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A Study on the Correlation between Disease Severity and Hepatic Dysfunction in Dengue Viral Infection

Sreejesh. A. S[1], Sreejith. P. N[2], *Rajesh. K. R[3]

[1]Senior Resident, Department of Medicine, Government Medical College, Thrissur, Kerala, India.
[2]Assistant Professor, Department of Medicine, Government Medical College, Thrissur, Kerala, India.
[3]Assistant Professor in Infectious Diseases, Department of Medicine, Government Medical College, Thrissur, Kerala, India.

Abstract

Background: Dengue fever is one of the major viral illnesses in Kerala.It can vary from asymptomatic infection to serious form of disease with organ system failure. Liver is one of the major organs affected. It can be in the form of simple elevation of transaminases or acute liver cell failure. The purpose of this study was to find out the correlation between disease severity and hepatic dysfunction.**Material and Methods:**The data from 80 patients, admitted in fever wards in our centre, diagnosed with dengue feverwere used in the present investigation. Themaximum numbers of patients belonged to the age group of 40-59 years, and male population was predominant. The liver function tests of the patients were analysed and correlated with the disease severity based on serum bilirubin, albumin, AST, ALT, ALP and INR.**Results:**Among the study population, maximum patients were in the age group of 40-59 years (36.3%) and males were predominant (55%).11% had severe dengue, 20% had dengue with warning signs and remaining had uncomplicated dengue fever. Bleeding manifestations occurred in only 15%and evidence of fluid accumulation, in 19%. One patient died (case fatality 1.25%). Total bilirubin was elevated in 4% and direct bilirubin in 1%. Hypoalbuminemia was present in 69% of the cases. Both AST and ALT were elevated more than two times the normal (>80 IU) in majority on all days of illness with maximum elevation on days 3 and 4, and decreasing on subsequent days. AST and ALT elevations wereclosely associated with increased severity of the disease on all days of illness. Alkaline phosphatase levels were in near normal range in majority (92.5 %) of the patients and INR was found to be abnormal in only 4% of them.**Conclusion:**Hepatic dysfunction occurs in majority of the cases of dengue fever; most importantly elevation of the liver enzymes AST and ALT. The severity of the illnessis also closely associated with AST and ALT levels, especially when they are raised more than five times normal (>200 IU). Abnormal INR and bilirubin values arethe other parameters that match withthe disease severity.

Keywords: Dengue Fever, Hepatic Dysfunction, Liver Function Tests.

***Corresponding Author:**Rajesh K. R,Assistant Professor in Infectious Diseases, Department of Medicine, Government Medical College, Thrissur, Kerala, India.Email: ijkrajesh@gmail.com

Introduction

Dengue fever is one of the most common viral febrile illnesses seen in the medical wards in our hospital settings. The infection is caused by any of the four closely related viruses of genus Flaviviridae; dengue serotypes 1-4. Dengue virus is transmitted by the bite of female Aedes mosquito. The symptomatic cases are categorized as undifferentiated febrile illness (UF), dengue fever (DF), dengue haemorrhagic fever (DHF), dengue shock syndrome (DSS) and unusual dengue (UD) or expanded dengue syndrome (EDS). Warning signs of dengue are

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abdominal pain, persistent vomiting, mucosal bleeding, clinical fluid accumulation, hepatomegaly (>2 cm) and increase in haematocrit (with concurrent decrease in platelet) and lethargy. Mucosal bleeding and abdominal pain are the two most common warning signs. Presence of two or more warning signs warrant observation (10) in an IP care unit. Severe dengue is characterised by one or more of the following: (i) plasma leakage which may lead to shock and/or fluid accumulation, with or without respiratory distress, and/or (ii) severe bleeding, and/or (iii) severe organ impairment.

