ORIGINAL ARTICLE

Assessment of Dengue Fever Severity Through Liver Function Tests

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ABSTRACT

Objective: To assess the utility of liver function tests (LFTs) for early recognition and prediction of severity of Dengue fever in hospitalized patients.

Study Design: An analytical study.

Place and Duration of Study: Services Institute of Medical Science and Fatima Memorial Hospital, Lahore, from September - December 2010.

Methodology: Admitted cases of Dengue fever were divided into 3 groups; mild, moderate and severe increases in aminotransferases. Elevation in LFTs was co-related with good or bad outcome i.e. (survival or complication free stay) or (death or complications). Results were analyzed in SPSS version 18.

Results: Out of the 353 patients with mean age of 37.12 ± 15.45 years, 245 (69.4%) were males and 108 (30.6%) were females. Seventy five patients (21.2%) had mild elevation of aminotransferases (2 fold increases), 265 patients (75.1%) had moderate increases (3 to 4 fold) and 13 (3.7%) had severe (> 4 fold increase). ALT was statistically higher in patients with septicemia, hepatic and renal failure (p-value ≤ 0.05). AST was higher in almost all complications. Prolonged hospital stay was associated with raised LFTs and greater complications and mortality. AST was found to be twice as much raised as ALT.

Conclusion: AST and ALT were statistically higher in patients with worse outcome thus can lead to early recognition of high risk cases.

Key Words: *Dengue fever. Acute hepatitis. Liver function test. Encephalopathy. Septicemia.*

INTRODUCTION

Dengue fever is the most rapidly emerging viral infection in our part of the world and Pakistan reported its first outbreak in 1994.[1] Dengue fever is a vector borne disease that has become a major recurring health problem in South-East Asia,[2-4] with a frequency of 2 - 3 epidemics / year.[2] Clinical expression of DF varies from mild febrile illness to Dengue hemorrhagic fever and Dengue shock syndrome.[3] This leads to an inadequate or late treatment of a disabling and potentially lethal medical condition.

Biochemical alterations in body have been related to the severity of Dengue fever.[4] Although liver is not the major target organ, changes like centrilobular necrosis, fatty change, kuffar cells hyperplasia, acidophilic bodies, and monocytic infiltration of portal tracts have been reported in patients with Dengue fever.[5] Hepatic dysfunction is attributed to a direct viral effect on liver cells or as a consequence of deregulated host immune response.[6]

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Keeping this in view, alterations in the liver function test may serve as an early marker for timely diagnosis and identification of patients who might develop severe complication like Dengue shock syndrome, septicemia, hepatic encephalopathy, Dengue hemorrhagic fever and thus serve as an early biochemical predictor of severity of outcome of Dengue fever.

The objective of this study was to assess the utility of LFTs as a marker of early diagnosis and severity of Dengue fever and to see the association of complications, hospital stay and final outcome (survival/ mortality) with respect to the severity of disease.

METHODOLOGY

The analytical study was conducted at Services Institute of Medical Science and Fatima Memorial Hospital, Lahore, from September - December 2010. Both male and female patients of all age groups ranging from 4 to 80 years were included in the study. The diagnosis was made on the basis of Dengue fever scoring system; if a patient had a score of ≥ 6, patient was diagnosed as Dengue fever (Table I). Patients with known chronic liver disease due to any cause and those positive HBsAg, IgM to HAV or HEV were excluded. All patients who had taken any alternative medication or were on any other known hepatotoxic drug for the last 6 months were also excluded. Other diagnostic possibilities were investigated on an individual case to case basis.

Informed consent was taken and data was collected. Patients were divided into 3 groups and categorized to have mild, moderate or severe liver dysfunction. Group-I included patients who had two folds or lesser increase in liver enzymes; in Group-II patients, liver enzymes were between 3 to 4 fold greater than normal. Group-III patients had LFT's derangement greater than 4 fold or g normal. The range for ALT was taken 7 - 32 IU/L: normal, 33 - 66 IU/L: mild disease, 67 - 132 IU/L: moderate disease and 133 IU/L and above: severe disease. For AST, the grouping was 5 - 40 IU/L: normal, 41 - 80 IU/L: mild disease, 81 - 150 IU/L: moderate disease and 151 IU/L and above: severe disease.

The association of these groups with development of complications, mortality and number of days of hospital stay was studied. Good outcome was taken as survival and complication free pattern of disease, while bad outcome was taken as development of complication or mortality.

