical dysfunction showing generalised low amplitude discharges which indicated encephalitis. CSF examination was deferred as the patient had thrombocytopenia.

The patient was managed conservatively with antipyretics and intravenous fluids. To prevent further seizures, the patient was started on levetiracetam twice daily. Patient responded well to the treatment and her sensorium started to improve completely by the seventh day, and platelet count rose to 150 x 10^9/l cells. She was discharged to home and is doing well on one and three-month follow-up without any neurological sequelae.

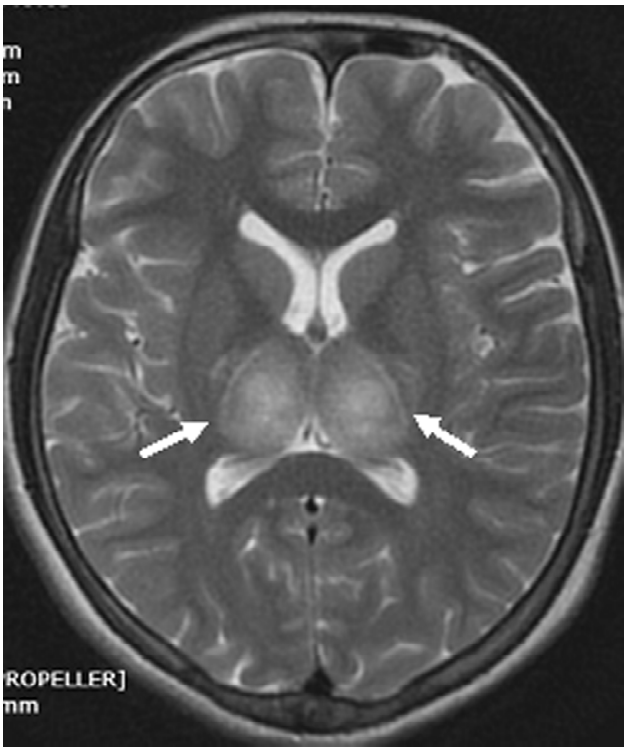


Fig. 1: *MRI T2 FLAIR sequence imaging of brain showing bilateral thalamic hyper-intensity (as pointed by white arrows).*

