

Hepatic Dysfunction in Dengue Fever- A Prognostic Indicator

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Abstract:

Background: Dengue fever is a tropical infection, presenting with a wide range of clinical manifestations. Hepatic dysfunction in dengue fever is not uncommon, and may lead to fulminant liver failure. This study aims to evaluate the hepatic dysfunction in dengue fever and assess the prognostic value of serum transaminases in determining the severity of dengue.

Materials and Methods: This prospective study was carried out at Bhagwan Mahaveer Jain Hospital, Bangalore, Karnataka, from September 2018 to September 2019. A total of 165 adult patients (both male and female), aged ≥ 18 years, who tested positive for dengue NS1 antigen or dengue serology (IgM/IgG) were included. Liver function tests were sent for all patients. Patients with elevated serum transaminases were classified into mild elevation (two fold increase), moderate elevation (three to four fold increase) and severe elevation (greater than 4 fold increase)

Results: The mean age was 33.43 ± 12.70 , with 56.4% males. Fever (100%) and headache (74.5%) were the most common symptoms reported. Bleeding manifestations were seen in 27.2% patients. 93.9% patients had elevated AST and 83.6% had elevated ALT. Patients with severe elevation of AST and ALT had more complications, manifesting as Dengue Shock Syndrome (DSS), Dengue Hemorrhagic Fever (DHF) and prolonged hospital stay.

Conclusion: The study shows the presence of hepatic dysfunction in majority of the patients with dengue fever, as evidenced by the elevation of AST/ALT enzymes. Patients with severe elevation of serum transaminases have prolonged hospital stay and severe complications of dengue (DHF, DSS, thus indicating increasing morbidity and poor prognosis.

Key Word: Dengue Fever, Transaminitis, Hepatitis

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I. Introduction

Dengue is a febrile illness caused by the dengue viruses (DENV) and transmitted by *Aedes aegypti* or *Aedes albopictus* mosquito. There are four DENV belonging to the genus *Flavivirus*, namely DENV-1, DENV-2, DENV-3, and DENV-4. DENV infection is one of the most important causes of acute febrile illness in the tropical and subtropical regions, with a 30-fold increase in incidence over the last 50 years¹. An estimated 50 million infections occur annually, and around 2.5 billion people live in dengue endemic countries². Although initially reported from urban areas, dengue is being reported from urban and rural areas alike in India today³, with seasonal transmission during monsoon and post monsoon. Outbreaks are now reported from all over the country, with the case fatality rate hovering at just above 1% in the last ten years³.

DENV affects multiple organs including the liver. A wide spectrum of hepatic manifestations has been described, ranging from mild elevation of serum transaminases to acute liver failure⁴. The main aim of this study is to evaluate hepatic dysfunction in patients with dengue, the use of Liver Function Tests (LFTs) as a marker to identify dengue early, and to determine whether serum transaminases can be of prognostic value in patients with dengue.

II. Material And Methods

This prospective study was carried out among patients admitted to the Department of General Medicine at Bhagwan Mahaveer Jain Hospital, Bangalore, Karnataka, from September 2018 to September 2019. A total of 165 adult patients (both male and female), aged ≥ 18 years, were included.

Study Design: Prospective, observational study

Study Location: Tertiary care teaching hospital based study, done in Department of General Medicine at Bhagwan Mahaveer Jain Hospital, Bangalore

Study Duration: 1st September 2018 to 1st September 2019

Sample size: 165 patients

Sample size calculation: The sample size was estimated on the basis of a single proportion design. A study done by Kumar et al⁵ was used as reference, where 70% of dengue patients had elevated AST level. Assuming 90% power, 5% level of significance and 10% relative precision, required sample size was calculated as 165.

Subjects & selection method: The study population was drawn from patients with dengue who presented to Bhagwan Mahaveer Jain Hospital, Bangalore, between 1st September 2018 to 1st September 2019. 165 patients, who tested positive for dengue NS1 or dengue serology (IgM/IgG) were observed. Patients who met the criteria for dengue fever, dengue hemorrhagic fever and dengue shock syndrome, according to WHO guidelines were subjected to a questionnaire of thorough medical history and clinical examinations. Written informed consent was taken.

