

Original Article

Severity of hepatitis & it's correlation with dengue hemorrhagic fever: Experience from a tertiary care hospital.

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Abstract:

Background: Dengue fever and dengue hemorrhagic fever is one of the most frequent febrile viral infections in our community as well as among patients admitted in Internal Medicine Department. This study examined the extent of hepatic involvement in dengue hemorrhagic fever

Objectives: To evaluate the incidence of hepatic involvement and its correlation in dengue syndromes.

Design: This Cross-sectional observational study done in Internal Medicine Department of BIRDEM General Hospital.

Method: A total 50 patients were included in this study who was serologically positive dengue fever patients (IgM ± IgG). These patients were admitted to Internal Medicine Department of BIRDEM General Hospital from July, 2011 to December 2011. Hepatic transaminases (AST and ALT) of these patients were measured and correlation was seen by standard methods. Informed written consent was taken from patients.

Results: Total number of patients was 50; their mean age was 45.98±18.37 years. Male: Female ratio was 1:1.85. Common co-morbidities were DM (48%) and hypertension (26%), CKD (8%) and bronchial asthma (6%). Among the 50 patients 23 had CD (Classical Dengue), 20 had DHF (Dengue Hemorrhagic Fever) grade 1, six had DHF grade 2 and one had DHF grade 3. Mean AST among CD and Grade 1, 2, 3 DHF were 58.48±8.99, 96.65±9.06, 217±31.82, 296.00 respectively. Mean ALT among CD and grade 1, 2, 3 DHF were 52.39±9.08, 88.10±13.14, 181.67±12.11 respectively. There was significant difference between AST (P value <0.001) and ALT (P value <0.001) in each group of patients. It was observed that rise of AST and ALT was significantly higher in grade 1, 2 and 3 when compared with CD. AST and ALT was higher in grade 2 then grade 1 DHF patients.

Conclusion: Rise of hepatic transaminases is common in patients with dengue syndromes. There is significant rise in AST then ALT. The rising pattern of these enzymes correlates with severity of dengue syndromes.

Keywords: Dengue hemorrhagic fever; hepatic transaminases

Introduction

Dengue is an acute infectious disease caused by an arbovirus of the flavivirus genus, and is transmitted by the female of the mosquitoes *Aedes aegypti*, *A. albopictus*, *A. scutellaris* and *A. polynesiensis*. It causes 4 spectra of illness which are an asymptomatic phase, acute febrile illness, Dengue fever (DF) which is also known as Classical Dengue (CD), Dengue Haemorrhagic Fever (DHF) which includes Dengue Shock Syndrome (DSS)¹. Dengue has been recognized as one of the world's biggest emerging epidemic². The classical form of

dengue is an acute and self-limited disease characterized by fever, prostration, headache, retro-orbital pain, myalgia, nausea, vomiting, skin rash, leucopenia and thrombocytopenia¹. Although DF can be quite debilitating, unlike dengue Hemorrhagic Fever (DHF) its outcome is seldom fatal³. The Hemorrhagic fever or Shock Syndrome is the severe variety, which could be fatal⁴. The patient suffers from high fever, bleeding from the nose, ears, gums and the skin and enters a state of shock due to blood loss. Most often death becomes inevitable and occurs within 24 hours, especially among children⁵. The major pathophysiological hallmark that determines disease severity and distinguishes DHF from DF is plasma leakage due to an increase in vascular permeability. Hypovolemic shock occurs subsequent to critical plasma loss and if accompanied by massive bleeding confers a grave prognosis⁶. Unusual clinical manifestations of dengue fever have become more common in last few years⁷. Although the liver is not a major target organ, pathological findings including centrilobular necrosis, fatty liver, kupffer's cell hyperplasia, acidophilic bodies, and monocyte infiltration at the portal tract have been reported in patients with DHF or Dengue Shock Syndrome (DSS)⁸. With such involvement, it would be expected that results of liver function tests would be abnormal. Liver involvement in dengue fever is manifested by the elevation of transaminases representing reactive hepatitis. In most cases hepatic involvement prolongs the clinical