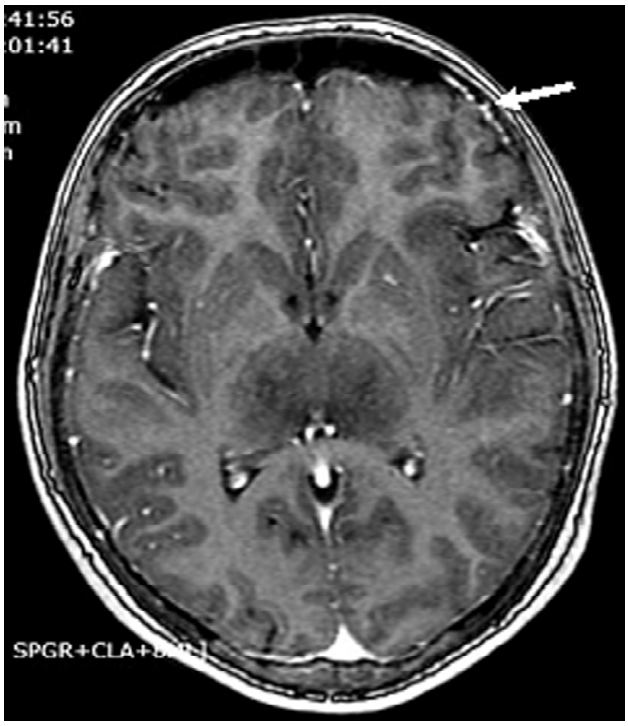


Fig. 2: *MRI T1 sequence imaging with contrast showing meningeal enhancement.*

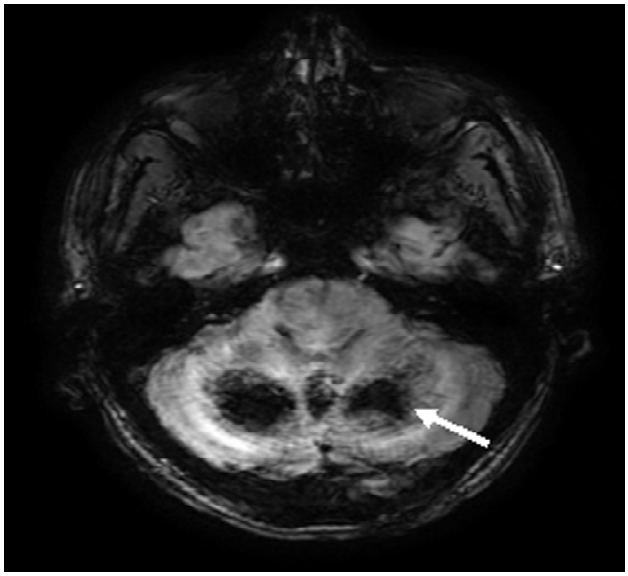
Case 2

A 28-year-old male presented with history of high-grade fever for 7 days and altered sensorium for 3 days. He had no other features suggesting involvement of any other organ system. On examination, he was unconscious, pupils were reactive bilaterally, and there was no neck rigidity. Babinski sign was positive and ankle clonus was seen. His blood pressure was 110/70 mm of Hg with pulse rate of 98 beats per min. His Glasgow Coma Scale (GCS) on admission was 4/15. Rest of the systemic examination was unremarkable.

Initial blood investigations revealed a haemoglobin of 20g/dl, platelets of 50 x 10^9/l and WBC count of 15 x 10^9/l. Electrolytes were deranged, and showed hypernatraemia (Na - 154 mmol/l). Liver function and renal function tests were within normal limits. QBC for malaria was negative. Dengue NS1 antigen and anti-dengue IgM antibodies were positive in the serum. Through appropriate tests, rickettsial infections and leptospirosis were ruled-out.

CT scan done on admission revealed hyper-densities in bilateral thalamic region and bilateral cerebellar hemispheres. MRI brain showed hyper-intensities in bilateral thalami and cerebellum as shown in Fig. 3 and 4. It also showed subarachnoid haemorrhage, diffuse cerebral

oedema, diffuse cerebellar oedema with tonsillar herniation. MRV revealed no cortical vein thrombosis. CSF examination deferred due to thrombocytopenia and features suggestive of elevated intracranial pressure.



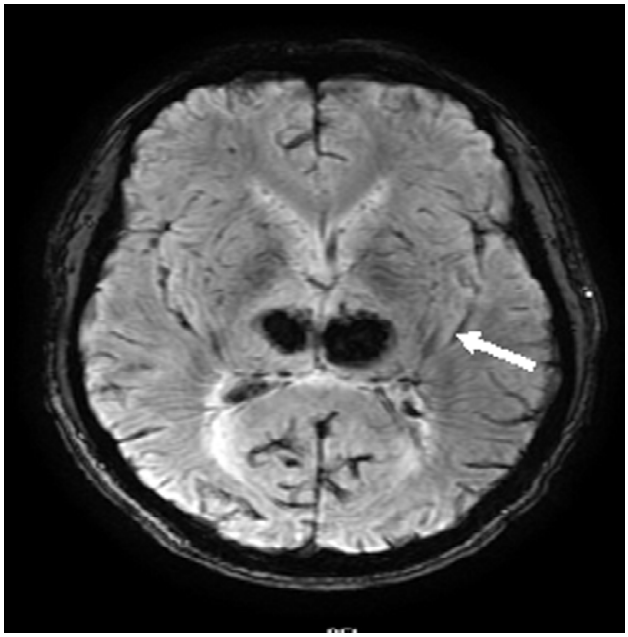


Fig. 3 and 4: *MRI 3D SWAN sequence showing haemorrhages in bilateral thalamus and cerebellum (pointed by white arrows).*

The patient was treated symptomatically with mannitol to reduce the intracranial pressure and levetiracetam to prevent seizures. Hypernatraemia improved with desmopressin. Despite improvement in sodium levels, the patient's sensorium failed to improve. In view of poor GCS score, the patient was intubated. In spite of the aggressive measures, the patient failed to recover and expired.

Discussion

Dengue viruses are arboviruses belonging to the genus flavivirus. There are four virus serotypes, which are named as DENV-1, DENV-2, DENV-3 and DENV-4. All four serotypes can cause clinical manifestations, which can range from simple dengue fever to severe dengue haemorrhagic fever[3]. Dengue fever usually presents with fever, headache, myalgia, arthralgia, maculopapular rash, leucopenia, and thrombocytopenia. Neurological features in dengue virus infection are uncommon[4].