Inclusion criteria:

Patients who met the World Health Organisation (WHO) criteria for Dengue Fever, Dengue Hemorrhagic Fever and Dengue Shock Syndrome

WHO Criteria for Dengue Fever (DF)

Fever <15days, plus 2 or more of the following: Headache, myalgia, arthralgia, retro-orbital pain, nausea/vomiting, skin rash and supportive serology

WHO Criteria for Dengue Hemorrhagic Fever (DHF)

1. Fever of 2-7 days
2. Bleeding manifestations indicated by positive tourniquet test/petechiae, ecchymoses, purpura/bleeding mucosa/hematemesis, melena
3. Platelet count <100,000/mm³
4. Plasma leakage as evidenced by rise in PCV>20%, fall in PCV by 20% after IV fluids, pleural effusion, ascites, hypoalbuminemia

WHO Criteria of Dengue Shock Syndrome (DSS)

DHF + weak pulse, hypotension, narrow pulse pressure and cold dry skin

Exclusion criteria:

1. Patients with alcoholic liver disease
2. Patients with drug induced toxicity
3. Patients with age below 18yrs
4. Patients with pregnancy
5. Patients with other causes of hepatitis

Procedure methodology

The study included 165 patients, from the Department of General Medicine at Bhagwan Mahaveer Jain Hospital, Bangalore. They were selected by the above mentioned inclusion and exclusion criteria. All subjects under the study were explained about the study and written informed consent was taken. Each recruited patient was subjected to a questionnaire of thorough medical history and clinical examination if the inclusion criteria was fulfilled. All investigations were done as per the routine protocol, and no special tests which would financially burden the patient were ordered. Detailed history including the duration of fever, headache, retro orbital pain, myalgia, and arthralgia were taken. Symptoms suggestive of hepatic dysfunction, including abdominal pain and vomiting were asked for. Patients were also questioned for symptoms suggestive of bleeding manifestations such as melena, hematemesis, gum bleeding, per vaginal bleeding, epistaxis and hematuria. A meticulous examination was conducted, which included vitals and general physical examination to see for icterus and petechial rashes. Systemic examination was done in detail to look for polyserositis such as pleural effusion and ascites. Hypochondriac tenderness suggestive of hepatic dysfunction was elicited. Blood samples were collected for dengue serology testing by rapid dengue test kit, which tested for NS1 antigen and

anti-dengue IgM and IgG antibodies. Investigations ordered included platelet count (PC), hematocrit, Liver Function Tests (LFT), serum creatinine, serum electrolytes, prothrombin time (PT), International Normalised Ratio (INR). Chest x ray and ultrasound were done to look for features indicative of polyserositis. LFT, PC and hematocrit were monitored on alternate days. Serum transaminases, aspartate aminotransferase (AST), [also known as serum glutamic-oxaloacetic transaminase (SGOT)] and alanine aminotransferase (ALT) [also known as Serum glutamic pyruvic transaminase (SGPT)], were monitored frequently in patients with severe thrombocytopenia, elevation of serum transaminases at time of admission and in patients with severe dengue. Patients with elevated serum transaminases were classified either as mild elevation (two fold increase), moderate elevation (three to four fold increase) or severe elevation (greater than 4 fold increase). The normal reference value of AST was considered as < 40 IU/L and that of ALT as < 41 IU/L. Patients were classified into DHF or DSS as per WHO criteria.

Statistical analysis

The results for each parameter (numbers and percentages) for discrete data and averaged (mean + standard deviation) for continuous data, were presented in tables for analysis. Proportions were compared using Chi-square test of significance (χ^2). Chi-square and Fisher exact tests were performed to test for differences in proportions of categorical variables between two or more groups. The level $P < 0.05$ was considered as the cutoff value or significance. The Student ‘t’ test was used to determine whether there was a statistical difference between the groups in the parameters measured. Data analysis was carried out using Statistical Package for Social Science (SPSS, V 10.5) package.

