Clinical and Laboratory Features of Severe Dengue Hepatitis (Liver Failure Mimics): Early Predictors of Fatality

Rajiv Mehta1*, Karsan Nandania2, Ketan Desai3, Anil Patel4 and Kiran Shah5

1Department of Gastroenterology, Smt. R. B. Shah Mahavir Super-Specialty Hospital and Surat Institute of Digestive Sciences (SIDS), India
2Department of Internal Medicine, Smt. R. B. Shah Mahavir Super-Specialty Hospital, India
3Department of Nephrology, Smt. R. B. Shah Mahavir Super-Specialty Hospital, India
4Department of Pulmonary Medicine, Smt. R. B. Shah Mahavir Super-Specialty Hospital, India
5Department of Hematology, Smt. R. B. Shah Mahavir Super-Specialty Hospital, India

Abstract

Objective: To determine early predictors of fatality among patients with severe dengue hepatitis based on clinical and laboratory findings.

Method: Forty-two patients who admitted to our hospital with the diagnosis of dengue fever (DF, diagnosed by either positive serology or positive PCR technique) and acute severe hepatitis (ALT≥10 times upper limit of normal) from March 2009 to July 2014 were included in the study. Various clinical and laboratory parameters of these patients on the day of admission were studied to identify early predictors of fatality.

Results: Forty-two patients (16 males, 26 females) were enrolled, out of which, twenty-six patients (62%) died. Univariate analysis showed that age less than 40 years (p=0.02), acute kidney injury (p=0.04), AST > 5000 IU/L (p = 0.03), LDH > 10000 IU/L (p < 0.001), Prothombin Time > 20 sec. (p = 0.04) were independently associated with mortality. Multivariate logistic regression analysis showed LDH > 10000 IU/L and AST > 5000 IU/L were associated with mortality.

Conclusion: Severe dengue hepatitis is associated with high mortality. A very high LDH and AST were early indicators of fatality.

ABBREVIATIONS
DF: Dengue Fever; DHF: Dengue Hemorrhagic Fever; DHS: Dengue Shock Syndrome; AST: Aspartate Aminotransferase; LDH: Lactate Dehydrogenase; CPK: Creatine Phosphokinase; AKI: Acute Kidney Injury

INTRODUCTION

Dengue viral infection is the most important arboviral infection transmitted by mosquito Aedes aegypti and Aedes albopictus. The Dengue viral infection has been recognized as one of the biggest emerging epidemic of the world [1,2]. As per estimates, over 50 million dengue infections with about 400,000 cases of dengue hemorrhagic fever (DHF) are reported annually worldwide, which is the leading cause of childhood mortality in several Asian countries [3]. The clinical spectrum of dengue infection ranges from asymptomatic infection to dengue fever (DF), DHF and dengue shock syndrome (DHS) [2,4]. Liver injury in dengue infection has been described since 1970 [5]. Transaminase elevation has been described in approximately 90% of patients with DF [6,7]. The studies also suggests that the levels of Aspartate Aminotransferase (AST) are usually higher than Alanine Aminotransferase (ALT). DF is a serious health problem in developing worlds but there is scarcity of literature about the severity and outcome of severe hepatitis in Dengue fever. Therefore we aim to assess the early predictors of fatality in severe dengue hepatitis.

METHODS

We included the patients admitted with severe dengue...
hepatitis in our hospital between March 2009 and July 2014 depending upon the inclusion and exclusion criteria. Diagnosis of dengue fever was made either by a positive NS1 antigen test or positive dengue IgM antibody test by ELISA method. The sensitivity of diagnosing acute dengue by NS1, antigen testing is 88.7% and specificity is 100% [8]. While sensitivity and specificity of IgM antibody test is 78% and 100% respectively [9]. Dengue PCR was performed in 10 patients mainly to confirm the serological assay. Severe Dengue hepatitis was defined as ALT > 10 times upper limit of normal [10,11].

Patients with 1) serologically positive Hepatitis A, B or E; 2) history of significant alcohol ingestion; 3) malaria; 4) leptospirosis and 5) H1N1 were excluded. We also excluded the patients with hypotension requiring vasopressor support at admission to minimize the bias of ischemic hepatitis reflected by rise in AST and LDH values. All patients underwent routine hematological testing like complete blood count and reticulocyte count, peripheral smear and malarial antigen assay for both plasmodium vivax and plasmodium falciparum. Baseline liver and renal function tests, arterial blood gas analysis, coagulation profile, plain radiograph of chest and various enzyme assay (Lactate Dehydrogenase, LDH; Creatine Phosphokinase, CPK; Amylase and Lipase) were also performed. Routine biochemical profile like complete blood count, renal profile, liver profile, Prothrombin time and LDH was performed daily till patient recovered or died.

Acute Kidney Injury (AKI) was defined as increase in serum creatinine level more than 1.5 mg/dl. Acute Lung injury was defined as acute onset hypoxaemia with PaO2/FI O2 < 40 with bilateral infiltrates on chest X-ray consistent with pulmonary edema and clinical absence of left atrial hypertension.

Primary outcome measure was mortality or clinical recovery from disease. Statistical analysis was performed using SPSS (Statistical Package for Social Science) Ver. 16.