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course of this self-limiting viral infection but it does not constitute a sign of worse prognosis. However, there have been reports of fulminant hepatitis with high mortality in patients with dengue infection⁹. Elevated transaminases in DF are due to many conditions like direct attack of virus itself and use of hepatotoxic drugs causing these unusual clinical manifestations. These in turn lead to more serious fate among the dengue patients^{10, 11}. In the Liver Function Tests (LFT) most common abnormality seen is elevated transaminases which are involved in amino acid metabolism. DF initiates the inflammatory responses leading to liver parenchymal changes and causing release of transaminases in circulation¹². Since DF is an emerging infection in Bangladesh and little is known about the severity of hepatitis and their outcome in patients with dengue fever. Therefore the aim of this study is to see the severity of hepatitis with different grades of DHF and to see their outcome. The purpose is to elaborate our knowledge about dengue, especially to see the nature & extent of hepatic involvement in dengue, both clinically & biochemically & also to see the outcome, so that it can enrich our knowledge & help us in diagnosis & effective management of dengue and follow up of these patients.

Materials and Method:

This cross sectional observational study on 50 patients was carried out in the Department of Internal Medicine of BIRDEM General Hospital from 1st July to 31st December 2011. All adult patients admitted in Department of Internal Medicine with fever for less than 7 days, serologically positive for dengue antibody (IgM ± IgG) were included in this study. Patient with fever for more than 7 days, having convincing evidence of fever for other causes and serologically negative for dengue (IgM negative) antibody were excluded.

Dengue fever is classified into Classical Dengue (CD) and DHF. CD is suggested by sudden onset of continuous fever with two or more of severe headache, retro-orbital pain, myalgia/arthritis/backpain, hemorrhagic manifestations, nausea/vomiting/ abdominal pain, leucopenia and high index of suspicion based on time period, population & place with absence of convincing evidence of any other febrile illness. DHF is classified into grade 1, 2, 3, and 4. Grade 1 DHF is diagnosed by all features of CD with positive tourniquet test and laboratory features of thrombocytopenia (<100,000/mm³) & hematocrit rise ≥20%. DHF grade 2 comprises similar laboratory findings with spontaneous bleeding. DHF grade 3 comprises features of CD with circulatory failure & similar laboratory findings. There is also DHF Grade 4 which is characterized by all features of CD & profound shock.

Informed written consent was obtained from all the patients. Collected data were checked every day carefully to identify any errors. A semi-structured case record form was prepared after pre-testing containing patient's profile. After data collection it was checked for omission, inadequacy,

irrelevancy and inconsistency. Omission was corrected by retaking history or re-examining the patient. Irrelevant and inconsistent data were discarded.

For analysis, Statistical Package for Social Sciences (SPSS) software was used for calculation of percentage resistance within 95% confidence interval (CI). Statistical analysis was done by Paired sample t-test. Level of significance was considered as p value less than 0.05. Ethical approval was taken from the Institutional Review Board (IRB), BIRDEM General Hospital prior to the commencement of the study.

Result:

There were 50 patients in our study group. Among them 23 (46%) were males and 27 (54%) were females. Male: female was 1:1.85. Their mean age was 45.98±18.37 years. Table 1 shows age distribution of the study subjects. Table 2 is shows distribution of the study subjects according to co-morbid conditions. Few patients had multiple co-morbidities. Table 3 shows distribution of the study subjects according to important examination findings. General physical examination revealed dehydration, anemia, skin rash & jaundice were present in 21 (42%), 6 (12%), 33 (66%), and 2 (2%) patients respectively. Table 4 shows important vital signs of the patients like pulse and blood pressure on different days after admission. It also showed that the difference between pulse and blood pressure on day 1 and day 3 were insignificant but there was significant difference between pulse & blood pressure on the day 1 and day 5 after hospital admission. Table 5 shows comparison among platelet count of different days after hospital admission.

