

Original Research Article

Evaluation of hepatocellular dysfunction and its association with severity in dengue patients

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ABSTRACT

Background: Dengue is a mosquito-borne infection that in recent years has become an important disease of international public health concern. Dengue virus infections and illness when symptomatic, that patients tend to present with a significantly wide variety manifestations. The aim of the study was to evaluate liver dysfunction in patients with dengue infections.

Methods: The present study was undertaken as an observational cross-sectional study the period June 2017 to December 2018. The details of all patients with serologically proved dengue fever admitted in the hospital were reviewed. Data including routine blood count, liver function test (LFT), prothrombin time (PT), activated partial prothrombin time (APTT), abdominal ultrasonography was studied. Statistical analysis: Data was analyzed using SPSS version 21.0. Difference between proportions was tested by using chi square test. Pearson correlation coefficient was used to measure linear correlation between two continuous variables. A p value <0.05 was considered statistically significant.

Results: Majority of the study participants were in the age group of 16-30 years (57.5%) and were males (64.5%). Fever, Headache and joint pain were the most common symptoms noted among the study participants. Majority of the study participants were found to have elevated levels of SGOT (75.3%), SGPT (64.2%) levels and lower levels of serum albumin (68.6%) on evaluation. Statistically significant association was observed between elevated liver enzymes and presence of features of dengue haemorrhagic fever.

Conclusions: Considerably high proportion of patients with dengue infection were found to have hepatic dysfunction in the form of deranged liver enzymes.

Keywords: Dengue, Liver dysfunction, Serum glutamic oxaloacetic transaminase, Serum glutamic pyruvic transaminase

INTRODUCTION

Dengue is a mosquito-borne infection that in recent years has become an important disease of international public health concern. Dengue is also the most prevalent mosquito-borne viral disease and it is estimated that over 50 million dengue virus infections occur each year

throughout the world.¹ In India epidemics of dengue infections

are observed to be occurring in cyclical trend and also the epidemics occurs more frequently, expanding into the rural areas. The clinical spectrum of dengue infection presents from a subclinical infection or mild flu like illness to a severe form of hemorrhagic fever which may

even become fatal. Dengue virus infections and illness when symptomatic, that patients tend to present with a significantly wide variety manifestations, from asymptomatic illness to a life-threatening illness viz dengue shock syndrome.^{2,3} Dengue illness among the population is usually classified into dengue fever (DF), a self-limited febrile illness, or a more severe form, dengue hemorrhagic fever (DHF), where the later presents by plasma leakage into the chest, abdominal cavities and bleeding diathesis.

However, it was also established that hypotension as a consequence of plasma leakage usually presents during 48 after the defervescence period, though onset, course and anatomic pattern of plasma leakage resulting to shock and circulatory deficit have not been studied in detail.⁴⁻⁹ It is noted that elevations of serum aminotransferases that are usually mild are common in dengue virus infections.¹⁰ Hepatocellular necrosis and councilman bodies with relatively little inflammatory cell infiltration are some of the typical pathologic findings in the livers of fatal cases of dengue, similar to the findings noted in yellow fever.¹¹ It is also suggested that liver injury is directly mediated by dengue virus infection of hepatocytes and Kupffer cells and in in-vitro research works dengue virus has been shown to infect and induce apoptosis in a human hepatoma cell.¹² Immune mediated injury of hepatocyte injury is also considered as a potential alternative mechanism of liver changes.¹³ The present study was carried out with an aim to evaluate liver dysfunction in patients with dengue infections.^{2,3}

METHODS

The aims and objectives of this study was to evaluate liver dysfunction in patients with dengue infections. To access the frequency and degree of hepatobiliary dysfunction in adult patients with dengue infection presenting to a tertiary care medical facility. The study was carried out in the Department of General Medicine, Mahatma Gandhi Medical College Hospital and research Centre, Pondicherry, South India. The hospital is located in the south eastern coast of India, in Pondicherry, a Union territory. The hospital caters to a population comprising of approximately six neighboring districts of in Tamil Nadu and Pondicherry. The present study was undertaken as an observational cross-sectional study during the period June 2017 to December 2018 among all Dengue patients admitted in the hospital during the study period. The final study sample consisted of 299 patients.

Inclusion criteria

- Inclusion criteria comprised of age ≥ 14 years, known clinically as well serologically proved (demonstration of dengue virus antigen in serum sample by NS1-card test for patients with history of fever for < 5 days or dengue-specific IgM by card test for patients with history of fever ≥ 5 days) cases of DF or DHF and dengue shock syndrome (DSS).

