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THE IMPACT OF DENGUE FEVER ON LIVER: OUR EXPERIENCE AT A TERTIARY CARE CENTER IN PUNJAB

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Abstract: Background- Hepatic involvement has been reported as a complication of dengue fever. Seasonal outbreaks of dengue are common in different parts of India including Punjab. This study was planned with the objective to study the incidence and effect of dengue fever on liver function test. Materials and Methods-Dengue was diagnosed by NS1 antigen test and / or MAC ELISA test in 239 clinically suspected patients reporting to a tertiary care teaching hospital in Punjab. Liver function test were done on admission along with the hematological tests. Results- Increase in liver transaminases was the most common abnormality observed in liver function test with only 2.5% patients having normal values of both the transaminases. The frequency and extent of elevation of aspartate transaminase (AST) was more compared to alanine transaminase (ALT). Median levels of AST were 148 IU/L compared to 80 IU/L of ALT. There were 26(10.9%) patients in which transaminases were elevated more than 10 times of reference interval indicating acute hepatitis. Conclusion- Transaminases should be measured routinely in all patients diagnosed with dengue fever. The severity of rise in liver enzymes is an indicator of hepatocellular injury though not related to prognosis.

Keywords: Dengue fever, Liver Function Test, Transaminases



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INTRODUCTION

Dengue is the most rapidly spreading mosquito-borne viral disease in the world ^[1]. According to the current estimates of World Health Organization (WHO), there may be 50–100 million dengue infections worldwide every year ^[2]. Cyclic epidemics of dengue are common in India and increase in frequency and in-country geographic expansion is occurring with a case fatality of 3-5% ^[1].

The dengue virus, a small single stranded RNA virus, belongs to the Flaviviridae family, and consists of four distinct serotypes (DEN1—DEN 4) ^[1]. The virus can infect many cell types and cause diverse clinical and pathological effects. Its main effects are on the vascular, muscular and hematological systems. However, liver involvement is common during acute dengue infection leading to rise in levels of transaminases ^[3]. It could be a direct viral effect on liver cells or be an adverse consequence of dysregulated host immune responses against the virus ^[4]. According to 2009 dengue guidelines of WHO, severe organ impairment involving liver has been proposed as one category of severe dengue in addition to severe plasma leakage and severe bleeding ^[1].

This study was conducted with the aim to study the liver profile of the dengue patients during a recent outbreak of disease in Punjab.

MATERIALS & METHODS

This was a retrospective study done in a tertiary care hospital in Punjab among the patients visiting the emergency or outpatient clinic during the dengue outbreak in October -November 2013. Dengue was suspected when high fever was present with two or more of the following symptoms: nausea, vomiting, retro orbital pain, myalgia, arthralgia, skin rash and hemorrhagic manifestations. Tests for detection of anti-dengue antibodies and nonstructural protein 1 (NS1) antigen test were carried out in all patients. Complete blood counts and liver function tests were done in these patients.

The serum samples were subjected to NS1 antigen detection test by using the kit manufactured by J. Mitra and Co Pvt Ltd. The immunoenzymatic assay for detection of IgM antibodies was done by Panbio dengue IgM-Capture ELISA kit. When results of either of these tests were positive, patients were considered to be infected with dengue virus, while cases in which the results were negative were considered unconfirmed. Patients with malaria and enteric fever were excluded from the study.

Liver function tests were done in the serum sample on the same day without any delay. The tests were performed on Mindray BS 400 using the reagents, calibrators and controls provided by Shenzhen Mindray biomedical electronics.

The degree of effect of dengue fever on liver was evaluated in these patients and classified into four groups according to the levels of aspartate transaminase (AST) and alanine transaminase (ALT). Grade A comprised of patients in whom AST and ALT levels were within reference range. The laboratory reference interval of AST and ALT were up to 35 U/L and 40 U/L respectively. Grade B was composed of patients in whom the level of at least one of the aminotransferases was increased but no higher than three times the reference range. When the values of at least one of the enzymes were raised up to 10 times the reference range, patients were classified as Grade C. Patients in whom there was an increase in one or both enzymes to levels more than 10 times the reference values, thereby defining the presence of hepatitis caused by dengue virus were classified as Grade D^[5].

Median values were used to analyze the patient data to avoid any effect of outliers on mean since there was wide fluctuation in values varying from within reference range to very high.

RESULTS

The study included the data from 239 patients diagnosed with dengue fever. Out of total, 178(74.5%) were males and 61(25.5%) were females. The mean age of patients was 37.9 years. A total of 175(73%) samples got the NSI antigen test for IgM/IgG positive. ELISA for IgM antibodies was positive in 212(88.7%) patients.

