Original Research Article

Study of hepatic dysfunction in dengue fever

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Abstract

Introduction: Hepatic involvement is a common feature in dengue fever, which prolongs the clinical course of this self-limiting viral infection and constitutes assign of worse prognosis, Vomiting and abdominal pain in the early stages point towards hepatic dysfunction. Various studies have shown that in all those patients who develop complications like dengue haemorrhagic fever, dengue shock syndrome, Hepatic failure, ARDS, Renal failure and Septicaemia, the levels of AST and ALT were raised significantly. The severity of hepatic involvement can be a major contributing factor in morbidity and mortality of such patients with Dengue fever. So AST and ALT can be a useful early marker to assess the severity of the disease which can thereby lead to early recognition of high risk cases.

Methods: The study is an observational descriptive study conducted at Vydehi Institute of Medical Sciences and Research Centre, Bangalore, in the Department of medicine between Jan 2013- Jan 2015 to study the profile of liver involvement among a group of adult patients suffering from dengue fever and the association of elevated liver enzymes with complications. Detailed history, a complete general physical and systemic examination, with relevant investigations was done on hundred patients as per the proforma.

Results: The results were analysed using SPSS-19.A total of 100 patients of dengue fever were studied, out of which seventy patients had elevated AST levels and seventy three had elevated ALT levels. Fever followed by headache was the most common symptoms at presentation while vomiting and pain abdomen in the early stage suggested hepatic dysfunction. AST and ALT were statistically higher in these patients and in those developing complications like DHF, DSS, hepatic failure, ARDS, ARF and encephalopathy.

Conclusion: Liver injury is universal in adult patients with Dengue fever. Though liver involvement is asymptomatic in a large majority, in some patients it leads to clinical manifestations. Severity of hepatic involvement can be a major contributing factor in morbidity and mortality of such patients with Dengue fever. So AST and ALT can be a useful early marker to assess the severity of the disease which can thus lead to early recognition of high risk cases.

Keywords: Dengue fever; AST; ALT; Hepatic dysfunction

1. Introduction

Dengue fever is an important arthropod-borne viral infection of humans. Worldwide, an estimated 2.5 billion people are at risk of infection.[1] It is estimated that more than 50 million infections occur each year, of which 500,000 hospitalisations are of dengue haemorrhagic fever, with the case fatality rate exceeding 5% in some areas.[1-4]

Liver injury is nearly universal in adult patients with dengue fever. Dengue virus antigen is found in Kupfer cells and sinusoidal lining cells in the liver. Detection of dengue antigen virus in hepatocyte suggests that such cells can support viral replication. Histopathological findings include centrilobular necrosis, fatty alterations, hyperplasia of the Kupfer cells, acidophil bodies and monocyte alteration of the portal tracts.[6-8]

In most cases hepatic involvement prolongs the clinical course of this self limiting viral infection and constitutes a sign of worst prognosis. This verity of hepatic involvement can be a major contributing factor in morbidity and mortality of such patients with Dengue fever. So AST and ALT can be a useful early marker to assess the severity of the disease which can thereby lead to early recognition of high risk cases.

2. Materials and methods

This study was conducted from January 2013 to Jan 2015 in the department of medicine in Vydehi Institute of Medical Sciences and Research Centre, Bengaluru, Which consisted of 100 patients admitted with signs and symptoms suggestive of dengue fever. The institutional ethical clearance for this study was obtained from the ethical

committee. After obtaining a detailed history, general physical examination and systemic examination, the patients were subjected to relevant investigations. Dengue Serology, Complete Blood Count, Liver Function Tests, Renal Function Tests, Ultrasound Abdomen were done on all patients. Dengue serology was done using rapid card tests and reported accordingly as NS1Ag, IgM and IgG. Patients above the age of 18 years who were serologically confirmed to have dengue fever were included in the study while we excluded those patients below the age of 18 years, those having other infections which cause thrombocytopenia like malaria, enteric fever and patients suffering from alcoholic liver diseases.

3. Results and analysis

Table 1: Showing Age wise distribution

Age in years	No. of patients	%
18-20	19	19.0
21-30	48	48.0
31-40	23	23.0
41-50	10	10.0
Total	100	100.0

Total number of cases studied is 100. Mean age: 28.24 years
Age range: 18-50years

Maximum incidence of dengue fever occurred in the age group of 21-30 years followed by 31-40 year.