All data was entered and analyzed by using Statistical Package for Social Sciences (SPSS) version 18. Mean ± SD was used for quantitative data like age (years), duration of fever and duration of hospital stay. Median IQR (interquartile range) was used for LFTs, TLC, PT and APTT etc. Frequency (%) was used for qualitative data, like gender, severity of disease and complications. Mann Whitney U test was applied to determine the difference of LFT's and other parameters with respect to different qualitative variable namely complications (DHF, DSS, hemorrhage, and septicemia, hepatic failure, encephalopathy, respiratory failure and renal failure). Chi-square/Fisher's exact test was applied to determine any association between severity of disease and complication. Spearman's rank correlation was applied to determine any relation between quantitative data. P-value < 5% was taken as significant.

RESULTS

The mean age of patients was 37.12 ± 15.45 (4 years to 80 years). There were 245 (69.4%) males and 108 (30.6%) females. All patients presented with fever for a mean duration of 5.49 ± 2.65 days (1 day to 34 days). In 118 (33.4%) patients, there was history of bleeding while in 235 (66.6%) patients there was no bleeding. The mean duration of hospital stay was 2.73 ± 1.41 days.

There was a significant positive correlation between duration of fever with TLC (r = 0.118, p = 0.027) and ALT (r = 0.122, p = 0.022). AST was also positively correlated with TLC (r = 0.120, p = 0.024) and ALT (r = 0.222, p < 0.001). The positive significant correlation was also seen in ALT with PT (r = 0.266, p < 0.001) and APTT (r = 0.134, p = 0.012), AST with PT (r = 0.155, p = 0.004) and APTT (r = 0.109, p = 0.041). Moreover, PT and APTT were also significantly correlated (r = 0.288, p < 0.001).

There were 75 (21.2%) patients with mild (two-fold increase in LFT's i.e. 33 - 66), 265 (75.1%) with moderate (three to four-fold increase in LFT's i.e. 67 - 132) and 13 (3.7%) with severe (greater than four-fold increase in LFT's i.e. 133 and above) Dengue.

According to complication of the patients, DHF was seen in 24 (6.79%) patients, in which 12 (50%) had mild, 11 (45.8%) had moderate and 1 (4.2%) patient had severe liver dysfunction. DSS was seen in 12 (3.39%), in which 4 (33%) had mild, 4 (33%) had moderate and 4 (33%) had severe liver dysfunction. Septicemia developed in 5 (1.41%) patients, in which 2 (40%) had moderate and 3 (60%) had severe type of liver dysfunction. In 5 (1.41%) patients hepatic failure was seen, in which 1 (20%) had moderate and 4 (80%) had severe type of liver dysfunction. The frequency of encephalopathy was in 4 (1.13%) patients, in which 2 (50%) had mild, 1 (25%) had moderate and 1 (25%) had severe type of liver dysfunction. Respiratory failure was seen in 4 (1.13%) patients in which 2 (50%) had severe type of liver dysfunction. Renal failure occurred in 2 (0.56%) patients and both the patients had severe type of liver dysfunction. All complications except hemorrhage were statistically associated with severity of disease, ($p \leq 0.05$).

ALT was higher in patients with septicemia, hepatic failure, renal failure and patients who died, while ALT

Table I: Spearman's correlation in different variables .

		Duration of fever	TLC	ALT	AST	PT	APTT
Age of patients	Correlation Coefficient	0.047	0.071	0.016	-0.013	0.049	-0.003
	p-value	0.378	0.181	0.763	0.813	0.360	0.956
Duration of fever	Correlation Coefficient		0.118*	0.122*	<0.001	-0.021	-0.055
	p-value		0.027	0.022	0.995	0.699	0.305
TLC	Correlation Coefficient			0.062	0.120*	0.042	-0.052
	p-value			0.243	0.024	0.437	0.328
ALT	Correlation Coefficient				0.222**	0.266**	0.134*
	p-value				<0.001	<0.001	0.012
AST	Correlation Coefficient					0.155**	0.109*
	p-value					0.004	0.041
PT	Correlation Coefficient						0.288**
	p-value						<0.001

** Correlation significant at the 0.05 level (2-tailed), ** Correlation significant at the 0.01 level (2-tailed).*

was low in patients with DHF and was statistically same in DSS, hemorrhage and encephalopathy. Moreover, AST was twice as much as mean ALT and statistically higher in patients with DHF ($p \leq 0.05$). It was statistically same in DSS, septicemia, hepatic failure, encephalopathy, respiratory failure and in those who died ($p \leq 0.05$).