III. Result

A total of 165 Patients with dengue fever were observed. Age group selected was in the range of 18-70, with a mean of 33.43±12.70. 93 patients (56.4%) were males and 72 (43.6%) were females.

More than 50% of patients presented with typical features of dengue fever (fever, headache myalgia and retro orbital pain). Mean duration of symptoms observed was 4.37±1.620 days and median was 4.00 days. History of fever was seen in all the patients (100%). Other symptoms reported include headache (74.5%), myalgia (57%), retrorobital pain (51.5%), arthralgia (50.9%), vomiting (27.3%), rash (19.4%), abdominal pain (18.2%), and diarrhea (18.2%). Bleeding manifestations were seen in 27.2% of the patients, with melena being the most common form.

Among 165 patients, 153 (92.7%) patients were positive for NS1 antigen, 50 (30.3%) patients for IgM Antibodies, and 48 (29.1%) for IgG antibodies. 46 (27.8%) patients were positive for both NS1 Antigen and IgM antibodies. At the time of admission almost all patients 99.3% had thrombocytopenia.

As the study was mainly performed to prognosticate dengue outcome based on hepatic dysfunction, a thorough clinical examination performed to evaluate for signs of hepatic dysfunction. Hepatomegaly was seen in 58 (35.2%) patients, pleural effusion in 38 (23%), ascites in 36 (21.8%), splenomegaly in 24 (14.5%) and icterus in 20 (12.1%) patients.

Table no 1: Shows signs of hepatic dysfunction seen in the patient population

Sign	Male (n=93)		Female (n=72)		Total (n=165)	
	n	%	N	%	n	%
Icterus	7	7.5	13	18.1	20	12.1
Pleural effusion	13	10	25	34.7	38	23.0
Ascites	21	22.6	15	20.8	36	21.8
Splenomegaly	21	22.6	3	4.2	24	14.5
Hepatomegaly	34	36.6	24	33.3	58	35.2

To assess the degree of hepatic dysfunction, liver function tests were ordered on the day of admission, for all patients with confirmed dengue infection. Among 165 patients 39 (23.6%) patients had hyperbilirubinemia, 40 (24.2%) patients had direct bilirubinemia, and 20 (12.1%) patients had indirect hyperbilirubinemia. ALP was raised in 57 (34.5%) patients, GGT was raised in 98 (59.3%) patients and hypoalbuminemia was seen in 15 (9.1%) patients.

Serum transaminases were assessed on the day of admission, during the hospital stay and on day of discharge. 93.8% patients had deranged AST and 81.8% patients had raised ALT. During hospital stay severe elevation of AST was seen in 50.3% patients, while ALT was severely raised in 41.2% patients. By the time of discharge, the percentage of patients with severe elevation of AST & ALT, reduced to 38.7% and 30.9% respectively. Majority of the patients had moderately elevated AST and ALT by then.

Table no 2: Shows aminotransferase levels at different stages of hospital visit

Investigation		Hospital Admission		Hospital Stay		Discharge	
		No. of patients		No. of patients		No. of patients	
		n	%	n	%	n	%
AST	Normal	11	6.6	10	6.06	10	6.06
	Mild	43	26.06	29	17.5	40	24.2
	Moderate	48	29.09	43	26.06	51	30.9
	Severe	63	38.1	83	50.3	64	38.7
ALT	Normal	28	16.9	27	16.3	30	18.1
	Mild	50	30.3	28	16.9	34	20.6
	Moderate	37	22.4	42	25.4	50	30.3
	Severe	50	30.3	68	41.2	51	30.9

In this study most of the patients (66.1%) were discharged after 5 days of hospital stay. 29.1% patients were discharged after 6-10 days and 4.8% patients had 11- 15 days of hospital stay. Mild and moderate elevation of AST & ALT was associated with a hospital stay of 1 to 5 days. Severe elevation of AST (49.2%) and ALT (56%) was seen in patients with hospital stay duration of 6 to 10 days. All the patients who had prolonged hospital stay duration of 11 to 15 days had a severe elevation of AST & ALT.