Table 2: Gender distribution

Gender	No. of patients	%
Female	20	20.0
Male	80	80.0
Total	100	100.0

Table 3: Distribution of cases with respect to dengue serology tests

Tests	Gender		Total (n=100)
	Female (n=20)	Male (n=80)	
NS1 Ag	14(70%)	61(76.3%)	75(75%)
IgM	13(65%)	38(47.5%)	51(51%)
IgG	10(50%)	28(35%)	38(38%)

75 patients were positive for NS-1AG, 51 patients for IgM and 38 patients were positive for IgG. Out ofthese28 patients were positive for both NS-1Ag and IgM.

Table 4: Symptoms at the time of presentation

Symptoms	Gender		Total (n=100)
	Female (n=20)	Male (n=80)	
Fever	17(85%)	68(85%)	85(85%)
Headache	16(80%)	57(71.3%)	73(73%)
Myalgia	14(70%)	51(63.8%)	65(65%)
Retroorbital pain	15(75%)	55(68.8%)	70(70%)
Abdominal pain	7(35%)	47(58.8%)	54(54%)
Rash	4(20%)	12(15%)	16(16%)
Arthralgia	9(45%)	43(53.8%)	52(52%)
Bleeding	3(15%)	16(20%)	19(19%)
Vomiting	6(30%)	27(33.8%)	33(33%)
Diarrhea	4(20%)	15(18.8%)	19(19%)

Table 5: Signs at the time of presentation

Signs	Gender		Total (n=100)
	Female (n=20)	Male (n=80)	
Icterus	2(10%)	11(13.8%)	13(13%)
Pleural effusion	4(20%)	22(27.5%)	26(26%)
Ascites	3(15%)	11(13.8%)	14(14%)
Hepatomegaly	7(35%)	41(51.3%)	46(46%)
Splenomegaly	4(20%)	11(13.8%)	15(15%)

Hepatomegaly and pleural effusion were the most common findings in patients with dengue fever.

Table 6: Showing Percentage of patients having elevated AST levels

AST	No. of patients (n=100)	%
Normal	29	29.0
Mild Elevation	30	29.0
Moderate elevation	22	22.0
Severe elevation	19	19.0
Total	100	100.0

Table 7: Showing patients having elevated ALT levels.

ALT	No. Of patients(n=100)	%
Normal	27	27.0
Mild Elevation	32	32.0
Moderate elevation	30	30.0
Severe elevation	11	11.0
Total	100	100.0

70% of patients had elevated AST levels. This was further divided into mild (two fold increase), moderate (three to four fold increase) and severe (greater than 4 fold increase).

Table 8: Showing Liver Function Tests of the patient.

Variables	Gender		Total (n=100)
	Female (n=20)	Male (n=80)	
Total Bilirubin (mg/dl)			
□0	0(0%)	0(0%)	0(0%)
0-1.3	17(85%)	66(82.5%)	83(83%)
>1.3	3(15%)	14(17.5%)	17(17%)
AST (IU/L)			
<15	0(0%)	0(0%)	0(0%)
15-50	6(30%)	24(30%)	30(30%)
>50	14(70%)	56(70%)	70(70%)
ALT(IU/L)			
<10	0(0%)	0(0%)	0(0%)
10-35	6(30%)	21(26.3%)	27(27%)
>35	14(70%)	59(73.8%)	73(73%)
ALP(IU/L)			
<53	5(25%)	20(25%)	25(25%)
53-128	10(50%)	55(68.8%)	65(65%)
>128	5(25%)	5(6.3%)	10(10%)

Table 9: Showing complications

Complications	No. of patients (n=100)	%
Dengue Hemorrhagic Fever	19	19
Dengue Shock Syndrome	4	4.0
Septicemia	3	3.0
Hepatic failure	2	2.0
Encephalopathy	2	2.0
Renal failure	3	3.0
Acute Respiratory Distress Syndrome	3	3.0

DHF is the most common complication seen in this study.

Table 10: Time interval between onset of symptoms and hospitalization

Day of presentation	Number of patients	Percentage
1	6	6%
2	17	17%
3	31	31%
4	28	28%
5	10	10%
6	5	5%
7	3	3%

Most of the patients presented on the third and fourth day of the illness.

