

ORIGINAL ARTICLE

Clinico-pathological Correlation with Liver Enzymes in Dengue Infection

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Abstract:

Dengue infection is a major vector borne disease. The classical signs and symptoms include high fever, severe headache, chill, and rash. Atypical manifestations of dengue infection with hepatic involvement are frequently reported, ranging from mild elevations of liver enzymes to acute liver failure. Analysis of 110 serologically confirmed cases of dengue infection in Holy Family Red Crescent Medical College hospital a tertiary care hospital was done. Patients with normal aminotransferase levels were categorized into Grade A, patients with at least one of the enzymes raised above normal but less than 3 times were categorized into Grade B, those with at least one of the enzymes elevated more than 3 times but less than 10 times were graded as C, and those with elevations more than 10 times as Grade D. 83.7% patients had alterations of transaminase levels, with 45.5% categorized into grade b, 30.9% into grade C, and 7.3% into grade D or acute hepatitis (P value 0.224). Rise of aspartate aminotransferase (AST) levels were higher compared to the levels of alanine aminotransferase (ALT). Liver damage with alteration of aminotransferases is a common manifestation of dengue infection and also valuable markers for monitoring these patients.

Introduction:

Dengue is a most rapidly spreading mosquito-borne viral disease in the world and in the last 50 years the incidence has increased by 30 folds with the expansion of geographical distribution. This increase is thought to be due to worldwide expansion of trade and travel which increased the spread of mosquitoes as well as rapid urbanization which increased mosquito breeding sites. The mosquito *Aedes aegypti* is the vector. Dengue infection has now become the global health threat. Around 2.5 million people in 100 epidemic countries are susceptible to dengue infections. Epidemic dengue is major public

health problem in south-East asia including Bangladesh.

Dengue fever (DF) was first documented in Bangladesh in mid-1960s but an outbreak of Dengue haemorrhagic fever (DHF) was not reported that decades¹. On June 2000 ELISA proved cases of DHF with an outbreak of DF (>5000 hospitalized cases reported) occurred in Dhaka and other major cities of Bangladesh².

The classical signs and symptoms of this infection include high fever, violent headache, chill and rash. However, there are a number of

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atypical forms of dengue infection in response to severe dengue cases where viremia is high including liver dysfunction³. Hepatic involvement is characterized by right hypochondriac pain, hepatomegaly, jaundice, and elevated aminotransferase levels peaking at ninth day and gradually decreasing to normal within four weeks⁴. Histopathology finding of liver involvement include centrilobular necrosis, fatty alteration, hyperplasia of Kupfer cells, acidophil bodies, and monocyte infiltration of portal tract⁵. Debate continues as to whether dengue associated hepatic dysfunction indicates a direct viral effect, arises secondary to an aggressive host immune response to the virus, or reflects a complex interaction of these two mechanisms⁶.

Materials and method:

Total 110 serologically positive patients attending Holy Family Red Crescent Medical College hospital a private tertiary care hospital in Dhaka city from June 2015 to November 2016 were included in this study. Complete blood count, serological tests for dengue and liver function tests were done. Dengue NS1 antigen was done from 1-4 days of illness and IgM, IgG

antibodies were done ≥ 7 days of illness. Patients of NS1 antigen and/or IgM antibody positive cases were included in this study.

The degree to which liver was involved was classified into 4 groups based on aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. The reference value of AST and ALT was $<40\text{IU/L}$. Patients with normal aminotransferase levels were grouped as Grade A. Those with levels of at least one of the aminotransferases elevated but <3 times the reference value were grouped as Grade B. Patients with the levels of at least one of the aminotransferases >3 times but <10 times the reference value were grouped as Grade C and those with an increase level of one or both enzymes >10 times were classified as Grade D and thereby defining the presence of acute hepatitis. Data were analyzed on SPSS soft ware and Chi-square test was done to measure the level of significance.

Results:

Age of the patient was 12-80 yrs. Average age was 35.5 ± 14.6 . Among the patients, 64(58.2%) were male and 46(41.8%) were female.

Table-I: Transaminases levels

Sex	Different groups				Total	p-value
	Grade A	Grade B	Grade C	Grade D		
Male	10 (15.6)	32 (50.0)	20 (31.3)	2 (3.1)	64	
Female	8 (17.4)	18 (39.1)	14 (30.4)	6 (13.0)	46	
Total	18 (16.4)	50 (45.5)	34 (30.9)	8 (7.3)	110	0.224

Most of the patients 44(40%) had platelet count $>100000/\text{cm}^3$, 34(30.90%) had platelet count between $50,000 - 100000/\text{cm}^3$, and 32(29.09%) patients had platelet count $<50000/\text{cm}^3$. Transaminase level $>40\text{IU/L}$ was considered as high. 83.7% patients had alteration of transaminases with 45.5% in grade B, 30.90% in grade C and 7.3% in grade D or acute hepatitis (P value 0.224). Aspartate aminotransferase levels were higher compared to levels of alanine aminotransferase. Enzyme levels were depicted in table I.