DSS and DHF were the complications taken into account in the study. 40 (24.2%) patients had DHF and 8 (4.8%) patients had DSS. Almost all the patients with complications had elevated AST and ALT. More than 20 patients with dengue hemorrhagic fever had severe elevation in ALT and AST. Among 8 patients with dengue shock syndrome, 7 patients had severe elevation in transaminases.

Table no 3: Shows patient sub groups with complications of Dengue Fever, and corresponding increase in serum transaminases

Complications		Normal		Mild Elevation		Moderate Elevation		Severe Elevation		Total
		AST	ALT	AST	ALT	AST	ALT	AST	ALT	AST/ALT
DHF	n	1	2	6	8	9	10	24	20	40
	%	2.5	5	15	20	22.5	25	60	50	100
DSS	n	0	0	0	0	1	1	7	7	8
	%	0	0	0	0	12.5	12.5	87.5	87.5	100

Table no 4: Shows value in elevation of transaminases according to Dengue complications

Serum transaminases	Group	n	Mean (IU/L)	Standard Deviation	P value
AST	DHF/DSS	48	2772.77	4097.129	<0.001
	DF	117	297.13	499.708	
ALT	DHS/DSS	48	1383.10	1704.177	<0.001
	DF	117	172.75	220.101	

In this study the elevation of AST in patients with Dengue Fever complications like DHF, DSS had a mean value 2772.77 IU/L. This was more than the mean value of AST in patients with Dengue fever without complications, which was 297.13 IU/L. This was statistically significant. Mean value of ALT (1383.10 IU/L) in patients with complications (DHF, DSS) was more than that of patients without complications (172.75 IU/L). This too was statistically significant.

IV. Discussion

Dengue virus (DEN) is a small single-stranded RNA virus comprising of four distinct serotypes (DEN 1 to DEN 4). All dengue serotypes can be responsible for similar symptoms, ranging from subclinical infection to dengue fever, DHF and eventually DSS. The first case of dengue was reported in India in 1780 in Chennai. Since the 1970's, there have been several outbreaks of the dengue epidemic in various parts of the country. The increasing need for hospitalization places severe stress on the financial and health care system.

The mean age of the patients in our study was 33.43±12.70, with maximum patients in the age group of 21-30 years (35.2%). In previous studies done in the late 1990's in India, maximum case load was seen in the 5-20 year age⁶. However, more recent studies done by Nishat Hussain et al⁷, Monira Pervin et al⁸ and Ekta Gupta et al⁹, show a shift in the mean age group to 21-30 years, as consistent with our study. The possible explanation for shift in the mean age of population given by Nishant Hussain et al⁷, was the existence of nonimmune adult population. The present study has a male to female ratio of 1.2:1 which is similar to other studies done in India by Ekta Gupta et al⁹ and Seema Avashi et al¹⁰. This gender variation may be attributed to more outdoor activities performed by males, making them more susceptible to *Aedes* bite, and differences in healthcare seeking behavior¹¹.

Dengue fever is an acute febrile illness of 2-7 days duration, with two or more of the following manifestations: headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, and

leucopenia. All patients in our study had a history of fever (100%), which is in unison with most other studies^{12,13,14}. Headache (73.1%), myalgia (59.1%) and retro-orbital pain (51.6%) were reported. These symptoms overlap with clinical presentation in other entities like typhoid, enterovirus and leptospirosis, which can lead to a possible delay in diagnosis of dengue. Consequently, late initiation of treatment may lead to increased morbidity. Bleeding manifestations were seen in 45 (27.2%) patients with melena (31.4%) being the most common form of bleeding, similar to previous reports¹⁵. Deranged liver functions may have a significant role in bleeding, in addition to thrombocytopenia.