Exclusion criteria

Previously known or newly detected patients of chronic liver disease of any etiology (as evident by the clinico-radiologic and biochemical parameters), patients with known recent history of intake of any hepatotoxic or similar drugs causing derangements of liver functions, patients having other known infections causing hepatitis such as viral hepatitis A and E, leptospirosis, falciparum malaria, etc., patients with altered liver functions secondary to sepsis or as a part of multiple organ dysfunction syndrome (MODS) unrelated to dengue infection, diabetic and hypothyroid patients with nonalcoholic fatty liver disease (NAFLD).

Non-alcoholic steatohepatitis (NASH) were excluded from the study.

The details of all patients with serologically proved dengue fever admitted to MGMCRI a tertiary care hospital was prospectively reviewed.

Data including routine blood count, liver function test (LFT), prothrombin time (PT), activated partial prothrombin time (APTT), abdominal ultrasonography were collected. Institutional human ethics committee clearance was sought and obtained before the study was begun. Informed written consent was obtained from all the participants in their own language before including them in the study.

Statistically analysis

Data was entered in MS Excel 2013 and analyzed using SPSS version 21.0. Descriptive statistics was depicted in the form of proportions and means with standard deviation. Difference between proportions was tested by using chi square test. Pearson correlation coefficient was used to measure linear correlation between two continuous variables. A p value < 0.05 was considered statistically significant.

RESULTS

Majority of the study participants were in the age group of 16-30 years (57.5%). The mean age of the study participants was observed to be 28.37 ± 13.5 years. Majority of the study participants were males (64.5%), while 35.5% of them were females (Table 1).

On testing with NS1 Ag most of the study participants (78.9%) were found to be positive on evaluation whereas only 21.1% showed positive for IgM antibody tests. Authors have also found that most of the study participants (81.6%) required platelet transfusion during management due to marked thrombocytopenia. Only 2.7% of all study participants were found to have elevated levels of total bilirubin on evaluation. But most of the study participants (75.3%) and (64.2%) were found

to have elevated levels of SGOT and SGPT respectively on evaluation.

Table 1: Distribution of study participants based on demographic characteristics (n=299).

Age (in years)	Frequency	Percentage
<15	32	10.7
16-30	172	57.5
31-45	63	21.1
46-60	20	6.7
>60	12	4.0
Gender		
Male	193	64.5
Female	106	35.5
Comorbidity		
Diabetes	22	7.4
Hypertension	13	4.3
Smoking	37	12.4
Alcoholism	25	8.4

Table 2: Distribution of study participants based on clinical presentation (n=299).

	Frequency	Percentage
Requirement of platelet transfusion	244	81.6
Requirement of ICU management	242	80.9
Positive for NS1Ag	236	78.9
Positive for IgM	63	21.1
Elevated total bilirubin	8	2.7
Elevated SGPT	225	75.3
Elevated SGOT	192	64.2
Low serum albumin	94	31.4
Serum globulin		
Low	5	1.7
Elevated	21	7.0
Total	299	100.0

Table 3: Association between SGOT and patient characteristics (n = 299).

	SGOT		Total N (%)	p value*
Age (in years)	Normal N (%)	Elevated N (%)		
<15	7 (21.9)	25 (78.1)	32 (100.0)	0.925
16-30	44 (25.6)	128 (74.4)	172 (100.0)	
31-45	14 (22.2)	49 (77.8)	63 (100.0)	
46-60	5 (25.0)	15 (75.0)	20 (100.0)	
>60	4 (33.3)	8 (66.7)	12 (100.0)	
Gender				
Male	41 (21.2)	152 (78.8)	193 (100.0)	0.058
Female	33 (31.1)	73 (68.9)	106 (100.0)	
Malena				
Present	5 (8.1)	57 (91.9)	62 (100.0)	0.001
Absent	69 (29.1)	168 (70.9)	237 (100.0)	
Sub conjunctival haemorrhage				
Present	9 (12.9)	61 (87.1)	70 (100.0)	0.008
Absent	65 (28.4)	164 (71.6)	229 (100.0)	
Bleeding gums				
Present	4 (9.3)	39 (90.7)	43 (100.0)	0.011
Absent	70 (27.3)	186 (72.7)	256 (100.0)	
Petechiae				
Present	7 (10.0)	63 (90.0)	70 (100.0)	0.001
Absent	67 (29.3)	162 (70.7)	229 (100.0)	
Pleural effusion				
Present	20 (12.9)	135 (87.1)	155 (100.0)	<0.001
Absent	54 (37.5)	90 (62.5)	144 (100.0)	
Ascites				
Present	20 (12.8)	136 (87.2)	156 (100.0)	<0.001
Absent	54 (37.8)	89 (62.2)	143 (100.0)	
Dengue testing				
NS1Ag positive	50 (21.2)	186 (78.8)	236 (100.0)	0.006
IgM positive	24 (38.1)	39 (61.9)	63 (100.0)	