Table 11: Showing Complications with relation to AST levels

Complications	AST			Total (n=100)
	Mild Elevation (n=29)	Moderate Elevation (n=22)	Severe Elevation (n=19)	
Dengue Hemorrhagic Fever	7(24.1%)	10(45.5%)	2(10.5%)	19(19%)
Dengue Shock Syndrome	0(0%)	2(9.1%)	2(10.5%)	4(4%)
Septicemia	0(0%)	1(4.5%)	2(10.5%)	3(3%)
Hepatic failure	0(0%)	0(0%)	2(10.5%)	2(2%)
Encephalopathy	0(0%)	1(4.5%)	1(5.3%)	2(2%)
Renal failure	0(0%)	1(4.5%)	2(10.5%)	3(3%)
ARDS	1(3.3%)	0(0%)	2(10.5%)	3(3%)

Table 12: Showing complications with relation to ALT levels.

Complications	ALT			Total (n=100)
	Mild Elevation (n=32)	Moderate Elevation (n=30)	Severe Elevation (n=11)	
Dengue Hemorrhagic Fever	7(87.5%)	10(93.3%)	2(18.2%)	19(19%)
Dengue Shock Syndrome	1(3.1%)	1(3.3%)	2(18.2%)	4(4%)
Septicemia	1(3.1%)	0(0%)	2(18.2%)	3(3%)
Hepatic failure	0(0%)	0(0%)	2(18.2%)	2(2%)
Encephalopathy	0(0%)	1(3.3%)	1(9.1%)	2(2%)
Renal failure	1(3.1%)	0(0%)	2(18.2%)	3(3%)
ARDS	1(3.1%)	0(0%)	2(18.2%)	3(3%)

4. Discussion

In our study it was noted that the incidence of dengue fever varied from minimum age of 18 years to a maximum age of 47 years with majority noted in the 3rd decade (48%). Similar result was noted by Nishat Hussain *et al*,[9,10] (Table-1). Male patients (80) outnumbered the females (20) [10-12] (Table-2)

According to the present study, 85 out of the 100 patients presented with fever. Headache was seen in 73 patients, retro orbital pain in 70 and myalgia in 65 patients. Bleeding manifestations were seen in 19 patients which was statistically significant in patients with raised AST ($p<0.001$) and raised ALT ($p<0.005$) levels. 11 had Upper Gastrointestinal bleed, four patients had bleeding gums, three had epistaxis and one patient had haemoptysis. 54% of the patients had abdominal pain with tenderness mainly in the right hypochondrial region. 33% of the patients had vomiting at the time of presentation.

The presence of vomiting from day one may indicate hepatic dysfunction early on.[11,13] 75 patients were positive for NS-1AG, 51 patients for IgM and 38 patients were positive for IgG. Out of these 28 patients were positive for both NS-1Ag and IgM. (Table-3)

Skin rashes were seen in 16% of the patients which was significant in patients with raised AST ($p<0.004$) and raised ALT ($p<0.002$). 46% of the patients had hepatomegaly, 15% of patients had splenomegaly with or without hepatomegaly. Pleural effusion was the second most common finding seen in 26% of patients at presentation. Icterus and ascites were seen in 13% and 14% of patients respectively (Table-4).

In the study done by Zhang *et al* in China in 2014 it was shown that a total of five symptoms/signs significantly predict dengue patients progressing in to DHF/DSS, these were vomiting/nausea, abdominal pain, skin rashes, bleeding, and hepatomegaly[12] (Table-4), Ascites in these patients were mild and usually detected on ultrasonography (Table-5) in our study19 patients had DHF and four had DSS all of whom had the above mentioned symptoms. Bradycardia was seen in 27% of patients mainly in the recovery phase of dengue fever. Thrombocytopenia was seen in 76% of the patients. Leucopenia was seen in 60% of the patients. In our study AST was raised in 70% of the patients. Of these 30 patients had a mild elevation, 21 had moderate and 19 of them had severe elevation of AST levels (table 6) Total bilirubin was raised in 17 % of the patients with theme an bilirubin being 1.21+1.4 mg/dl (Table 9).

In a study done by Prakash *et al* at Belgaum it was shown that 25% of the patients had an elevated total bilirubin level.[13] This was similar to a study done by Asim A *et al* in Lahore, Pakistan in 2014 where he had divided the patient shaving elevated liver enzymes in to three groups i.e., mild (two fold increase in LFT), moderate (3-4 fold increase in LFT) and severe (greater than 4 fold increase in LFT based on

the degree of elevation of the liver enzymes.[14] Kunal G *et al* showed that 85% of the patients had an elevated AST level.[15] ALT levels were raised in 73% of the patients, 32 of whom mild, 30 had moderate and 11 had severe elevation of the enzyme.

