Degree of Impairment of Liver Function in Dengue Fever Correlates to the Severity of its Complications

Samir Uchadadia, Babita Ghodke, Kunal Bhuta, Amrit Kejriwal, Jaishree Ghanekar

ABSTRACT

Background: Dengue fever with its severe manifestations, such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) has emerged as a major public health problem of international concern. Dengue, presenting as dengue fever (DF) or DHF or DSS, also has some effect on liver function. This study was conducted to find out the impact of dengue on liver function and correlation between clinical manifestation of dengue fever and degree of liver injury.

Materials and methods: This prospective randomized study was done on 200 outpatient department/inpatient department (OPD/IPD) patients in age group of 12 to 60 years including both sexes who confirm to the predetermined inclusion and exclusion criteria. Investigation included measurements of serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), prothrombin time/international normalized ratio (PT/INR) and creatinine. Degree of liver involvement was classified in four groups.

Results: Out of 200 cases, 181 (90.5%) were diagnosed as dengue fever, nine (4.5%) as DHF, five (2.5%) as DSS, five (2.5%) as hepatorenal involvement; 24 (12.0%) had grade 0 liver injury, 126 (63.0%) had grade 1 liver injury, 34 (17%) had grade 2 liver injury, 10 (5.0%) had grade 3 liver injury and six (3.0%) had grade 4 liver injury.

Conclusion: Mild elevation of the liver enzymes is a common feature of dengue infection. There is high relation between the degree of liver damage and the appearance of the complications.

Keywords: Degree of liver injury, Dengue fever, Dengue hemorrhagic fever, Dengue shock syndrome, Prothrombin time.


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INTRODUCTION

Dengue virus is a member of the flaviviridae family, which includes west nile virus, yellow fever virus, Japanese encephalitis virus and tick-borne encephalitis virus, among others.1 Dengue is caused by four antigenically distinct viruses, designated as dengue virus type 1 to 4 and is transmitted between vertebrate hosts by an insect vector—Aedes aegypti. The most serious manifestations of the infection are dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). No effective vaccine or antiviral drug therapy is currently available against dengue virus.1 Dengue viral infection has been recognized as one of the world’s biggest emerging epidemics. Throughout the tropics, this virus infection has an annual incidence of 100 million cases of dengue fever (DF), 250,000 cases of DHF and mortality rate of 24,000 to 25,000 per year.2,4

Typically, people infected with dengue virus are asymptomatic (80%) or only have mild symptoms, such as an uncomplicated fever.5,6 Others have more severe illness (5%), and in a small proportion it is life-threatening.5,6 The incubation period ranges from 3 to 14 days, but most often it is 4 to 7 days. The characteristic symptoms of dengue are: sudden-onset of fever, headache (typically behind the eyes), muscle and joint pains, and rash. The alternative name for dengue, ‘break-bone fever’, comes from the associated muscle and joint pains.5,7

This severe disease is marked by two problems: dysfunction of the endothelium and disordered blood clotting.8 Endothelial dysfunction leads to the leakage of fluid from the blood vessels into the chest and abdominal cavities, while coagulation disorder is responsible for bleeding complications. Higher levels of virus in the blood and involvement of other organs (such as the liver) are associated with more severe disease.9 Dengue may occasionally affect several other body systems.10 This may be either in isolation or along with the classic dengue symptoms.9 Hepatic dysfunction is common in dengue infection, and is attributed to a direct viral effect on liver cells or as a consequence of deregulated host immune responses against the virus. Other contributing factors include: race, diabetes, hemoglobinopathies, pre-existing liver damage and the use of hepatotoxic drugs.10,11 Although there are isolated case reports of fulminant...
hepatic failure, the derangements in the transaminases are usually mild and self-limiting. Although the number of patients affected by the virus is increasing each year, little work has been done in the studied area (regarding the pathogenicity, changes in the liver and the complications of dengue infection). Therefore in this study, we aimed to evaluate the degree of liver injury by measuring the level of the liver enzymes, prothrombin time (PT) and creatinine. These parameters were compared with the clinical presentation of the patients; to see how was the degree of liver damage related to the complications of the disease. The first significance of this study is increasing the awareness of the local health staff about the degree of severity of liver damage in dengue infected patients. The second is the importance of measuring the liver enzymes like aspartate aminotransferase (AST) in the follow-up of dengue virus infection. Thirdly, this research forms a baseline for future studies in the region regarding the outcome, mortality, hospital stay and the prognosis of dengue infection according to the level of liver damage.

