ABSTRACT

Dengue fever is a widely prevalent tropical infectious disease caused by an arbovirus. The disease has a wide spectrum of presentation ranging from mild febrile illness to life threatening manifestations in the form of Dengue Hemorrhagic Fever (DHF) & Dengue Shock Syndrome (DSS). DHF & DSS can lead to death due to shock secondary to hemorrhage and vascular leak, cerebral edema, cerebral hypoperfusion and multisystem organ dysfunction. [3] Dengue usually does not lead to neurological manifestations because dengue virus is a non-neurotropic virus. The incidence of neurological manifestations ranges from 1-5%. [10] Although very rare, the mechanisms by which Dengue virus can lead to neurological disorders include direct CNS viral invasion, metabolic disturbances, autoimmunity and hemorrhagic disorders. [2] Here we present a case of dengue fever leading to acute hemorrhagic leukoencephalitis.

INTRODUCTION

Dengue fever is a widely prevalent tropical infectious disease caused by an arbovirus. The disease has a wide spectrum of presentation ranging from mild febrile illness to life threatening manifestations in the form of Dengue Hemorrhagic Fever (DHF) & Dengue Shock Syndrome (DSS). DHF & DSS can lead to death due to shock secondary to hemorrhage and vascular leak, cerebral edema, cerebral hypoperfusion and multisystem organ dysfunction. [3] Dengue usually does not lead to neurological manifestations because dengue virus is a non-neurotropic virus. The incidence of neurological manifestations ranges from 1-5%. [10] Although very rare, the mechanisms by which Dengue virus can lead to neurological disorders include direct CNS viral invasion, metabolic disturbances, autoimmunity and hemorrhagic disorders. [2] Here we present a case of dengue fever leading to acute hemorrhagic leukoencephalitis.

CASE REPORT

A 23 year old male presented to the emergency department of Pt. B D Sharma Post graduation institute of medical sciences Rohtak Haryana state, India in September 2016 with history of fever and severe headache for four days. Fever was high grade associated with chills & rigors. There was no history of bleeding from any site or body rash. On examination, he was conscious, oriented to time, place & person. His vital parameters were stable. Neurological examination was essentially normal. Fundus examination was normal with no evidence of papilledema. Cardiovascular, respiratory and abdominal examination was normal. Laboratory investigations revealed blood hemoglobin of 15 g/dl, total leucocyte count of 5,000 cells/cumm, and platelet count of 90,000 cells/cumm. Liver and renal parameters were within normal limits. USG of the abdomen revealed mild bilateral pleural effusion and minimal free fluid in pelvis. Patient’s serum was positive for dengue NS1 antigen by ELISA thus confirming the etiology. Malaria antigen, IgM antibodies against leptospira and scrub typhus in serum were negative. Patient was conservatively managed with fluids and antipyretics. After two days, general condition of the patient started deteriorating. On examination, he was stuporous and developed neck rigidity. Bilateral plantar reflexes were extensor with exaggerated deep tendon reflexes. Repeat laboratory investigations revealed blood hemoglobin of 13.5 g/dl, total leucocyte count of 5,000 cells/cumm, and platelet count of 90,000 cells/cumm. Liver and renal parameters were within normal limits. USG of the abdomen revealed mild bilateral pleural effusion and minimal free fluid in pelvis. Patient’s serum was positive for dengue NS1 antigen by ELISA thus confirming the etiology. Malaria antigen, IgM antibodies against leptospira and scrub typhus in serum were negative. Patient was conservatively managed with fluids and antipyretics. After two days, general condition of the patient started deteriorating. On examination, he was stuporous and developed neck rigidity. Bilateral plantar reflexes were extensor with exaggerated deep tendon reflexes. Repeat laboratory investigations revealed blood haemoglobin of 13.5 g/dl, neutrophil count of 4,500 cells/cumm, and platelet count of 70,000 cells/cumm. There was no evidence of bleeding from any site and skin rash. Contrast enhanced computed tomography (CT) scan of the head showed bilateral symmetrical hyper densities involving thalamic region. Confluent periventricular white matter densities were seen in B/L fronto parieto occipital region. Cerebrospinal fluid (CSF) examination revealed mildly elevated protein with lymphocytosis and no red blood cells (RBC). Magnetic resonance imaging (MRI) was performed to confirm the diagnosis. Axial T2-weighted (T2W) images showed multiple altered signal intensity lesions showing hyperintensities in gray white matter junction, bilateral thalami and bilateral cerebellar hemispheres.(FIG 1) Axial Diffusion weighted imaging (DWI), Apparent diffusion coefficient (ADC) and Gradient echo (GRE) images at level of basal ganglia revealed diffusion restriction and blooming suggestive of hemorrhage within
the lesions. (Fig 2) Sagittal T2 W images revealed hyperintense lesions in thalami and cerebellum, in mid sagittal sections. (Fig 3)

MRI findings were suggestive of acute haemorrhagic leukoencephalitis. Diagnosis of dengue haemorrhagic encephalitis was confirmed by a positive dengue Polymerase Chain Reaction (PCR) in CSF. PCR in CSF was negative for Herpes and JE virus. Patient was started on intravenous methyl prednisolone. The patient’s general condition deteriorated and therefore was referred to a higher centre, where he expired after one day.