The mean age of patients who died was 35.57 ± 3.81 years, their mean duration of fever was 4.57 ± 0.202 days and their mean hospital stay was 3.86 ± 0.769 days. The mean hospital stay in patients who died was statistically higher as compared to discharged patients ($p = 0.008$).

Table II: Comparison of TLC, ALT, AST, PT and APTT in different complications and their p-value (using Mann Whitney U-test).

		Media (IQR)				
		TLC	ALT	AST	PT	APTT
DHF	Yes	4.89 (1.85)	98.5 (56.29)	234.18 (83.82)	16.35 (3.93)	33.50 (2.41)
	No	4.77 (1.59)	100.29 (0.00)	234.18 (0.00)	16.71 (0.00)	34.50 (0.0)
	p-value	0.393	0.006	0.031	0.006	< 0.001
DSS	Yes	4.05 (2.19)	100.29 (136.0)	343.50 (157.07)	16.71 (1.78)	34.75 (4.14)
	No	4.9 (1.57)	98.29 (7.29)	14.17 (0.00)	16.71 (0.00)	34.50 (0.00)
	p-value	0.437	0.357	< 0.001	< 0.001	< 0.001
Hemorrhage	Yes	3.9 (2.75)	99 (35.29)	234.178 (43.82)	16.71 (0.36)	34.40 (0.00)
	No	4.71 (1.50)	100.29 (0.00)	234.178 (0.00)	16.71 (0.00)	34.40 (0.00)
	p-value	0.457	0.078	0.003	0.902	0.015
Septicemia	Yes	2.90 (1.55)	201.0 (533.71)	345 (0.00)	28 (43.29)	34.4 (4.30)
	No	4.77 (1.59)	100.29 (12.04)	234.17 (0.00)	16.71 (0.00)	34.40 (0.00)
	p-value	0.055	0.002	< 0.001	< 0.001	0.167
Hepatic failure	Yes	3.20 (1.50)	201.0 (934.5)	234.17 (110.82)	28.0 (44.34)	34.40 (4.30)
	No	4.77 (1.59)	100.29 (12.04)	234.17 (0.00)	16.71 (0.00)	34.40 (0.00)
	p-value	0.070	0.002	0.022	0.005	0.167
Encephalopathy	Yes	3.80 (1.63)	56.14 (813.32)	382.5 (50)	24.0 (8.47)	42.20 (16.65)
	No	4.77 (1.68)	100.29 (7.29)	234.17 (0.00)	16.71 (0.00)	34.40 (0.00)
	p-value	0.21	0.418	< 0.001	< 0.001	0.096
Respiratory failure	Yes	4.53 (1.72)	150.64 (163.18)	315.00 (139.37)	38.35 (43.29)	35.70 (4.09)
	No	4.77 (1.63)	100.29 (11.29)	234.17 (0.00)	16.71 (0.00)	34.40 (0.00)
	p-value	0.627	0.224	< 0.001	0.003	0.003
Renal failure	Yes	2.90 (0.00)	1084.50 (0.00)	289.58 (0.00)	22.35 (0.00)	33.70 (0.00)
	No	4.77 (1.57)	100.29 (11.29)	234.17 (0.00)	16.71 (9.35)	34.40 (0.00)
	p-value	0.094	0.004	0.079	0.038	0.052
Final outcome	Discharge	4.77 (1.58)	100.29 (12.54)	234.17 (0.00)	16.71 (0.00)	34.40 (0.00)
	Died	4.30 (3.60)	743.00 (866.0)	345.00 (1445.82)	16.71 (43.29)	34.40 (2.59)
	p-value	0.739	< 0.001	< 0.001	0.001	0.233

Table III: Comparison of severity of liver disease in relation to different complications and final outcome.

		Severity of liver disease			p-value
		Mild	Moderate	Severe	
DHF	Yes	12	11	1	0.002
	No	63	254	12	
DSS	Yes	4	4	4	< 0.001
	No	71	261	9	
Hemorrhage	Yes	8	18	3	0.077
	No	67	247	10	
Septicemia	Yes	0	2	3	< 0.001
	No	75	263	10	
Hepatic failure	Yes	0	1	4	< 0.001
	No	75	264	9	
Encephalopathy	Yes	2	1	1	0.019
	No	73	264	12	
Respiratory failure	Yes	1	1	2	< 0.001
	No	74	264	11	
Renal failure	Yes	0	0	02	< 0.001
	No	75	265	11	
Final outcome	Discharge	75	265	6	< 0.001
	Died	0	0	7	

Table IV: Dengue fever scoring system.