* Chi square test was applied to test statistical difference in proportions

Table 4: Association between SGPT and patient characteristics (n = 299).

Age (in years)	SGPT		Total N (%)	P value*
	Normal N (%)	Elevated N (%)		
<15	10(31.3)	22(68.8)	32(100.0)	0.419
16-30	60(34.9)	112(65.1)	172(100.0)	
31-45	21(33.3)	42(66.7)	63(100.0)	
46-60	9(45.0)	11(55.0)	20(100.0)	
>60	7(58.3)	5(41.7)	12(100.0)	
Gender				
Male	65(63.7)	128(66.3)	193(100.0)	0.305
Female	42(39.6)	64(60.4)	106(100.0)	
Malena				
Present	15(24.2)	47(75.8)	62(100.0)	0.032
Absent	92(38.8)	145(61.2)	237(100.0)	
Sub conjunctival haemorrhage				
Present	17(24.3)	53(75.7)	70(100.0)	0.022
Absent	90(39.3)	139(60.7)	229(100.0)	
Bleeding gums				
Present	13(30.2)	30(69.8)	43(100.0)	0.412
Absent	94(36.7)	162(63.3)	256(100.0)	
Petechiae				
Present	18(25.7)	52(74.3)	70(100.0)	0.045
Absent	89(38.9)	140(61.1)	229(100.0)	
Pleural effusion				
Present	44(28.4)	111(71.6)	155(100.0)	0.006
Absent	63(43.8)	81(56.3)	144(100.0)	
Ascites				
Present	44(28.2)	112(71.8)	156(100.0)	0.004
Absent	63(44.1)	80(55.9)	143(100.0)	
Dengue testing				
NS1Ag positive	80(33.9)	156(66.1)	236(100.0)	0.188
IgM positive	27(42.9)	36(57.1)	63(100.0)	

In present study SGOT was increased in 91.1% of patients with malena compared to 70.9% of patients without malena with $p=0.001$. SGOT was raised in 87.1% of patients with subconjunctival hemorrhage compared to 71.6% of patients without conjunctival hemorrhage with $p=0.008$. SGOT was raised in 90.7% of patients with bleeding gums compared to 72.7% of patients without bleeding gums with $p=0.011$. 90.0% of patients with petechiae had elevated SGOT compared to 70.7% of patients without petechiae with $p=0.001$. SGOT was raised in 87.1% of patients with pleural effusion and 87.2% of patients with ascites compared to patients without pleural effusion (62.5%) and patients without ascites (62.2%) respectively with $p<0.001$. 78.8% NS1Ag positive patients had raised SGOT compared to 61.9% of IgM positive dengue patients with $p=0.006$ (Table 3).

In present study authors found that SGPT was elevated in 66.3% of male patients compared to 60.4% of female patients with $p=0.305$. SGPT was elevated in 75.8% of patients with malena compared to 61.2% of patients

without malena with $p=0.032$. 75.7% of patients with sub conjunctival hemorrhage had raised SGPT compared to 60.7% of patients without sub conjunctival hemorrhage with $p=0.022$. SGPT was raised in 69.8% of patients with bleeding gums compared to 63.3% of patients without bleeding gums with $p=0.412$. 74.3% of patients with petechiae had raised SGPT compared to 61.1% of patients without petechiae with $p=0.045$. SGPT was elevated in 71.6% of patients with pleural effusion compared to patients without pleural effusion (56.3%) with $p=0.006$. 71.8% of patients with ascites had elevated SGPT compared to 55.9% of patients without ascites with $p=0.004$. 66.1% of NS1Ag positive patients, 57.1% of IgM positive patients had elevated SGPT with $p=0.188$ (Table 4).