The disease has direct influence on multiple organ systems, particularly the liver.It can progress from asymptomatic elevation of liver enzymes to acute liver failure.[1] The most common abnormality is raised transaminase levels (often with AST more than ALT). The median AST and ALT values have been found to be higher for severe forms of dengue suggestive of possible association between transaminase levels and disease severity.[2] The elevations are usually modest (i.e. 2-5 times the upper limit of normal values) but marked elevations (5 to 15 times the upper limit of normal) can also occur. Normal plasma AST is a strong negative predictor to exclude dengue haemorrhagic fever.[3] Elevation of alkaline phosphatase (ALP), an evidence of hepatobiliary involvement, is unlikely in dengue induced liver disease.[4] Several studies have shown that elevated levels of liver enzymes have direct correlation with disease severity.[5,6] Coagulation abnormalities may be present but there is only weak correlation between prothrombin time and AST/ALT, suggesting that synthetic function is usually well preserved. Acute liver failure, though uncommon, occurs about one week after the onset of fever with evidence of severe hepatitis, coagulopathy and encephalopathy. Alterations in other liver function parameters such as bilirubin, albumin have also been reported leadingon to abnormalities such as hyperbilirubinemia and hypoalbuminemia.[7]Since there are not many studies on this topic from Kerala, this study attempts to delineate the hepatic involvement in dengue infection in our setting.

Material and Methods

For the prospective study of hepatic dysfunction, patients with acute febrile illness who was diagnosed with dengue fever bypositive IgM antibody or NS1antigen test, admitted in medical wards/ ICU (Department of General Medicine, Thrissur Medical College) during one year period wereconsidered. The sample population was 80, among which maximum patients were in the age group of 40-59 years (36.3%) and males were predominant (55%). Liver function Test (LFT) was analysed for every patient and correlated with the disease severity based on Serum Bilirubin, Albumin, AST, ALT, ALP and INR. The study was carried out after getting clearance from IRB, at MCH, Thrissur and was with consent taken from the patient or his/ her legally valid immediate relative.

Results& Discussion

Among the study population of 80 patients, maximum patients were in the age group of 40-59 years (36.3%) and males were predominant (55%) (Figure 1(a)). Dengue NS1 was the most common diagnostic test that was positive (62%). Of the total cases, 11% had severe dengue, 20% had dengue with warning signs and remaining had uncomplicated dengue fever (Figure 1(b)). Bleeding manifestations occurred in only 15% of the study group and 19% had clinical evidence of fluid accumulation. One patient in the study population died with case fatality rate of 1.25%. Of the study group, 9% had hepatomegaly. Total bilirubin was elevated in 4% and direct bilirubin in 1%. Hypoalbuminemia was present in 69% of the cases and INR was elevated in 4% of the patients. Both AST and ALT were elevated more than two times the normal (>80 IU) in majority of the patients on all days of illness with maximum proportion of elevation on day 3 and 4 of illness, and decreasing on subsequent days. AST and ALT elevation was associated with increased severity of disease on all days of illness with a

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significant p value <0.05. More than five times elevation was seen in severe cases only. Other parameters such as bilirubin and INR elevation above normal were also associated with increased severity. However 75% of the patients with bleeding had normal INR and a normal INR did not exclude bleeding risk. And also, patients with ALP value >300, only showed some evidence of acalculous cholecystitis.

