

Evaluation of Alterations in Liver Function Tests in Dengue Fever

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Abstract

Objective: Purpose of this study was to evaluate alterations in liver function tests in dengue patients. **Material and Methods:** This is a retrospective observational analysis of liver function tests in 100 serologically-proven dengue patients. Patients were classified as classical dengue fever (DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). **Results:** Serum total bilirubin levels were increased in all patients. The increase was maximum in DSS patients as compared with DF and DHF patients ($p < 0.0001$). Mean value of Aspartate transaminase (AST) and Alanine transaminase (ALT) was increased in DF, DHF and DSS patients. Rise of AST and ALP was significantly more in DHF and DSS as compared to DF ($p < 0.0001$). Serum alkaline phosphatase levels were also increased in DF, DHF and DSS patients. It was more in DSS patients as compared to DF and DHF ($p < 0.0001$). In contrast to the increase in above parameters, we observed decreased levels of serum albumin in DF, DHF and DSS patients. **Conclusion:** Liver dysfunction in terms of raised serum bilirubin, SGOT, SGPT, alkaline phosphatase and decreased serum albumin was seen in dengue patients. AST levels were more than ALT levels,

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which was observed in patients who developed complications like DHF, DSS proving the fact that severity of hepatic involvement can be a major contributing factor in morbidity and mortality of such patients. Hence, AST and ALT can be a useful early marker to assess severity of disease leading to early recognition of high-risk cases.

Keywords: Dengue, Dengue hemorrhagic fever, Dengue shock syndrome, LFT

Introduction

Dengue is an acute febrile disease of viral etiology, the evolution of which is benign in its classic form, and serious when presenting as dengue hemorrhagic fever / dengue shock syndrome (DHF/DSS). The etiologic agent belongs to the *Flaviviridae* family and to the *Flavivirus* genus, with 4 serotypes [1].

Dengue virus presumably affects the reticulo-endothelial system of the body in skin, lymph nodes, spleen, marrow and liver [2]. DHF and DSS are caused by disorder of the immune system. In recovery phase (days 7–14) of first infection, another

serotype is superinfected. Then antibodies against first serotype binds with new entrant serotype antigen leading to immune complex formation, their deposition on endothelium leading to widespread vessel wall injury, hemorrhages and third spacing of fluid [3].

Today, this disease represents a major public health issue, principally in tropical countries where environmental conditions favor the development and proliferation of *Aedes Aegypti*, the principal vector of this zoonosis. This disease is transmitted by mosquito bites in a human-*Aedes aegypti*-human cycle. After ingestion of infected blood, the mosquito is able to transmit the virus following an extrinsic incubation period of 8-12 days.

Multiple outbreaks of dengue have happened in India. Reports have come from Bangalore, Punjab and Delhi [4,5,6]. The symptomatology of dengue varies highly from mild flu like illness to classical dengue fever (DF, bone break fever) and even some complicate into dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), which are life threatening [3,7].

There have been reports of dengue fever involving heart, nervous system and liver causing myocarditis, encephalitis and hepatitis [8]. Although, the number of patients affected by the virus is increasing every year; a very few studies have been carried out on liver involvement in dengue fever among adults. Hence, the present study was undertaken to evaluate any alterations in liver function tests in dengue infection on liver by assessing liver function tests.

I. MATERIAL AND METHODS

A total of 100 patients attending Ashwini Rural Medical College, Hospital and Research Centre, Kumbhari, Solapur between January 2022 to June 2022 were included in the study. All were with positive serological tests for dengue fever. Liver function tests were carried out in all the patients. Patient's history and clinical features were collected from the records.

Inclusion criteria: All patients of age more than 20 years, with symptoms of dengue fever and had positive serology (Dengue NS I positive cases / IgM Ab positive cases).

Exclusion Criteria: Patients with preexisting or coexisting liver disease due to any other etiology were excluded from the study (e.g. diagnosed Chronic Liver Disease co-existing or recent history of infectious disease like acute viral hepatitis, malaria, typhoid, leptospirosis, history of intake of any hepatotoxic drugs, alcoholic liver disease, history of Non-alcoholic Fatty Liver Disease (NAFLD), Wilson's disease, autoimmune hepatitis and heart failure, etc.).

Out of a total 100 patients, 58 were male and 42 were female. They were categorized into classical dengue fever (DF) 89%, Dengue hemorrhagic fever (DHF) 7% and Dengue shock syndrome (DSS) 4% as per WHO criteria [3].

