Dengue Hemorrhagic Fever: A Rare Cause of Acute Liver Failure
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ABSTRACT
Acute liver failure (ALF) is an acute medical emergency which carries high mortality without liver transplantation. Various hepatotropic viruses, drug induced liver injury, autoimmune hepatitis, and metabolic liver diseases are the commonly implicated etiologic agents. Liver involvement in dengue hemorrhagic fever (DHF) is quite common, but acute liver failure is its rare complication. Neurological complications are also commonly seen in DHF. A teenage girl presented with high grade fever and subconjunctival hemorrhage, and later developed jaundice due to acute liver failure. Liver transplantation could not be offered due to fungemia. During hospital stay, she had seizures and intracranial hemorrhage culminating in brain death. ALF with neurological involvement is a rare but very important and fatal complication of DHF; and it should be considered as a cause of acute liver failure, especially in endemic areas.


INTRODUCTION
Acute liver failure (ALF) is a rare disorder manifested as coagulopathy, an International Normalized Ratio (INR) ≥1.5, jaundice and altered mentation (hepatic encephalopathy HE) in a patient, without having pre-existing liver disease within a period of <26 weeks.1 It commonly affects young adults, and carries a survival of less than 15%,2 without liver transplantation, as reported in most case series. One year survival in patients with acute liver failure, after liver transplantation, is more than 65%.3 The common etiological agents are hepatotropic viruses causing hepatitis, drug induced liver injury, ischemic hepatitis, autoimmune hepatitis, metabolic liver diseases, and few cases caused by dengue hemorrhagic fever (DHF) are also reported.3

Here, we are reporting a rare case of ALF caused by DHF with neurological involvement.

CASE REPORT
An 18-year girl presented with history of high grade fever recorded up to 104°F associated with headache and vomiting for the last four days. During hospital stay, she developed jaundice, coagulopathy and abdominal distension. On general physical examination, she appeared toxic, had icteric sclera, tachycardia, tachypnea and hepatic flaps were also present. On abdominal examination, she had hepatomegaly and shifting dullness was present while respiratory examination revealed decreased breath sounds in right lower zone. Abdominal ultrasound revealed hypoechoic texture of liver with moderate ascites; ascitic fluid analysis showed high protein and low serum albumin-ascitic gradient (SAAG), consistent with serositis due to DHF. Hematological investigations showed thrombocytopenia with normal TLC and hemoglobin. Renal function tests were normal. However, serum electrolytes revealed hyponatremia. She had deranged INR of 3.0 and LFTs showed reversal of transaminases ratio. Three consecutive blood cultures showed growth of Candida tropicalis. On serological testing for cause of ALF, viral serology for hepatitis A, B, C, D and E were negative. Autoimmune serology and workup for Wilson's disease were also inconclusive. Doppler ultrasound of liver was normal. Only Dengue IgM was found to be positive. Ascitic fluid acid fast bacillus polymerase chain reaction was also negative. Dynamic computerized tomography scan of abdomen was performed, which revealed findings of acute hepatitis with bilateral pleural effusion and moderate ascites. However, there was no evidence of Budd Chiari Syndrome (BCS), tuberculosis or malignancy.

For the management of ALF, she was given intravenous (IV) N-acetyl cysteine (NAC) in the dose of 150 mg/Kg in 200 mL of 5% dextrose water over 20 minutes then 50 mg/Kg in 500 L of 5% dextrose water over 4 hours then 100mg/Kg in 1000 mL of 5% dextrose water over 17 hours. She was managed with IV Amphotericin B for fungemia and Meropenum 1.0g 8-hourly for E.coli associated UTI along with IV l-ornithine-l-aspartate (LOLA).

Her clinical condition improved, encephalopathy resolved and coagulopathy improved, INR became normal from 5 to 1.3. She was stepped down to general ward from high dependency unit. On the 20th day of admission, she suddenly became hypertensive with agitated behavior and later on had generalized tonic clonic (GTC) seizures, associated with tongue bite and frothing from

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mouth. Fundoscopic examination was normal. Arterial blood gases (ABGs) analysis revealed hypoxia and hypocarbia. She was intubated and placed on mechanical ventilation. MRI brain revealed intraventricular hemorrhage. Glasgow Coma Scale (GCS) deteriorated, and she became unresponsive to pain and auditory stimuli. Brain death was declared on the basis of electroencephalography (EEG); and on family’s request, mechanical ventilation was stopped and death was declared.

**DISCUSSION**

Deranged liver function tests are commonly observed in dengue infection. Case fatality rate of DHF is around 3-5% in Asian countries. ALF by dengue virus, which is transmitted in human after female *aedes aegypti* mosquito bite, is a rare but fatal complication. Its exact incidence is unknown and is reported in small case series and case reports.

Management of ALF in patients having dengue infection is to identify if there is any underlying chronic liver disease. In this case, patient had presented with acute liver failure and there was no underlying pre-existing liver disease. Most of the common causes were excluded through laboratory investigations and imaging studies including viral, autoimmune hepatitis, Wilson’s disease and Budd Chiari syndrome. Liver transplantation is the definitive management for patients with ALF. This patient was a transplant candidate according to the King’s College criteria. However, the presence of concurrent fungal infection precluded possibility of transplantation. Some studies have also reported the beneficial role of IV NAC. It enhances oxygenation of various tissues by providing hemodynamic stability, which has a beneficial effect in the recovery of acutely damaged liver parenchyma.

Patient was administered IV NAC that mitigated both coagulopathy and HE. Increase in ammonia concentration is observed in HE and arterial ammonia level of more than 200 ug/dL is strongly associated with cerebral herniation. To avoid this fatal complication, lactulose is administered, which lowers down serum ammonia levels and helps in reducing cerebral edema, though a randomized trial had concluded that there is no improvement in grade of encephalopathy or overall survival.

This patient received both lactulose and IV LOLA and had improvement in the grade of encephalopathy from grade II HE to minimal encephalopathy within a week of treatment, and her liver functions showed improving trend.

DHF is also notorious for central nervous system involvement. Sohler et al. reported that CT scan and magnetic resonance imaging of brain can be normal in these patients, they can also have myositis, proximal muscle weakness, which can be mild to severe, and can involve respiratory muscles as well. Other central nervous system (CNS) signs and symptoms classically associated with dengue fever are headache, dizziness, mental irritability, altered sensorium, seizures and coma. These features can develop before or after hemorrhagic manifestation. Possible pathophysiology of CNS involvement in DHF is not clear; but it could be secondary to capillary leakage and is strongly associated with shock, electrolyte imbalance, liver failure and systemic inflammatory response syndrome (SIRS).

This patient also had neurological involvement and muscle weakness. She had proximal muscle weakness, was unable to stand and walk without support. After 20 days of hospital stay, she had aggressive attitude, irritable
behavior, and later on had GTC seizures, followed by deteriorating GCS and irreversible brain damage.

This case was of a young female with SIRS, resistant fungemia, multi-organ failure, and succumbed to complicated DHF. Important consideration should be given towards assessing the liver function tests, coagulation profile, lactate dehydrogenase enzyme (LDH) testing and neurological examination including signs of proximal myopathy for early identification and management of this potentially treatable infectious disease is of key importance. For parents, it is important to take their child to a tertiary care hospital whenever there is history of high grade fever for more than two days, to avoid pitfalls in management. These small steps, during management of such cases, would be helpful in reducing morbidity and mortality.

REFERENCES