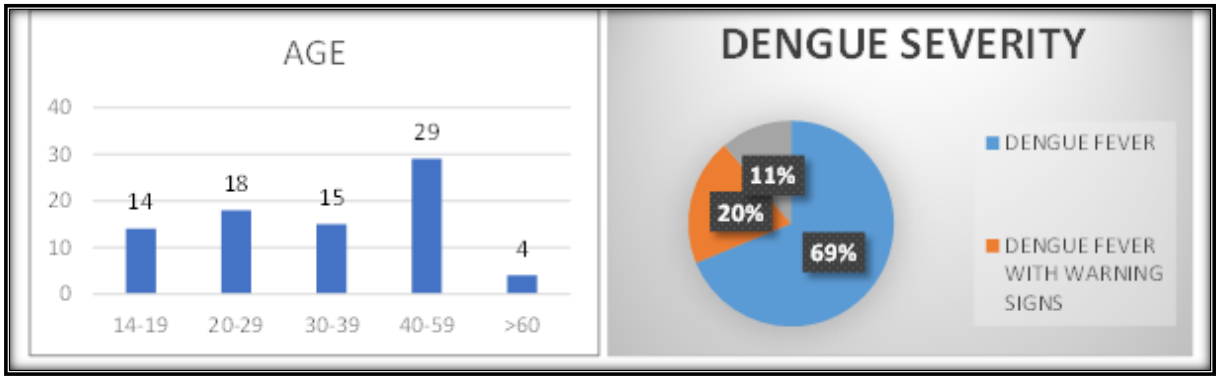

Figure 1: (a) Age Distribution of Patients, (b) Dengue Severity

Of the total 80 cases, 11% had severe dengue, 20% had dengue with warning signs and remaining had uncomplicated dengue fever.

Pattern of Hepatic Dysfunction in Dengue

Based on the LFT results of the patients, the observed pattern of liverfunctions-serum bilirubin, albumin, AST, ALT, alkaline phosphatase and INR- are listed below.

Bilirubin

In the study population only 4% had elevated total bilirubin and 1% had elevated direct bilirubin. Jaundice has been detected in 1.7%-17% in various series. [2]Mild elevations in serum bilirubin are described in similar studies. A study in Punjab showed bilirubin elevation in 19 % of the total dengue patients.[8]

Albumin

Hypoalbuminemia was seen in 69% of the patients. Similar studies have observed a low albumin, <3.5g/dl in 73 % of the patients.[4] Albumin is a marker of chronic liver disease and low levels are seen in chronic cases. However, none of the study population included was having chronic liver disease. In this study hypoalbuminemia was seen in significant number of patients with dengue fever.

AST in Dengue Fever

Aspartate aminotransferase (AST) is one of the major liver enzymes which can be elevated in liver injury. AST is found in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes in decreasing order of concentration. Normal value is taken as 10–40 IU/L. The inter-laboratory variation in normal range is due to technical reasons; no reference standards exist to establish upper limits of normal for ALT and AST. For practical purposes we take more than two times elevation as abnormal. The AST levels of various days after the onset of fever is given below. It was noted that around 78.75 % of the patients had elevated AST levels, above two times the normal, on day 3 or 4 after the onset of fever, the percentage of which decreased during the subsequent days. On day 8 or 9 after the onset of fever only 37.5 % of patients had elevated AST [Figure 2(a)].

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 01, 2022

ALT in Dengue Fever

Alanine aminotransferase (ALT) is another major liver enzyme which is more specific for liver. Similar to AST, ALT levels are elevated in the initial days of fever decreasing in trend as days progress. In this study 65% had more than 2 times elevation on day 3 or 4 of fever with only 22.5 % having elevated ALT on day 8 or 9 after the onset of fever [Figure 2(b)].

A similar study showed highest AST value on day 5 or 6 of illness.[4] Elevated AST and ALT occurred in 86% and 46% according to another study.[9] It is also noted that AST is elevated in more proportion of patients than ALT on all days of illness. Similar study in south India has showed that elevation of AST occurred in most cases either together with ALT elevation or as a lone alteration. ALT levels were normal in 22% of the patients compared to normal AST levels in 15% patients.As there is prominence of musculoskeletal symptoms in dengue, skeletal muscle injury could explain the higher AST levels.[10]