Comparison among average pulse at different days after hospital admission is shown in Fig 1. Comparison among average systolic and diastolic blood pressures of different days after hospital admission is shown in Fig 2 & 3 respectively.

The trend of change in platelet count is shown in Fig: 4.

There was significant difference between AST (Aspartate Amino transferase) and ALT (Alanine Aminotransferase) in different groups of dengue patients as shown in Table-6. It was also observed that rise of AST and ALT was significantly higher in grade 1, 2 and 3 when compared with CD and AST and ALT was significantly higher in grade 2 then grade 1 (Table-6, Fig-5).

Mean AST and ALT among diabetic and non-diabetic dengue patients were also observed which was found to be insignificant as shown in Table-7. Serum albumin was significantly low in grade 3 DHF when compared to CD or grade 1 or 2 of DHF (Fig-6). Evidence of serositis was also much more common in grade 1, 2 and 3 than CD, shown in Fig- 7. Mean hospital stay among DHF grade 1 and 2 was equal but lower in CD and much higher in DHF grade 3 (Fig-8).

Table-1: (N=50)

Age group	Frequency	Percent
≤ 30	12	24.0
31-40	9	18.0
41-50	10	20.0
51-60	7	14.0
61-70	9	18.0
> 70	3	6.0
Total	50	100.0
Mean ± SD	45.98±18.37	

Table-2: (N=50)

Co-morbid condition	Frequency	Percent
DM	24	48.0
Hypertension	13	26.0
CKD	4	8.0
Bronchial asthma	3	6.0
No other co morbidities	23	46.0

Table-3: (N=50)

General examination findings	Frequency	Percent
Dehydration	21	42.0%
Anaemia	6	12.0%
Skin rash	33	66.0%
Jaundice	2	2.0%

Table – 4 (N=50)

Day	Pulse (Mean±SD)	SBP (Mean±SD)	DBP (Mean±SD)
Day 1	82.00±8.21	112.20±16.69	73.00±10.69
Day 3	80.18±5.79	111.70±12.99	73.80±8.72
Day 5	94.78±3.46	101.20±10.03	67.20±6.16
P value of Day 1 vs Day 3	0.13	0.81	0.60
P value of Day 1 vs Day 5	<0.001	<0.001	<0.001

SBP=Systolic blood pressure; DBP=Diastolic blood pressure

Table-5 (N=50)

Day	Platelet count (Mean±SD)
Day 1	110676.00±131942.25
Day 3	93727.00±112374.42
Day 5	98947.00±142714.24
P value of Day 1 vs Day 3	0.47
P value of Day 1 vs Day 5	0.66