All patients underwent liver function tests. Bilirubin testing was done by diazo method, alanine aminotransferase [ALT] and aspartate aminotransferase [AST] was tested by IFCC method. Alkaline phosphatase was tested by IFCC method. Serum

proteins were tested by Biuret method, Serum albumin was tested by BCG dye binding method.

Dengue serology test was done using Rapid test of Erba QiK for Dengue Duo (NSI Antigen + IgG/IgM test by ERBA Diagnostics Mannheim GmbH, Germany).

The ethical clearance for this study was obtained from the institutional ethical committee.

Results for continuous variables were expressed as means and standard deviation. Categorical variables were expressed as percentages. Student's t-test for continuous variables and Chi square test for discrete variables were used to test significance. Comparison of liver function tests in patients with DF, DHF and DSS were performed by ANOVA test followed by post hoc Bonferroni multiple comparison test. The p value of less than 0.05 was considered statistically significant. The SPSS v20.0 software was used for statistical analysis.

II. RESULTS AND DISCUSSIONS

A. Results.

One hundred confirmed cases of dengue fever were enrolled for this study. Of the total 100, 89(89 %) patients were classified as dengue fever, 7 (7%) as dengue haemorrhagic fever and 4 (4%) as dengue shock syndrome. Mean age of patients in our study was 46.72±5.53 years.

Table 1 shows mean values of various liver function tests which include serum total Bilirubin, alkaline phosphatase, AST, ALT and albumin.

Table No. 1: Showing comparison of liver function test in patients with Dengue fever (DF), Dengue Hemorrhagic fever (DHF) and Dengue Shock Syndrome (DSS).

Liver biochemical test	DF (n= 89)	DHF (n=7)	DSS (n=4)	P value
Total bilirubin (mg/dl)	0.87 ± 0.24	1.90 ±0.41	2.83±0.07	<0.0001
No (%) of patients with < ULN	26/89 (29.21%)	6/7 (85.71%)	4/4 (100%)	
AST (IU/L)	281.30 ± 12.99	770.28 ± 13.95	1510.25±27.17	<0.0001
No (%) of patients with < ULN	89/89 (100%)	7/7 (100%)	4/4 (100%)	
ALT (IU/L)	154.42 ±9.27	454.7 ±□5.62	1022±36.47	<0.0001
No (%) of patients with < ULN	89/89 (100%)	7/7 (100%)	4/4 (100%)	
ALP (IU/L)	122.08 ±40.96	163.85± 21.30	265.25±7.85	<0.0001
No (%) of patients with < ULN	26/89 (29.21%)	7/7 (100%)	4/4 (100%)	
Albumin (g/dl)	3.26 ±0.22	3.05 ± 0.09	2.60±0.21	<0.0001
No (%) of patients with < LLN	83/89 (93.25%)	7/7 (100%)	4/4 (100%)	

Serum Total Bilirubin levels were found to be elevated in 29% of DF patients whereas it was observed to be increased in all patients of DSS and DHF. The increase of total Bilirubin was significantly higher in DSS as compared DF ($p < 0.0001$) and DHF patients ($p < 0.0001$).

The elevated levels of SGOT and SGPT were observed above the upper limit of normal ($>40\text{IU/L}$) in all the dengue patients. It was also observed that mean value of SGOT and SGPT was significantly higher in DSS patients when compared with DF and DHF patients ($p < 0.0001$).

Serum alkaline phosphatase was elevated in 29% of DF patients but it was elevated in all the patients from group DSS ($p < 0.0001$) and DHF ($p < 0.0001$) and the increase was significantly higher.

In contrast to the above increase in the levels of serum total bilirubin, SGOT, SGPT and serum alkaline phosphatase, there was a decrease in serum albumin levels in dengue patients. 93% of DF patients showed a decrease in serum albumin level whereas all patients from DSS (100%) and DHF (100%) group showed decrease in serum albumin levels. It was found that DSS patients showed significant decrease ($p < 0.0001$) in serum albumin than DHF and DF patients.

Table no. 2 depicts post hoc Bonferroni multiple Comparisons between DF, DHF and DSS. The pairwise comparison was done among the parameters of liver function tests such as serum total Bilirubin, Alkaline phosphatase, ALT, AST and Albumin of DF patients were compared with DHF and DSS patients. Along with it, DHF patients were compared with DSS patients. It was observed that, all the liver function tests parameters were showing statistically significant difference in all three groups ($p < 0.001$).

Table No. 2. Post hoc Bonferroni multiple comparisons of the liver function tests parameters in DF, DHF and DSS.