Table II: Status of different antibody

Anti body	Positive	Negative	Total
IgM	67 (76.1)	21 (23.9)	88
IgG	22 (25.3)	65 (74.7)	87
NS ₁ antigen	35 (97.2)	1 (0.9)	36

Table III: Association of S. bilirubin with antibody IgM

S. Bilirubin	IgM		Total	p-value
	Positive	Negative		
Normal	57 (93.4)	19 (90.5)	76 (92.7)	0.653
Abnormal	4 (6.6)	2(9.5)	6 (7.3)	
Total	61 (100.0)	21 (100.0)	82 (100.0)	

Chi-square test was done to measure the level of significance

Table IV: Association of S. bilirubin with antibody IgG

S. bilirubin	IgG		Total	p-value
	Positive	Negative		
Normal	18 (90.0)	57 (93.4)	75 (92.6)	0.612
Abnormal	2 (10.0)	4 (6.6)	6 (7.4)	
Total	20 (100.0)	61 (100.0)	81 (100.0)	

Chi-square test was done to measure the level of significance

Table V : Association of S. bilirubin with anti body NS₁ antigen

S.bilirubin	NS ₁ antigen		Total	p-value
	Positive	Negative		
Normal	23 (85.2)	1 (100.0)	24 (85.7)	0.683
Abnormal	4 (14.8)	0 (0.0)	4 (14.3)	
Total	27 (100.0)	1 (100.0)	28 (100.0)	

Chi-square test was done to measure the level of significance

Among the patients IgM was positive in 67(76.1%), IgG was positive in 22 (25.3%), and NS₁ antigen was positive in 35 (97.2%) patients. Serum bilirubin was abnormal or high in 4 IgM positive cases, in 2 IgG positive cases and 4 in NS₁ positive cases.

Out of 110 patients, 103(93.64%) had classical dengue and 7(6.36%) had dengue haemorrhagic fever. No patient developed dengue shock syndrome and no patient has died. 83.64% patients had raised levels of AST and 76.36% patients had raised ALT level.

Discussion:

Liver involvement in Dengue may be characterized by manifestations such as pain in right hypochondrium, hepatomegaly, varying degrees of jaundice and an increase in transaminases, ALT and AST. Our study showed liver involvement was almost universal in patients with dengue infection which comparable with previous reports from other developing countries³. About 92% patients had mild to moderate liver dysfunction although about 8% had acute hepatitis without significant complications. None of the patients included in

this study had previous history of active liver disease.

In this study most patients had elevated AST levels. In patients of grade B, C or D elevation of AST occurred in most cases either or along with ALT elevation. ALT levels were normal in 23% patients whereas AST levels were normal in 14% patients. Similar finding was reported in other studies^{5,6}. This pattern of more AST elevation than ALT elevation quickly and peaking at high level is unusual and differs from those with acute hepatitis caused by hepatitis viruses⁷. This type of higher AST levels in dengue infection may be explained by insult to heart muscle, skeletal muscle, erythrocytes etc⁸.

De Souza et al. classified 42.5% of patients as grade B, 17.5% as grade C, and only 1.8% as grade D according to aminotransferase levels⁹. On the other hand in our study 45.5% were grade B, 30.9% grade C and 7.3% had grade D liver involvement.

Serum bilirubin was mildly raised in 7.27% cases but no one developed clinically detectable jaundice.

Liver damage was found more commonly among females in a large study from Brazil where 74.6% of females compared to 52.2% of males with 4.2% of them having acute hepatitis⁵. In our study females and males are equally affected 82.61% and 84.38% respectively with 13% had acute hepatitis. This difference may be because of our small study. A larger study is required to truly establish whether the aminotransferases could be used as a prognostic marker.

Conclusion:

Dengue has a wide spectrum of manifestations along with its typical febrile attack. The effects on liver are usually asymptomatic with elevated transaminase levels but may progress to fulminant hepatitis failure as well. Significant rise of liver enzymes indicate severe dengue. The variable manifestations are a big challenge to the clinicians treating the condition. Management is primarily supportive and the outcome is usually

good. Care must be taken regarding the diagnosis and use of drugs which may worsen the liver damage.

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