Median platelet count was 49000/cu mm. Liver transaminases levels were raised with more rise seen in AST as compared to ALT. (Table 1) While high levels of AST were present in 233(97.5%) patients, increase in ALT was observed in 198(82.8%) cases. When classified according to the extent of rise in level of enzyme, 66(27.6%),141(59%),and 26(10.9%) of patients were in Grade B,C and D respectively.(Figure 1) Among the 26 patients with more than 10 times rise in one or both transaminases,5 had very high enzyme levels in excess of 1000 U/L. They were excluded for calculation of group mean.

The warning signs of dengue include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, restlessness, liver enlargement >2 cm and increase in hematocrit concurrent with rapid decrease in platelet count^[1]. A statistically significant difference ($p < 0.001$) in levels of AST was found when levels were compared between dengue patients with and without warning signs. This difference was not statistically significant for ALT. (Table 2)

DISCUSSION

Our data shows that liver involvement was almost universal with 97.5% patients having elevated transaminases with level of at least one transaminase above reference range. Studies from other parts of India and world support this high rate of hepatic involvement. In some recent studies from other parts of India, the percentage of patients with elevated

transaminases ranged from 83.78% to 100% ^[6-9], though in these studies the number of patients was less than 100 compared to 239 in our study. The research from other parts of Asia have also reported similar incidence of raised transaminases; 86% in Singapore to 97% in Vietnam ^[3, 10-12]. Brazil, another country endemic for dengue, has reported a relatively lower rate of hepatic involvement being 64% approximately ^[5, 13].

The liver is one of the target organs for dengue and varying abnormalities in liver enzymes appear to be present in most patients with symptomatic dengue infections. There are different potential mechanisms to explain the hepatic injury. One of the potential insults includes direct effects of the virus or host immune response on liver cells causing an inflammatory response ^[13]. The liver is deprived of oxygen leading to lesions of the parenchyma, in which the injured hepatocytes release transaminases that is detectable in the peripheral blood ^[14]. Some investigators suggest that liver damage may be potentiated by the intake of drugs (such as acetaminophen and anti-emetics) during the early phase of the illness ^[4]. A recent study has suggested the binding of dengue virus NS1 with C1q complement protein as an interacting partner with liver proteins in causation of hepatic dysfunction ^[15].

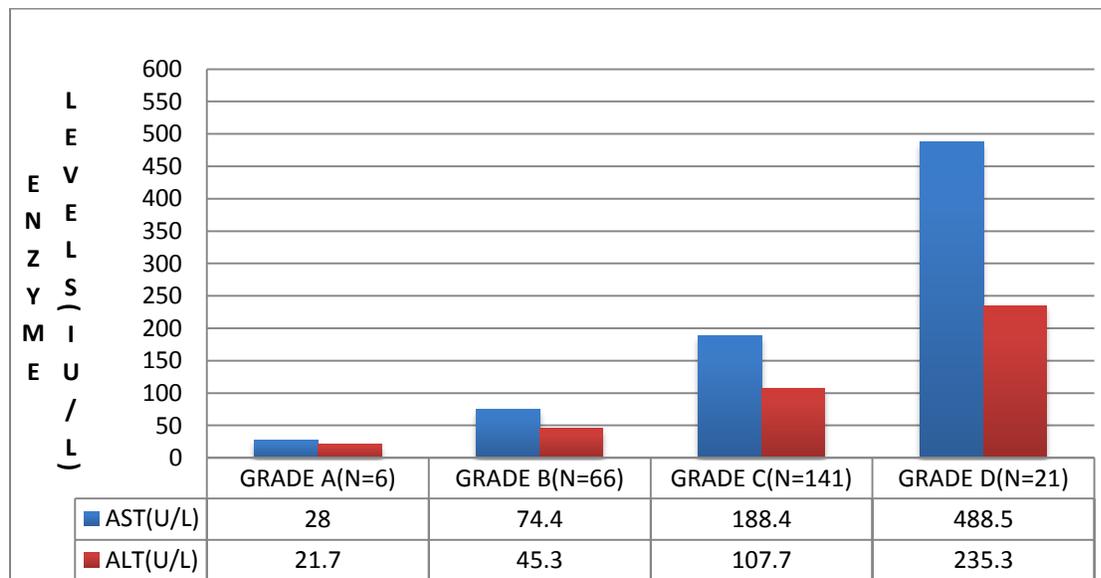
In dengue infections, levels of transaminases begin increasing early, from day 1–3 of illness and peak during the second week of illness. Serums AST levels increase more quickly and attain higher peaks and then revert to normal sooner than ALT. This differs from the general pattern in acute viral hepatitis, in which ALT levels are usually higher than or equal to AST levels but it is similar to that seen with alcoholic hepatitis ^[12]. The exact significance of this pattern seen in dengue is uncertain. AST is expressed in the heart, skeletal muscle, red blood cells, kidneys, brain, and liver, while ALT is secreted primarily by the liver. 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 ^[3]. Given the prominence of musculoskeletal symptoms in dengue, skeletal muscle injury could explain the higher AST levels ^[7]. Rise in creatine kinase has been reported in acute dengue fever in a previous study ^[16]. Early fall in AST levels can be explained by its shorter half-life of 16 hours compared to 24 hours for ALT ^[17]. The results of present study were also consistent with this pattern with more number of the patients having elevated and higher AST levels compared to ALT. The levels of ALT were within reference range in 17.2% cases compared to 2.5% for AST. Similar trends have been reported in many previous studies also ^[7, 9, 12-13]. When classified according to severity in elevation of enzymes, 27.6%, 59% and 10.9% patients were in grade B, C and D respectively. In another Indian study done in 50 patients 37%, 30% and 22% patients were in grade B, C and D respectively ^[7]. This percentage in a study done in Brazil in 336 patients was 42.1%, 17.5% and 1.8% respectively ^[5]. Another large study of 3850 patients reported 3.8% patients to be suffering from acute hepatitis with grade D liver enzymes ^[13]. In most cases, the high levels of transaminases show the degree of hepatocellular injury, prolonging the clinical course of the