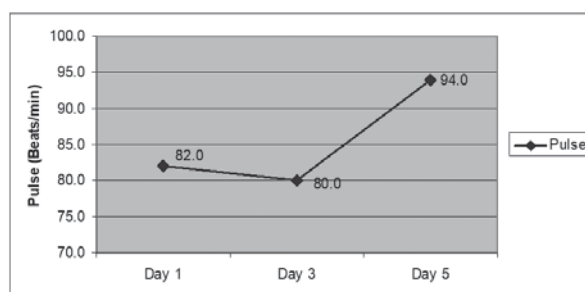


Fig: 1

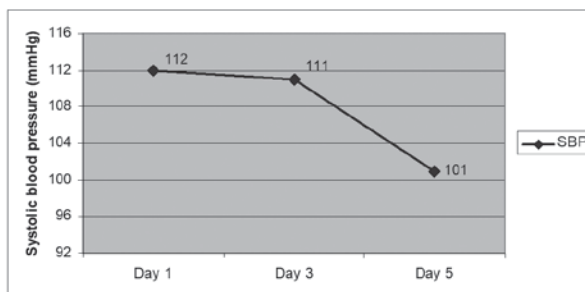


Fig: 2

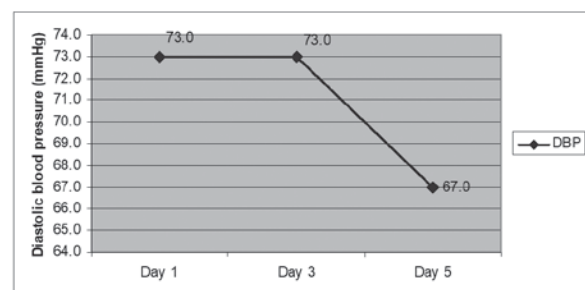


Fig: 3

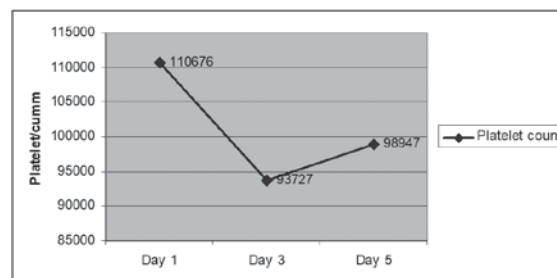


Fig: 4

Table-6 (N=50)

DF Grade	Number of patients	AST (U/L) (Mean±SD)	ALT (U/L) (Mean±SD)
CD	23	58.48±8.99	52.39±9.08
Grade-I	20	96.65±9.06	88.10±13.146
Grade-II	6	217.17±31.82	181.67±12.11
Grade-III	1	296.00	230.00
P value of CD vs Grade-I		< 0.001	< 0.001
P value of CD vs Grade-II		< 0.001	< 0.001
P value of Grade-I vs Grade-II		< 0.001	<0.001

Table-7 (N=50)

	Number of patients	AST (U/L) (Mean±SD)	ALT (U/L) (Mean±SD)
Diabetic	24	100.04±62.81	89.75±53.68
Non-Diabetic	26	95.23±55.76	82.04±40.25
P value of Diabetic vs Non Diabetic		0.77	0.56