There was statistical association between SGOT, SGPT with clinical features (malena, sub-conjunctival hemorrhage, bleeding gums, petechiae, pleural effusion and ascities) (Table 3 and 4). Statistically significant association was observed between elevated liver enzymes

and presence of features of dengue hemorrhagic fever (Table 3 and 4).

Also, a significant negative correlation was noted between SGOT/ SGPT levels and baseline platelet counts levels (Figure 1 and Figure 2). The Pearson correlation between platelet count and SGOT showed $r = -0.278$ and $p < 0.05$ which proves that when platelet count decreases, the SGOT levels increases (Figure 1).

Similarly, for the correlation between platelet count and SGPT showed $r = -0.192$ and $p < 0.05$ which proves that when platelet count decreases, the SGPT levels increases (Figure 2).

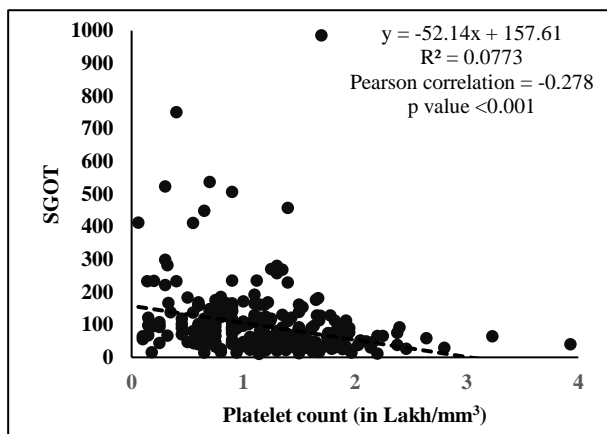


Figure 1: Correlation between platelet count and SGOT levels (n=299).

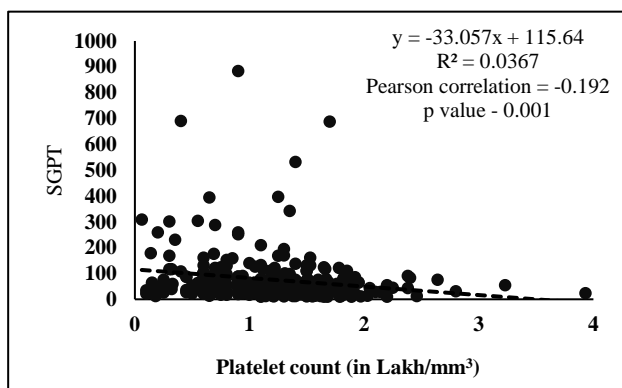


Figure 2: Correlation between platelet count and SGPT levels (n=299).

DISCUSSION

The present study was carried out with an aim to assess the frequency and degree of hepatobiliary dysfunction in adult patients with dengue infection presenting to a tertiary-care medical facility. The present study was undertaken as an observational cross-sectional study the period June 2017 to December 2018. The details of all patients with serologically proved dengue fever admitted to MGMCRI a tertiary care hospital was prospectively reviewed. Data including routine blood count, liver

function test (LFT), prothrombin time (PT), activated partial prothrombin time (APTT), abdominal ultrasonography were collected.

Gandhi K et al, in a research work carried out in South India, studied profile and degree of liver involvement in patients affected during a recent outbreak of dengue fever. It was reported in their study that 51% had a positive serological test, with 63% males and 37% females.¹⁴ Soni A et al, studied 281 inpatients (>18years) who were diagnosed with dengue infection. The study findings noted that the mean age was 43.13 (+15.50) years and male: female ratio was 2:1.¹⁵ Bagepally RS et al, assessed the prognostic value of transaminases and other factors on the outcome of patients with dengue infection. Out of 105 patients, males were 74 (70%).¹⁶

Mukherjee S et al, study revealed that majority of the cases was in the age group of 15-30 years, (69.5%) and the mean age was 27 years. Out of 82 patients 63 (77%) were males and 19 (23%) were females.¹⁷ These demographic characteristics observed in the above discussed studies where a male and middle age preponderance was noted is similar to that of the findings of the present study.