Dengue infection may lead to fulminant hepatitis with high mortality. Hepatitis in dengue may be due to direct damage of hepatocytes and Kupffer cells and immune mediated damage by T-cell activation, and cytokine storm. Pathological changes include midzonal hepatocyte necrosis, micro-vesicular steatosis, inflammatory infiltration and Councilman Bodies, indicating viral induced apoptosis of the hepatocytes.

Common features suggesting liver involvement are the presence of hepatomegaly, clinical jaundice, abdominal pain, anorexia and vomiting. In our study, hepatomegaly, splenomegaly, pleural effusion and ascites were considered as signs of liver dysfunction, similar to other studies^{16,12}. The presence of jaundice in dengue fever is said to be a sign of fulminant liver failure. Omesh Goyal¹⁷ et al and Srivenu Itha¹⁸ et al observed increased morbidity due to circulatory collapse and dengue shock syndrome in patients with elevated bilirubin. In our study 73.5% of the patients with elevated bilirubin had evidence of DSS/DHF. Hence clinical jaundice may indicate severe hepatitis and poor prognosis in dengue fever.

Elevation of transaminases and liver injury were considered the major predictors in dengue outcome by Ahmed et al¹⁹ and a study conducted by Trung and colleagues in South Vietnam²⁰. 93% of the patients in our study had elevated AST and 87% had elevated ALT. We report higher values of AST and ALT in our study population, than reported by Wong et al, and other studies^{19,21,22}. We could assume that the reason for higher transaminases levels in our population is either due to a more virulent strain of dengue virus, or that the virus is more hepatotoxic.

Another noteworthy point is that AST elevation was higher than that of ALT. This may be because of extra-hepatic release of AST, from various sources such as the liver, heart, muscle and red blood cells. ALT is almost exclusively secreted by the liver. Similar results were published by Chung et al, and they attributed it to the release of ALT from damaged monocytes²³.

In our study, severe elevation in AST/ALT was associated with prolonged hospital stay (11-15 days), whereas mild/moderate elevation was seen in patients with shorter hospital stay. This is in unison with a study by Ahmed et al, which showed a positive correlation between raised ALT and increased hospital stay¹⁹.

Severe dengue may present as DHF/DSS characterized by increased capillary leakage, serositis, multi organ dysfunction, circulatory shock²⁴. Majority of the patients with dengue complications of DHF/DSS had severely elevated transaminases and liver impairment as reported by Ahmed et al¹⁹ and Kumar Basu et al²⁵. The study undertaken by Parkash and colleagues similarly showed that liver impairment (ALT > 300 IU) in Dengue fever was associated with extended hospitalisation, hemorrhage, kidney failure and mortality²⁵. Similarly, our study observed that 87.5% of patients with DSS and 60% of patients with DHF had severely elevated transaminases. This possibly shows that liver dysfunction majorly affects the prognosis of dengue fever.

In conclusion, our study found a high prevalence of hepatitis in hospitalized patients with dengue fever. AST elevation was greater than ALT elevation. The study population had a mortality of 1.8%. An obvious limitation of our study is that since it is a hospital based observational study, the sample size is small. A confirmatory study, with a larger sample size is needed. Further immunological studies need to be done in order to understand the precise pathophysiology of hepatic involvement in dengue fever.

V. Conclusion

Our study shows a high prevalence of hepatitis among patients hospitalized with dengue. Hepatic dysfunction is evidenced by the elevation of AST/ALT enzymes. Since these enzymes are elevated from the time of admission, they can help in identifying probable dengue fever, since the diagnosis of dengue may be difficult in some cases and ELISA for dengue may not be positive in the first few days of infection. Elevated transaminases, not only help in diagnosing dengue, but also may predict morbidity and prognosis. This is evidenced by the fact that patients with severe elevation in AST/ALT had prolonged hospital stay, and severe complications like DHF/DSS. Hence elevated transaminases can be used as an early marker to assess dengue severity, and can help identify high risk cases.

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