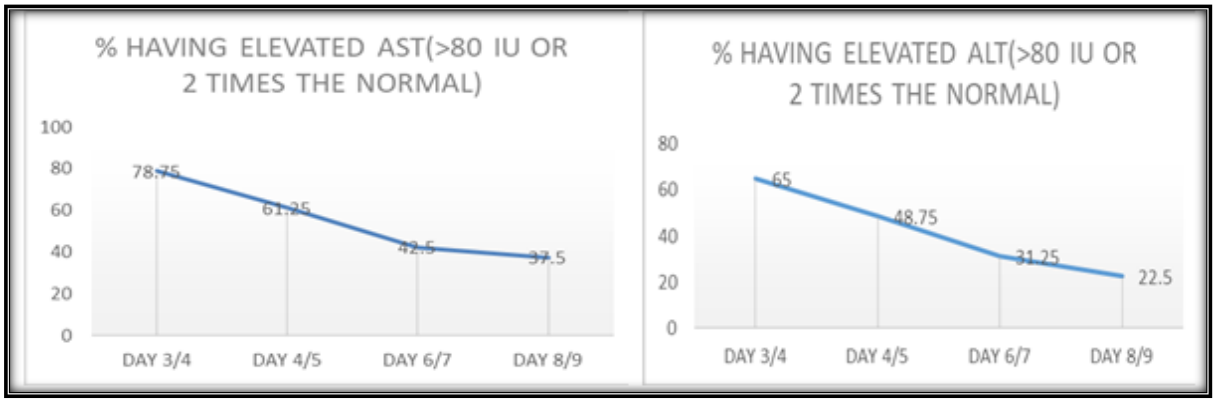

Figure 2: Trend of AST in Dengue fever, (b) Trend of ALT in Dengue fever

ALP in Dengue Fever

Alkaline phosphatase levels are in near normal range in 92.5 % of the patients with dengue fever. More than 3 times elevation is seen only in 2.5 % of the patients. Elevation of ALP has been found up to 32% in some studies.[8]

INR in Dengue Fever

INR was above the normal value in only 4% of the study population.Sanjaya et al has found that INR is elevated in 12% of the patients with dengue fever.[11] INR was within the normal range or only slightly increased according to another similar study.[12]

Clinical Profile of Dengue Fever and Liver Function Tests

The clinical profile of dengue fever is best explained by its WHO clinical classification of severity. Hence dengue is classified as severe and non-severe dengue and its association with various parameters of liver function tests is compared.Severe dengue is characterized by one or more of the following: (i) plasma leakage which may lead to shock and/or fluid accumulation, with or without respiratory distress, and/or (ii) severe bleeding, and/or (iii) severe organ impairment.

Liver Enzymes and Dengue Severity

AST and Severity

Here the relation between AST and dengue severity is compared. AST value more than five times is taken as the cut off. When comparing the AST on day 3/4 of fever and dengue severity, it is seen that out of the 9 severe dengue cases 5 patients (55.6%) had AST more than five times the normal. The % of cases having AST more than five times decline to 25 %,

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for patients with warning signs, and 3.6 % for patients with simple dengue fever. This is statistically significant with a p value of 0.0001[Figure 3 (a)].