RESULTS

A total of 42 patients with severe dengue hepatitis were included in the study. Among the enrolled patients, 62% were female. Mean age of the patients was 35±13 years. Mean duration of fever was 3±1 days. Out of 42 patients, 26 patients died with mortality rate of 62%. Tourniquet test was performed in all the patients.

The result of univariate analysis showed that age < 40 years was more common among fatal cases (85% v/s 25%, P = 0.02) while gender and duration of fever were similar between fatal and nonfatal cases (p > 0.05). Presence of AKI was more common in fatal cases (54% v/s 12.5 %, p = 0.04). However, ALI was similar in both cases (Table 1). Platelet count, serum bilirubin level and activated partial thromboplastin time (APTT) were similar between fatal and non-fatal cases. AST > 5000 IU/L, LDH > 10000 IU/L and Prothrombin time > 20 sec. were also more common in fatal group (p = 0.03, p < 0.001, p = 0.04 respectively). Only one patient with LDH > 10,000 IU/L at hospital admission survived. Average LDH level in non-fatal cases was 4750 IU/L (range: 2500 – 11328 IU/L) while it was 18750 IU/L (range 13500 – 75000 IU IU/L) in fatal cases. Other enzymes like CPK, Lipase and Amylase were similar in both cases. Encephalopathy was not a common feature even in fatal cases.

Upon multivariate logistic regression analysis (Table 2), AST > 5000 IU and LDH > 10000 IU were significantly associated with mortality in patients with severe dengue hepatitis (p = 0.004, P < 0.001, respectively).

DISCUSSION

Although liver injury due to dengue is known since 1970, there is scant literature of severe dengue hepatitis. Majority of previously published data show mild hepatitis in patients with DF [6,12]. But several cases of fulminant hepatitis with high mortality rate have been reported, mainly in children and young adults [13-15]. Dengue infection is endemic in the region where the hospital is located and our study is the first one to evaluate the early prediction of mortality in severe dengue hepatitis. Report from Pakistan [7] showed analysis of 103 patients with severe dengue hepatitis with mortality around 10.6%.

Mortality in our study was much higher than reported earlier.

| Table 1: Univariate analysis of various parameters in fatal and non-fatal cases of severe dengue hepatitis. |
|----------------------------------------------------------|------------------|------------------|------------------|
| Characteristic | Fatal cases (N=26) | Non-Fatal Cases (N=16) | p value |
| Age < 40 years | 22 (84.6%) | 04 (25%) | 0.02 |
| Gender (M: F) | 9:17 | 7:9 | NS |
| Platelet count (< 20,000/mm³) | 10 (38.4%) | 08 (50 %) | NS |
| Acute Kidney Injury (AKI) | 14 (54%) | 02 (12.5%) | 0.04 |
| Bilirubin (> 3 mg%) | 06 (23%) | 02 (12.5%) | NS |
| Alanine aminotransferase (ALT) level (> 1000) | 16 (61.5%) | 07 (43.7 %) | NS |
| Aspartate aminotransferase (AST) level (> 5000) | 21 (80.7 %) | 03 (18.7 %) | 0.03 |
| Lactate dehydrogenase (LDH) level (> 10000 IU) | 26 (100%) | 01 (6%) | <0.001 |
| Prothrombin time (> 20 sec.) | 14 (53.8%) | 02 (12.5%) | 0.04 |
| Activated partial thromboplastin time (APTT) (>60 sec.) | 15 (57.6%) | 05 (31.2%) | NS |
| Acute lung injury (ALI) | 16 (61.5%) | 4 (25%) | NS |
| Encephalopathy | 04 (15%) | 01 (6%) | NS |
Central are early predictors of fatality among dengue patients. Very high AST and LDH on presentation indicate younger the patient more enhanced immune response. In our study, mortality was higher in patients with age < 40 years, we had excluded all other possible causes of acute hepatitis. In disproportionate to ALT and very high LDH level suggest more of liver failure which lead to mortality or it is cytokine storm which unanswered questions in present study, i.e. whether it is true liver failure (“liver failure mimics”), while very high AST and mild elevation of prothrombin time in fatal cases indicates death of the patient [19]. Low incidence of encephalopathy and mast cells produce large amounts of cytokines. There are few [16,17].

Chaturvedi et al [18] showed that monocytes, B cells, T cells and mast cells produce large amounts of cytokines. There are few unanswered questions in present study, i.e. whether it is true liver failure which lead to mortality or it is cytokine storm which causes death of the patient [19]. Low incidence of encephalopathy and mild elevation of prothrombin time in fatal cases indicates not a true liver failure (“liver failure mimics”), while very high AST disproportionate to ALT and very high LDH level suggest more of immune mediated injury like cytokine storm. In present study, we had excluded all other possible causes of acute hepatitis. In our study, mortality was higher in patients with age < 40 years, indicates younger the patient more enhanced immune response.

The main limitation of this study includes:
1. Unable to perform liver biopsy to evaluate histology on course of illness.
2. Unable to check for the type of dengue virus.

We concluded that severe dengue hepatitis carries very high mortality. Young age, very high AST and high LDH on presentation are early predictors of fatality among dengue patients.

REFERENCES