DISCUSSION

Dengue virus belongs to Flavivirus genus and is a single stranded RNA virus classified into four serotypes. [11] The vast majority of dengue infections are asymptomatic but a proportion manifest as nonspecific febrile illness or even severe disease. The spectrum of presentation of dengue fever ranges from classical flu like illness to dengue hemorrhagic fever and dengue shock syndrome. The characteristic presentation of dengue viral fever includes biphasic fever, headache, myalgias, joint and abdominal pain, rash, bleedings and lymphadenopathy. Being a non-neurotropic virus, it rarely leads to neurological disturbances. [9] Neurological manifestations although rare are commonly associated with serotypes 2 and 3. Direct tissue invasion by the virus, capillary hemorrhage, disseminated intravascular coagulation and increased vascular permeability are the various pathophysiological mechanisms. [6] Murthy has classified the spectrum of neurological manifestations of dengue fever into 3 categories. [8] First category includes manifestations like encephalitis, meningitis and myelitis which are related to neurotropic effect of the virus. Second category includes post infectious complications like encephalomyelitis, Acute Inflammatory Demyelinating Poly radiculoneuropathy (AIDP) & optic neuritis. Third category includes systemic complications like stroke, encephalopathy & delirium. The presence of dengue virus by PCR or positive serology in patient’s CSF with encephalitis suggests the possibility of direct cerebral invasion. Virus entry in brain can occur through infected macrophages, although the exact mechanism is not clear. Our patient was positive for Dengue NS 1 antigen in serum and dengue virus was detected in CSF by PCR.

Dengue encephalitis can present with headache, decreased level of consciousness and seizures. Our patient initially presented with complaints of headache and later on developed decreased consciousness level and had no classical rash or mucosal bleeding on presentation. The typical symptoms of dengue may present in only 50% of dengue encephalitis patients. [10] Hence clinicians should exercise high index of suspicion to diagnose this treatable entity. There are very few case reports of dengue encephalitis published in literature. Imaging plays a supportive role in confirming the diagnosis of encephalitis along with biochemical tests and clinical symptoms. MRI findings are diverse. Hemorrhages diffuse cerebral oedema, focal abnormalities involving the globus pallidus, the hippocampus, the thalamus and internal capsule can be found, the lesions are hyper-intense as visualized by MRI. [12] Involvement of hippocampus, temporal lobe, bilateral gangliocapsular location, pons, mid brain and spinal cord on MRI has been described in various case reports. [1] Most of the times MRI findings are nonspecific and therefore common etiologies of viral encephalitis like JE & herpes virus should be considered in differential diagnosis. [5]. CSF analysis is required to confirm the etiological virus because sometimes it becomes difficult to differentiate dengue haemorrhagic encephalitis from other viral etiologies solely on the basis of MRI findings. Although dengue can lead to intracerebral hemorrhage due to profound thrombocytopenia, hemorrhage due to infection itself is rarely reported. In our case although platelet count was low (70,000/cumm) but thrombocytopenia was not that profound to cause bleed and there was no sign of bleeding from any other site.

Treatment is mainly supportive for dengue encephalitis. There is no specific treatment for dengue or its neurological complications. The mortality in dengue infection generally is reported to be 3-5%. The mortality in patients who develop neurological complications ranges from 5-30% depending on the neurological disorder. Adequate oxygenation, hydration & nutrition are a part of general management. Mannitol & steroids may help in reducing raised intracranial pressure and anti-epileptic agents should be used to control seizures if present [7] There may also be a role for immunosuppression because there is a role of host immunity in increasing the severity of illness. Intravenous steroids and immunoglobulins (IVig) may have a role in the treatment of dengue encephalitis. There are no specific antiviral agents against dengue virus but studies have shown inhibition of viral replication in cell culture by agents like ribavirin and genetici. [4] These agents may play a successful role in treatment this fatal manifestation of dengue.

CONCLUSION

Dengue fever rarely presents as hemorrhagic leukoencephalitis, but it carries a serious prognosis. Neurological complications including hemorrhagic leukoencephalitis should always always be suspected in a patient presenting with fever & altered sensorium, especially in countries with warm climates in the Pacific-Asian region, the Americas Middle East and Africa where dengue is rampant. It has a high fatality rate, therefore early diagnosis and development of effective treatment should be given an utmost importance.
This study has not been funded by any external or internal agency or grant

Statement of Authorship
All authors have given approval to the final version submitted.

Conflict of Interest
All the authors have declared no conflict of interest to the work carried out in this paper.

Patient consent form has been procured prior to the case report study.
REFERENCES