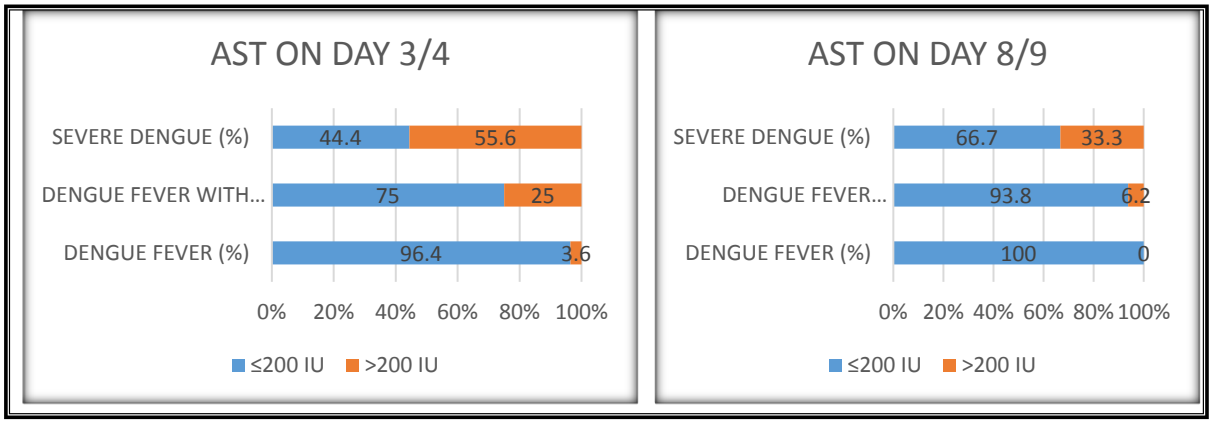

Figure 3: (a) AST on day 3 / 4, (b) AST on day 8 / 9

On day 8/9 after the onset of fever, only none of the patients with fever without warning signs dengue had elevated AST above five times. 6.2 % of the patients with warning signs had AST elevation and 33.3 % of the patients with severe dengue had AST more than five times the normal. This was statistically significant with a p value of 0.001 [Figure 3 (b)].

ALT and Severity

Similar to AST, the values of ALT were compared with severity of dengue. In severe dengue 44.4 % had ALT values above five times the normal. In dengue with warning signs this was 18.7 % and in dengue fever it was 5.5 %.This is statistically significant with a p value of 0.003 [Figure 4 (a)]. On day 8/9 after the onset of fever only severe dengue patients had high ALT values. However, this was not statistically significant with p value of 0.113 [Figure 4 (b)].

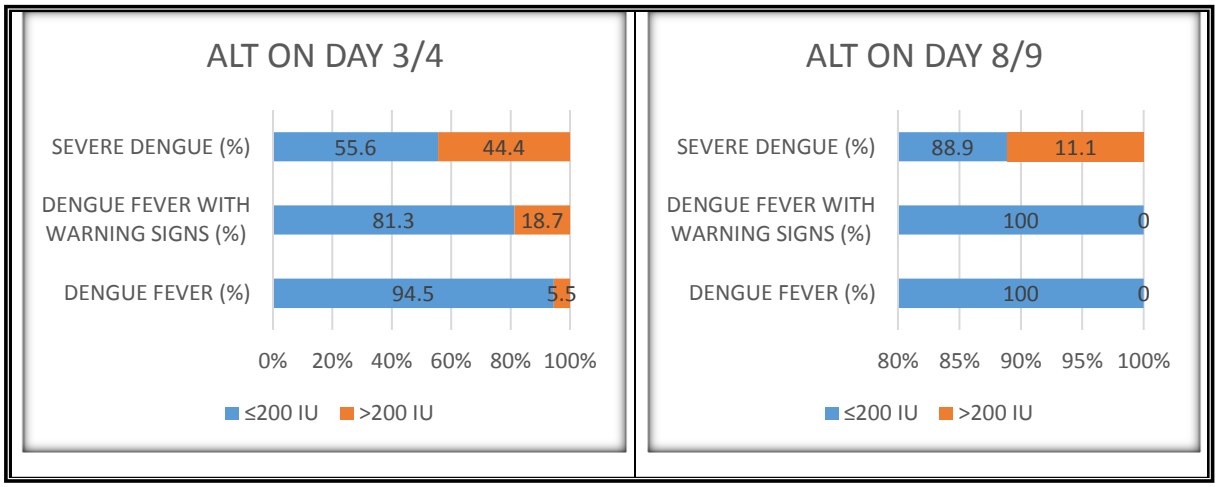

Figure 4: (a) ALT on day 3 / 4, (b) AST on day 8 / 9

AST and ALT on various days of illness was compared with the disease severity. The comparison was made between elevated AST and ALT above five times the normal and disease severity. It was found that proportion of patients with increased AST and ALT, i.e. more than five times the normal, was more in severe dengue and dengue with warning signs group than simple dengue fever on all days. This was statistically significant with a significant p value<0.05 except for ALT on day 8 or 9 of illness. Thus AST or ALT levels

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 01, 2022

above five times the normal is associated with more severe disease and clinical manifestations with maximum proportion occurring in severe dengue fever. Thus in any patients with AST or ALT more than 200 IU on any day of illness we have to anticipate complications. Compared to ALT, proportion of abnormal AST elevation is higher on all days of illness.