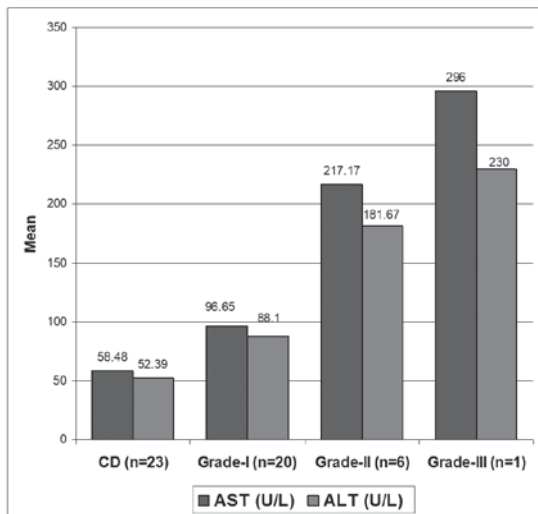


Figure-5

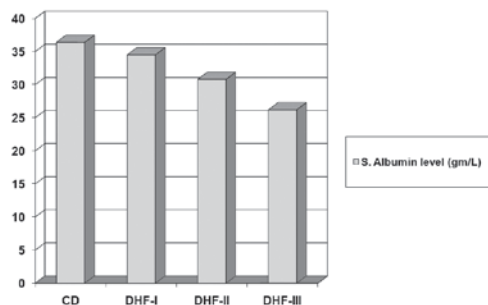


Figure-6

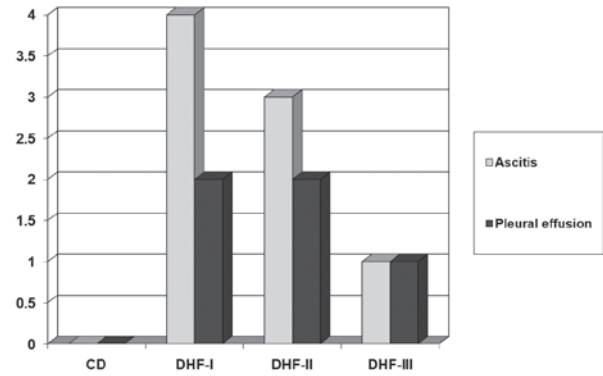


Figure-7

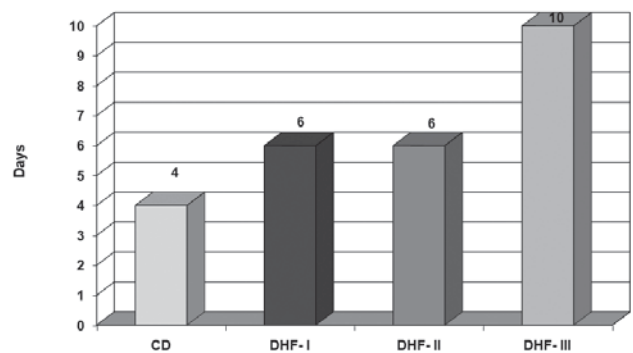


Figure-8 (hospital stay)

Discussion:

This study was done to evaluate hepatic involvement in patients with dengue syndrome in BIRDEM General Hospital. Mean age of the study population was 45±18.37 years. 29 (58%) patients were between 41- 70 years of age. So among the study population this is the predominant age group. Mean age of study population of similar type of study held in Pakistan was 31.87± 13.55¹³. Whereas in similar type of study done in Malaysia most of the study patients were 21- 40 years of age⁹. In similar type of study done in Punjab, India the mean age was 31.6 years, which is almost similar to our study¹⁴. Of the total 50 patient male were 23 (46%) and female were 27 (54%). Male female ratio was 1:1.85. In similar study done in Pakistan male was 65% and female was 35%¹³. In similar type of study held in Malaysia the ratio of male: female was 1.63:1⁹. In Punjab study the ratio was 3.3:1¹⁴.

In Thailand a prospective study showed severity of hepatitis was associated with development of encephalopathy in children aged 4 months to 15 years¹⁵.

Type of fever was classified as CD and DHF (grade 1, 2, 3 and 4). No patient was found in grade 4 possibly due to early therapeutic intervention. In Punjab study grade 4 DHF patients were 11 (5.1%)¹⁴. In Pakistan study 2% patient had DHF grade 4¹³.

Mean AST and ALT of CD, DHF grade 1, 2, 3 were estimated and it showed mean AST was significantly higher than mean ALT among these groups. In Pakistan study it was seen that AST rises more than ALT in dengue patients with increasing disease severity¹³. Similar observation was seen in different studies done in Punjab¹⁴, and Malaysia⁹. Mean AST and ALT between diabetic and non-diabetic DF patients were also compared which was found to be insignificant.

Serum albumin was found to be very low in DHF grade-3. Similar observations were also seen in study done in Punjab, India¹⁴. Study done in Malaysia showed their study population didn't have significant change in serum albumin level in DHF patients⁹.

Evidence of serositis like ascites and pleural effusion was more with increasing severity of dengue syndromes. Mean length of hospital stay was increased with increasing severity of dengue syndromes. Similar observation was seen in study at Pakistan, where mean length of hospital stay was 3.88 ± 2.7 days¹³.

Limitations:

The present study had the following limitations. The number of total study subjects were small. Whether the rise of hepatic transaminases is due to dengue fever or concomitant other cause was not evaluated. Only one center was involved in this study. Multiple centers would give more credible results.

Conclusion:

Rise of hepatic transaminases is common in patients with dengue syndromes. The rising pattern of these enzymes correlates with severity of dengue syndromes. Comparison of AST and ALT levels between diabetic and non-diabetic dengue patients showed insignificant difference. Mean serum albumin level was decreasing with increase in severity of dengue syndromes. Evidence of serositis was more with increasing severity of dengue syndromes. Length of hospital stay was increasing with severity of dengue syndromes. The findings of this study is expected to help clinicians to correlate severity of dengue fever with severity of hepatic involvement.

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