Kunal G *et al* showed that 77.8% of the patients had an elevated ALT level.[15] (Table 9) for severe dengue by WHO 2009 classification, AST and ALT were significantly higher during the febrile and critical phases. Liver involvement may be characterized by manifestations such as pain in the right hypochondrium, hepatomegaly, varying degrees of jaundice, chyluria and an increase in liver markers, principally ALT and AST, similar to those found in acute hepatitis caused by the A, B, C, D and E viruses.

Kuo *et al* [16,17] reported that approximately90%ofthepatients in that study had abnormal AST levels, while abnormal levels of ALT, bilirubin, alkaline phosphatase and gamma-glutamyl transferase (GGT) were found in80%, 7%, 16% and83%, respectively of patients with classic dengue. Therefore, AST, ALT and globulin are valuable parameters for the evaluation of these verities of the infection. The study done by Dinh The Trung in 2010 revealed that in terms of correlation between transaminase levels and markers of diseases verity, during the critical period, AST and ALT levels were significantly higher in the dengue patients who experienced shock compared with those without shock.[20]

In addition, the AST and ALT levels for dengue patients correlated significantly with bleeding severity in the critical and convalescent periods. Transaminase levels began to increase from an early stage (day1–3of illness) and peaked during the second week of illness. In our study most of the patients reported second to third day of symptoms (Table-8) Severe liver involvement (acute liver failure and/or jaundice) was rare, but also commonly occurred during the second week of illness. By follow-up, AST levels had returned to normal levels in most patients, but ALT levels remained slightly increased above the normal range in approximately one-third of the patients; This general pattern, with AST increasing more quickly and peaking at a higher level and then reverting to normal sooner than ALT levels, is unusual and differs from that commonly seen during acute hepatitis caused by hepatitis viruses.

The etiology of elevated aminotransferase levels during acute dengue illness is unclear since AST is expressed in the heart, skeletal muscle, red blood cells, kidneys, brain, and liver, while ALT is secreted primarily by the liver.[17] Because dengue infection can cause acute damage to these non-hepatic tissue types that express AST, raised aminotransferase levels may not be entirely due to severe liver involvement. It is therefore possible that the patients with high AST levels were also more likely to be classified as severe dengue under the 2009 criteria due to the common pathways to non-hepatic tissue damage, even though there is no association with poorer outcome.

5. Analysis of complications

19% of patients had DHF. The most common manifestation being upper gastrointestinal Bleed.(table-10) This study has also shown a higher elevation of AST and ALT in DHF patients. In this study, four patients had developed Dengue shock syndrome, out of which two had severe and two had moderate levels of elevation of AST levels. With regard to ALT two had severe and one patient each had mild and moderate levels of elevation of ALT levels (Table-11 and 12).

In a study done by Uchadadia *et al*. It was shown that 77% of the patients with DHF and 80% of patients with DSS had 3-10 times elevation of the liver enzymes.[18] In our study, two patients had developed hepatic failure both of whom had severe elevation of liver enzymes.

In a study done by Asim Ahmed *et al* in Lahore 5 patients had developed hepatic failure out of which 1 had moderate and 4 had severe type of liver dysfunction.[14] In this study, two patients had developed encephalopathy, one of whom had moderate and one had severe elevation of liver enzymes. In this study, three patients have developed septicaemia of whom two patients had severe and one had moderate elevation of liver enzymes. This was comparable to the study done by Asim Ahmed *et al* in Lahore.[14,15] Acute renal failure (ARF) is a potential complication of severe dengue infection and is typically associated with hypotension, rhabdomyolysis, or hemolysis Three of our patients had developed renal failure.[16,17] In this study, three patients had developed ARDS out of which two had severe elevation of liver enzymes. One patient expired and the other two required ICU stay and ventilator support. TV Devarajan *et al* had published 2 case reports of dengue patients who had mild elevation of liver enzymes and both of whom required mechanical ventilation.[19,20]

6. Conclusion

This study showed that Dengue fever was seen in the third decade and that AST and ALT levels were raised in the majority of these patients. It was also found that AST levels were more than ALT levels, which was uniformly observed in all those patients who developed complications like DHF, DSS, Hepatic failure, ARDS, Renal failure and Septicaemia, proving he fact that severity of hepatic involvement can be a major contributing factor in morbidity and mortality of such patients with Dengue fever. So AST and ALT can be a useful early marker to assess the severity of the disease which can thus lead to early recognition of high risk cases.

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