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Sig.
Bilirubin	DF	DHF	-1.02*	.000
		DSS	-1.96*	.000
	DHF	DSS	-0.93*	.000
Alkaline Phosphatase	DF	DHF	-41.77*	.024
		DSS	-143.16*	.000
	DHF	DSS	-101.39*	.000
Albumin	DF	DHF	0.21*	.042
		DSS	0.66*	.000
	DHF	DSS	0.45*	.005
AST	DF	DHF	-488.98*	.000
		DSS	-1228.94*	.000
	DHF	DSS	-739.96*	.000
ALT	DF	DHF	-300.28*	.000
		DSS	-868.32*	.000
	DHF	DSS	-568.04*	.000

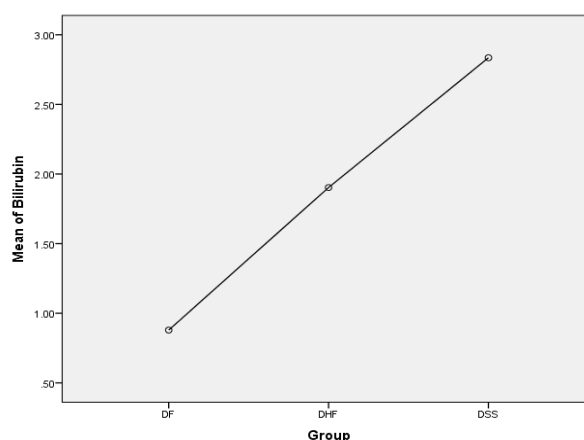
* The mean difference is significant at 0.05 level

Table no. 3 shows the comparison of liver function tests between male dengue patients and female dengue patients.

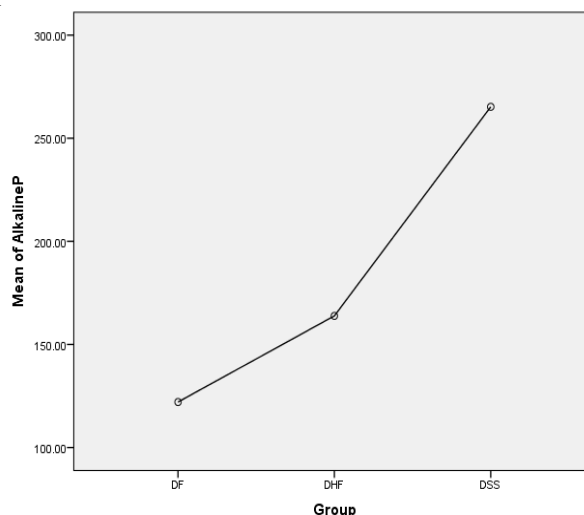
Table No 3. Shows Comparison of liver function tests between male Dengue patients and female Dengue patients

Characteristics	Male	Female	P value
Total Bilirubin (mg/dl)	0.99±0.42	0.94±0.49	0.59
AST (IU/L)	343.0±160.4	304.4±157.6	0.19
ALT (IU/L)	189.1±99.9	186.3±153.8	0.91
ALP (IU/L)	119.6± 38.3	129.6± 52.4	0.24
Albumin (gm/dl)	3.24±0.2	3.23± 0.2	0.89

Graphic 1. Representing the maximum increase in serum total Bilirubin in DSS patients than DF and DHF patients.



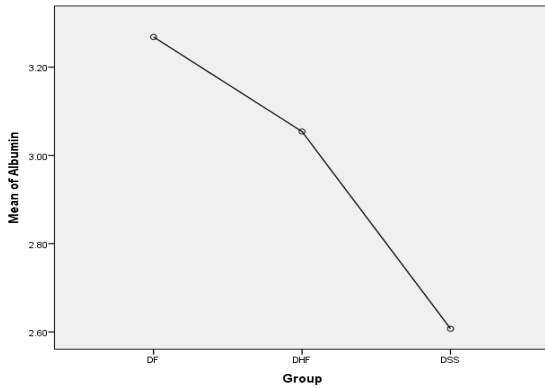
Graphic 2. Serum alkaline phosphatase activity is depicted in Graphic no. 2 which is also highest in DSS than DF and DHF patients.