Similar studies have shown a similar association that the median Aspartate transaminase (AST) and Alanine transaminase (ALT) values have been found to be higher for severer forms of dengue than for uncomplicated dengue fever.[13]Acute insult to the non-hepatic tissues by the dengue virus can result in higher elevations of AST when compared to ALT rise. Studies in children also have produced a similar result,[14] which observed that the rise in the levels of the enzymes were significantly more in DSS and DHF group (severe dengue). Another study showed that transaminase values five-fold higher than the normal values ($p < 0.005$) were observed in 36.8% and 74.4% of patients with classical dengue and DHF respectively with AST more predominant in both groups.[10]

Other Parameters

In this study 12.5% of patients with dengue with warning signs and 11.2 % of patients with severe dengue had increased bilirubin more than 2 mg/dl. None of the patients with dengue fever without warning signs had increased bilirubin. This is statistically significant with a p value of 0.028. Direct bilirubin was elevated in only one patient with severe dengue and all others had normal value. However no statistical association was found for direct bilirubin.Similar studies have shown that serum bilirubin was higher in DHF compared to DF. [15]

Hypoalbuminemia was found in 81.8% of patients with dengue fever, 50% of patients with dengue with warning signs and 22.2 % of patients with severe dengue. This was statistically significant with a p value of 0.0001. Hypoalbuminemia is more consistent with uncomplicated dengue according to the study. Most patients (77.8%) with severe dengue had normal albumin levels compared to simple dengue.The heterogeneity in the population and severity of the disease may be responsible for such an observation. [2]

Abnormal INR was found in patients with severe dengue and dengue with warning signs only and all patients with uncomplicated dengue fever had normal INR. 12.5% of the patients with dengue with warning signs had INR more than 1.3 and 11.2 % of the patients with severe dengue had increased INR. This was statistically significant with p value of 0.028. But a similar study showed that Prothrombin time was unrelated to the severity of disease.[16] Another study showed that although a raised INR showed a significant association it was raised only in few patients, limiting the value of using it as a predictor.[10] The association between INR and bleeding was analyzed and this showed that 75% of the patients with bleeding had normal INR and 25% with bleeding had elevated INR. Thus a normal INR does not exclude the risk of bleeding and increased INR is associated with increased risk of bleeding. Some studies showed that INR higher than 1.5 is associated with increased bleeding risk.[17]

ALP and acalculous cholecystitis

The association between acalculous cholecystitis and ALP was studied. It was found that out of the 6 patients with acalculous cholecystitis 33.4 % had ALP levels above 300. None of the patients with ALP less than 300, had acalculous cholecystitis. This was statistically significant with a P value of 0.0047.

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 01, 2022

Conclusion

Dengue fever is predominantly found in the age group 40 to 59 years with a male predominance. Among the diagnostic tests commonly used, Dengue NS1 antigen detection is the most common positive test obtained. The proportion of severe dengue cases in the study was 11%. Hepatic dysfunction was seen in majority of the dengue cases with most common abnormality being elevation of the liver enzymes AST and ALT. The pattern observed was increased AST and ALT during the initial days of illness with falling trend as disease progressed. Bilirubin and INR were abnormal only in very few patients though hypoalbuminemia was a common observation. The severity of dengue is associated with both AST and ALT elevation, with increased risk of developing severe dengue for patients having AST or ALT more than five times the normal (>200 IU).The proportion of patients having AST elevation is more than ALT elevation on the same day of illness. An abnormal INR and elevated bilirubin are also associated with increasing disease severity. An increased INR is usually associated with increased risk of bleeding but a normal INR never excludes the risk of bleeding.

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ISSN: 0975-3583,0976-2833 VOL13, ISSUE 01, 2022

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