Epidemiology	Score
Recent travel to Southeast Asia or 4 endemic dengue fever in Taiwan within 1 week	4
Clinical symptom	
Skin rash	3
Bleeding signs (Included petechia, gum bleeding, epistaxis, gastrointestinal bleeding, hemoptysis, hematuria and menorrhagia)	3
Fever	2
Headache, retro-bulbar pain, bone pain, myalgia	1
GI symptoms (poor appetite, abdominal pain, diarrhea and nausea)	1
Absence of cough and rhinorrhea	1
Differential diagnosis	
Fever > 7 days	-8
Identified infection focus (e.g. Escher of scrub typhus and upper respiratory infection)	-10

If total score > 6 then patient has high chances of having Dengue fever. This scoring system carries sensitivity = 90.7%; specificity = 86.9%; positive predictive value = 81.4%; negative predictive value = 93.6%.

DISCUSSION

Dengue is a mosquito-borne viral infection of humans which affects up to 100 million people across the tropical world.[7] There are four serotypes of the virus and spectrum of disease ranges from asymptomatic infection to acute Dengue hemorrhagic fever with complications.[8]

Acute Dengue hemorrhage fever begins as a febrile illness categorized by high grade fever, bone pains, headache and other non-specific symptoms[9,10] difficult to distinguish from any other viral illness.[11] More severe cases develop circulatory collapse due to increased vascular permeability, multiple organ failure. Dengue shock syndrome, bleeding due to thrombocytopenia and deranged hemostasis. No specific antiviral therapy is available.

In recent years, there has been a marked increase in cases of Dengue fever in South-East Asia in adult population with Dengue fever requiring hospitalization, thus increasing the economic burden.[12] To combat the problem, it is required to study the clinical profile and evolution of different laboratory parameters in this infection.

Dengue virus directly affects the reticuloendothelial system of the host. Hepatic dysfunction is thus a well-recognized feature of Dengue infections.[13-15] Injury to liver cells could result both from direct effect of the virus or due to unregulated immune response of the host,[16] hence liver function tests are of significance for timely diagnosis and assessment of severity of Dengue fever. It was observed in this study that mortality and complications of acute Dengue fever significantly co-related with liver dysfunction and raised amino-transferases. ALT was higher in patients with septicemia, hepatica and renal failure and in patients who died, AST was significantly raised in patients with DHF, DSS, septicemia, hepatic and respiratory failure, also in patients with encephalopathy. Moreover, AST was twice as much raised as ALT unlike in other viral infections.

In a similar study conducted by Trung and colleagues in South Vietnam, 650 patients were recruited and raised transaminases were found in all patients. This also co-related with diseases severity in terms of vascular leakage and bleeding.[17] Another study conducted in Alexandria Hospital[18] in November 2003, December 2004, 90.6 patients had raised AST and 71.7% had raised ALT. The study did not, however, advocate raised transaminase as an early predictor of fatal outcome. No case of clinical jaundice, liver failures, hepatic encephalopathy or fulminating hepatic failure was observed in the study. Raised aminotransferase were also reported by Souza *et al*.[19] and in a study conducted by Chhina and colleagues in Ludhiana[18] both also found AST level greater than ALT. However, these studies did not correlate raised LFTs with complication severity and outcome of Dengue fever.

It was also observed in this study that 100% mortality was seen in patients with severe liver dysfunction (four-fold increase in LFT). Prolonged hospital stay also correlated positively with increased complication and raised ALT.

Similar results were obtained in study undertaken in 2010 at The Agha Khan University Hospital, Karachi, Pakistan by Parkash and colleagues.[1] Severe hepatitis (SGPT > 300 IU) in Dengue fever was associated with prolonged length of stay, mortality, bleeding and renal failure.

Severity of hepatic involvement can be a major contributing factor in morbidity and mortality of Dengue patients and can be used as an early marker to assess the severity of disease, however, further immunological studies need to be undertaken to establish the exact pathophysiology of hepatic involvement.

This study has limited external validity as it did not include outdoor patients and patients from other cities. Viral serology was also not done which limits implication of results.

CONCLUSION

AST and ALT were statistically higher in patients with worse outcome thus can lead to early recognition of high risk cases.

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