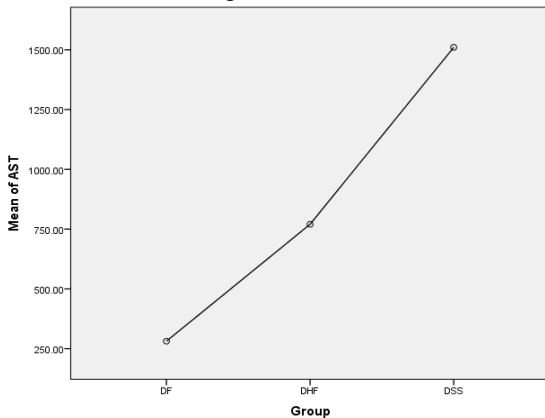
The transaminase activity (AST and ALT) was observed to be highest in DSS as compared with DF and DHF. On the contrary to the above results, serum albumin level was found to be lowest in DSS patients when compared with DF and

DHF patients suggesting a drastic decrease in proteins in dengue patients as severity increases. Graphical representation of increased serum bilirubin, alkaline phosphatase, AST and ALT is shown in graph number 1,2 ,4, 5 respectively and decreased serum albumin is shown in graph no. 3.

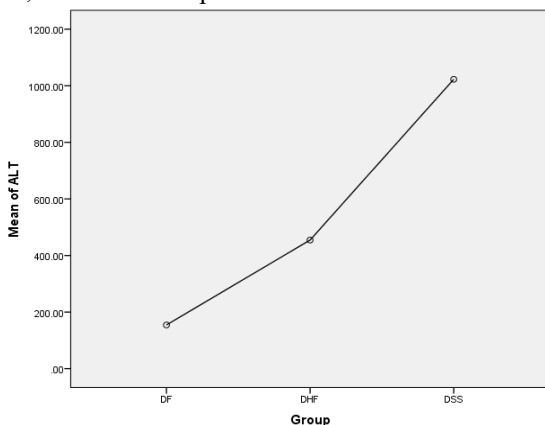
Graphic 3. Mean value of serum albumin levels in DF, DHF and DSS patients



Graphic 4. Mean value of serum Aspartate transaminase levels in DF, DHF and DSS patients



Graphic 5. Mean value of serum alanine transaminase levels in DF, DHF and DSS patients



B. Discussion.

Dengue is endemic in many parts of India and is a significant cause of morbidity. The outbreaks have been

repeatedly reported from many states of India [4,5,6]. Although the involvement of liver leading to hepatitis is commonly noted in dengue fever [8], the involvement of liver in dengue fever among adults and changes in biochemical parameters is rarely studied and reported. Hence, the present study was undertaken to evaluate any alterations in liver function tests in dengue infection by assessing various biochemical parameters.

Our data showed that there was a significant derangement in liver function tests in dengue patients suggesting liver involvement was almost common in them which is similar to the previous reports from the other developing countries[9,10].

Hepatic dysfunction is a crucial feature seen in dengue infection. Hepatocytes and Kupffer cells are prime targets for dengue infection. Pathogenesis of hepatic injury in dengue is believed to be primarily a T cell-mediated process involving interaction between antibodies and the endothelium and a concomitant cytokine storm [11, 12, 13, 14]. It was found that the mean value of AST and ALT have been found to be higher for severe forms of dengue (DHF, DSS) than for uncomplicated dengue fever. These findings are in accordance with other similar studies [14, 15]. This hints at a possible association between increased transaminase levels with increasing disease severity. However, a study by Souza et al. [7] observed that AST and ALT were deranged only in 63.4 % and 45% patients respectively and have confirmed that liver damage with elevation of aminotransferases and reactive hepatitis was a common complication of dengue virus infection in these patients.

We also noted a preferential elevation of liver enzymes, with AST being higher than ALT. This abnormality may be as an early indicator of dengue infection. Liver dysfunction, in the form of increased transaminases, was found in all the patients in our study. A study by Ambreen Zubair et al. [16] states that severe hepatitis and specifically raised alanine transaminase levels is a poor prognostic indicator of outcome in dengue fever. A very few studies have compared liver function tests between male and female patients. In view of this, the present study has compared the laboratory parameters of LFT between male dengue patients and female dengue patients but there was no significant difference found. Similar to our results a large study from Brazil also found that there was no significant difference in the level of transaminases between male and female dengue patients but they found that the liver damage was more common among females [17].

III. CONCLUSION

We thus report the alterations in liver function tests in almost all dengue patients. The derangement in LFT was significantly more in the DSS group as compared to the DF and DHF group. There was no significant difference of liver function tests between males and females in our study. A large scale of future studies with viral titer and liver function tests may help to identify the connection between dengue fever and hepatic injury.

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Conflicts of Interest: None.

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