Gandhi K et al, observed that the albumin level was significantly lower in confirmed cases ($P = 0.03$).¹⁴ The present study also found a significant proportion of dengue patients with low serum albumin levels. Gandhi K et al, observed that twenty-three (85%) of the patients had elevation of at least one of the liver enzymes ($P < 0.001$) with alterations in AST seen in 85% and ALT seen in 77.8% of the patients.¹⁴ AST elevations were much higher than those of ALT (390.7U/l vs. 296.9U/l). Roy A et al, carried out a study to estimate the range of hepatic involvement in dengue infection in children. The results of the study research work reported that the spectrum of hepatic manifestations included hepatomegaly (80.8%), hepatic tenderness (46.3%), jaundice (60%), raised AST, ALT and prolonged prothrombin time (41.7%) and reduced serum albumin (56%).¹⁸

Narasimhan D et al, studied 100 IgM positive dengue patients and it was revealed in their study findings that 33% had less than 2-fold increase in ALT levels, 18% had 2-4 fold increase, 20% had 4-10 fold increase and 11% had more than 10 fold increase.¹ Overall 18% had normal values and 82% had values of ALT above normal. With regard to AST 8% had normal values, 26% had less than 2-fold normal, 26% had 2-4-fold increase, 25% had 4-10-fold increase and 15% had greater than 10-fold increase. 92% of patients had values above normal.¹⁹ Bilirubin levels were elevated in 5% of cases. Soni A et al, observed that rearranged serum SGOT and/or SGPT was present in 98.9% of patients.¹⁷ The mean total bilirubin, SGOT, SGPT and albumin, were 0.95mg/dl, 687.28U/L, 293.65U/L, and 3.71g/dl respectively. The mean value of SGOT was significantly higher than SGPT. The degree of rise of SGOT, SGPT,

and Bilirubin was significantly more in DHF and DSS, as compared to DF.¹⁵ Kumar S et al, studied 100 patients with dengue fever, out of which seventy patients had elevated AST levels and seventy-three had elevated ALT levels.²⁰ Also, AST and ALT were statistically higher in these patients and in those developing complications like DHF, DSS, hepatic failure, ARDS, ARF and encephalopathy.²⁰

Bagepally RS et, stated that aminotransferases were elevated in majority of patients.¹⁶ The main differences between survived (n=93) and mortality (n=12) group were as follows; mean value of SGPT was 260IU/mL (survived) and 931IU/mL (mortality group), and mean value of SGOT was 390IU/mL (survived) and 1075IU/mL (mortality group).¹⁶ Mukherjee S et al, study revealed that out of 82 only 18 (22%) cases required blood transfusion Out of 82, 35 (43%) cases required platelet transfusion. The average days of hospital stay was 4.4 days range (1-10).¹⁷ These observations on proportion of patients who required platelet transfusion and duration of hospital stay were similar to the findings of the present study.

Mukherjee S et al, study findings also stated that the range for aspartate transaminase (AST) was 26-1104U/L (AST normal range: 12-38U/L) with a mean of 130U/L. Out of 82 cases more than 100IU/L of AST level was documented in 29 (35.36%) cases.¹⁷ The range for Alanine transaminase (ALT) was 10-372U/L with a mean of 79.6U/L. (ALT normal range: 7-41U/L). The range for serum alkaline phosphatase was 48-268U/L with a mean of 145.1U/L. Raised levels of aspartate transaminase (AST) (84%) and alanine transaminase (ALT) (84%) among 100 patients with serologically positive dengue fever aged above 18 years in the research work by Chikkaveeraiah SK et al.²¹

These findings were in agreement to the results of the present study. Statistically significant association was observed between elevated liver enzymes and presence of features of dengue hemorrhagic fever. The study involved a significantly larger number of samples as compared to that of other studies carried out in the region. This has significantly improved the power of the study findings. One of the limitations is its cross-sectional study. Considerably high proportion of patients with dengue infection were found to have hepatic dysfunction in the form of deranged liver enzymes. Furthermore, the severity of dengue infection predicted the severity of liver derangements.

CONCLUSION

Considerably high proportion of patients with dengue infection were found to have hepatic dysfunction in the form of deranged liver enzymes. In the study participants (75.3%) were found to have elevated levels of SGOT, SGPT levels (64.2%) and lower levels of serum albumin (68.6%) on evaluation.

Statistically significant association was observed between elevated liver enzymes with fall in platelet levels and presence of features of dengue hemorrhagic fever. Furthermore, the severity of dengue infection predicted the severity of liver derangements. It is recommended that Patients with dengue infections be screened for hepatic dysfunction, and also patients with suspicion of dengue fever in the form of other clinical parameters should be complimented by deranged liver function tests.

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