disease; however, there is no correlation with prognosis^[3,4,18-20] and are not independent predictors of severity^[16]. There was uneventful recovery in majority of patients in the present study with no case of fulminant hepatic failure. Though during some dengue epidemics, greater degrees of liver damage leading to poorer prognosis and outcome has been reported^[11]. This may be a consequence of different dengue serotypes having varying tissue tropism and virulence^[4, 12].

One of the limitations of this study was that the levels of other muscle enzymes e.g creatine kinase were not measured to collaborate the explanation for more elevated levels of AST compared to ALT. A larger prospective study should be planned to find out the association if any between rise in CK and AST in dengue patients.

In conclusion liver involvement is a very common phenomenon in dengue fever and so measurement of transaminases must be a part of routine laboratory work up in diagnosed cases. Though in most cases recovery of normal hepatic function occurs without significant complications, certain virulent strains can lead to poor prognosis. Rising levels of transaminases can be useful in identifying such patients and aid decision making in management.

FIGURE 1: Classification of patients with different grades of hepatic involvement as measured by enzyme levels



Grade A-Within reference range (AST up to 35 IU/L, ALT up to 40 IU/L)

Grade B- Rise in at least one transaminase up to 3 times.

Grade C-Rise in at least one transaminase between 3- 10 times

Grade D- Rise in at least one transaminase more than 10 times of reference range. Five patients having transaminases >1000 U/L were excluded for group mean calculation.

Table 1: Median Values of various hematological and biochemical parameters

| Parameter | Median (Range) |
|-----------------------|---------------------------|
| Hemoglobin | 14.4g/dL (3.7-19.3) |
| Total Leucocyte Count | 4500/cu mm (1200-18000) |
| Platelet count | 49000/cu mm (8000-500000) |
| Total Bilirubin | 0.5mg/dL (0.5-5.9) |
| Total Protein | 6.3 g/dL (5.9-8.4) |
| Albumin | 3.6 g/dL (1.8-4.6) |
| Globulin | 2.6g/dL (2.1-3.8) |
| AST | 148 U/L (14-6700) |
| ALT | 80 U/L (10-3256) |
| ALP | 106 U/L (46-800) |

Table 2: Comparison of transaminases between dengue fever with and without warning signs

| Dengue fever without warning signs(n=114) | | | *Dengue fever with warning signs(n=120) | | |
|---|----------------------|----------------|---|----------------|---------|
| Parameter | Median(Range) U/L | Mean±SD U/L | Median(range) U/L | Mean±SD U/L | P value |
| AST | 116 (24-684) | 155.7±116.9 | 158 (38-704) | 199.4±128 | 0.005 |
| ALT | 73 (14-561) | 96.6±83.4 | 84 (10-336) | 101.4±66.1 | 0.50 |

*Enzyme level of 5 patients with values>1000U/L were not included for calculations.

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