In recent years, neurological complications of the disease have been increasingly reported. However, the exact incidence rates of neurological manifestation remain unanswered. In a large descriptive study on neurological manifestations of dengue fever by Kulkarni *et al,* the incidence of CNS involvement was 2.64% (154 out of 5,821 patients). Isolated encephalitis was seen in only in 25 out of 5,821 patients (0.4%)[5]. Pathogenesis of the neurological complications of the dengue virus infection is likely to be associated with metabolic alterations, direct invasion of the central nervous system by the virus, and autoimmune reactions. Based on the pathogenesis, CNS complications of the dengue infection can be categorised into[6,7]:-

1. Metabolic disturbances: which includes encephalopathy.
2. Viral invasion: which includes encephalitis, meningitis, myositis, myelitis.
3. Autoimmune disease: which includes Guillian Barre syndrome, optic neuritis, neuromyelitis optica, acute disseminated encephalomyelitis.

Dengue encephalopathy, is a rare but well-recognised entity. Amongst CNS manifestations due to dengue virus, encephalopathy due to metabolic disturbances are common. The possible mechanisms leading to encephalopathy are hepatic failure and shock leading to cerebral hypoperfusion, vascular leak leading to cerebral oedema, electrolytes derangement and intracranial bleeding secondary to low platelet count or coagulopathy. In others, encephalitis leads to encephalopathy. Various studies have demonstrated the ability of dengue virus to cause encephalitis through direct viral neurotropism. Soars *et al*, defined the dengue encephalitis as[8]:-

a. Fever.
b. Clinical features of acute cerebral involvement.
c. Presence of dengue NS1 antigen and/or anti-dengue

IgM antibodies in the serum and/or CSF.

d. Excluding other causes of viral encephalopathy and encephalitis.

Dengue encephalitis cases have been reported by Solomon *et al*, from Vietnam, who diagnosed nine dengue encephalitis cases. Misra *et al* described 11 cases of dengue encephalitis[9]. In similar case series, Kankirawatana *et al* described eight patients[3] and Kularatne *et al* described six patients with dengue encephalitis[10]. No classical clinical features of dengue encephalitis have been described. Common features from the case series studies described above are fever, headache, altered consciousness, and seizures. Out of nine cases described by Solomon *et al*, virus or antibody in CSF was demonstrated only in two patients[4]. Eleven cases described by Misra *et al*, were based on the serological tests and no CSF study was reported[9].

The imaging findings of the dengue encephalitis are variegated[5,11,12]. Imaging findings that are described in the literature include diffuse cerebral oedema, haemorrhages and focal abnormalities in the region of thalamus, globus pallidus, hippocampus and internal capsule. In the MRI, lesions are visualised as hyper-intensities. Lesions are usually localised. Extensive lesions caused due to dengue encephalitis have not been widely reported in the literature. Kamble *et al*, described a case of dengue encephalitis with extensive lesion, which involved bilateral thalami, posterior pons, and midbrain[12].

In the first case, on admission, the patient had history of fever, altered sensorium and generalised tonic-clonic seizures. Blood tests showed presence of dengue NS1 antigen and anti-dengue IgM antibodies. These features pointed towards the diagnosis of dengue encephalopathy. Biochemical parameters were not deranged enough to cause encephalopathy. Subsequent investigations with MRI showed features of encephalitis. Through other appropriate tests we ruled-out other causes of viral encephalitis. MRI brain showed extensive involvement of the brain parenchyma, which showed hyper-intensities in both thalamic, posterior limbs of internal capsules and periventricular region of bilateral occipital lobes. Haemorrhage was noted within the bilateral thalamic lesions.

In the second case, the patient had a history of fever and altered sensorium. CT scan on admission revealed extensive involvement of the brain parenchyma. Serology revealed rise in anti-dengue IgM antibodies and NS1 antigen positivity. Therefore, this case apropos to the case definition of dengue encephalitis. Lumbar puncture was avoided in the patient, as he had a low platelet count and clinical features suggestive of raised ICT. Prognosis in case of dengue encephalitis is often good as described in previous reports and case series. However, mortality may be seen in extensive disease as described above. Management is symptomatic and there is no proven therapy specific for dengue encephalitis. This case series highlights the not so common manifestation of dengue fever.

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