MATERIALS AND METHODS

It is a prospective randomized hospital based study. Two hundred OPD-IPD patients in age group of 12 to 60 years including both sexes, who confirmed to the pre-determined inclusion and exclusion criteria, were included in the study. The study was carried out between November 2012 and October 2014 in the MGM Hospital, Kamothe, Navi Mumbai, Maharashtra, India.

Inclusion Criteria

- Age ≥ 12 and ≤ 60 years.
- Diagnosed with dengue fever (immunoglobulin M/NS1 Ag).
- Willing to get investigated for serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum creatinine, prothrombin time/international normalized ratio (PT/INR).
- Willing and able to complete study information sheet and questionnaires.
- Willing and able to provide written informed consent prior to enrollment in the study.

Exclusion Criteria

- All the patients below the age of 12 years.
- All the patients above the age of 60 years.
- All the patients who refuse to participate in the study after informed consent.
- Positive for malaria, typhoid and leptospira.
- HbsAg positive.

Grading of Liver Injury

- Grade 0—Normal levels of liver enzymes;
- Grade 1—Mild elevation in the liver enzymes, more than two times of reference value;
- Grade 2—Elevated liver enzymes, with the levels of the enzymes increased to more than three times the reference values;
- Grade 3—Acute hepatitis, with liver enzymes’ levels increased to at least 10 times their normal values;
- Grade 4—Evidence of hepatic failure (high PT) or hepato-renal involvement (high creatinine).

All liver function tests were done on fully automated AU480 biochemistry analyzer.

Serum bilirubin total and direct analysis were done by 2,5-dichlorophenyldiazonium (DPD) color test, and indirect bilirubin was calculated.

Serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase analyses were done by kinetic UV and alkaline phosphatase by kinetic color.

Prothrombin time—INR analysis was done by Thromborel S coagulation method.

Serum creatinine was analyzed by Jaffe’s kinetic color test.

RESULTS

In the present study, 200 cases were enrolled; of which 104 cases (52%) were males and 96 cases (48%) were females. In the population studied, maximum cases were in 20 to 40 age group (115 cases—57.5%), and 79.5% in 20 to 50 age group. Among all the subjects studied, the eldest was 59 years old and the youngest was 16 years old. Out of the 200 cases, 181 (90.5%) were diagnosed as DF, 9 (4.5%) as DHF, 5 (2.5%) as DSS and 5 (2.5%) as hepato-renal involvement (Table 1 and Graph 1). Among the 200 cases, 24 (12.0%) had grade 0 liver injury, 126 (63.0%) had grade 1 liver injury, 34 (17%) had grade 2 liver injury, 10 (5.0%) had grade 3 liver injury and 6 (3.0%) had grade 4 liver injury (Table 2 and Graph 2).

- Grade 0 liver injury—100% had DF
- Grade 1 liver injury—98% had DF and 2% had DHF
- Grade 2 liver injury—85% had DF, 9% had DHF and 6% had DSS
- Grade 3 liver injury—40% had DF, 40% had DHF and 20% had DSS
- Grade 4 liver injury—83% had hepato-renal involvement and 17% had DSS

Table 1: Distribution of patients according to diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency (patients)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue fever</td>
<td>181</td>
<td>90.5</td>
</tr>
<tr>
<td>DSS</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>DHF</td>
<td>9</td>
<td>4.5</td>
</tr>
<tr>
<td>Hepato-renal</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>200</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

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Thus, there is a high correlation between the degree of liver damage and the appearance of the complications (Table 3 and Graph 3).

The mean rise in SGOT levels was 171.27 ± 190.03 and that in SGPT levels was 144.71 ± 162.77. Therefore, SGPT (AST) levels (171.27 ± 190.03) tend to be greater than SGOT (alanine transaminase) levels (144.71 ± 162.77) (Table 4).

**DISCUSSION**

Dengue fever is one of the most important arboviral infections. It has become a major global public health problem. Classical dengue fever is an acute febrile illness, but in a small percentage of dengue infection, a more severe form of disease known as DHF occurs. Early recognition and meticulous management are very important to save precious lives from this killer disease.

The importance of this study lies in the severity of liver damage in dengue infection. In this research, we included dengue patients with mild symptoms seen in the outpatient department and severe cases who were admitted in the inpatient units. Therefore, this study covers both mild as well as severe cases of dengue virus infections.

Till date, there are two hypotheses that explain the damage of the liver in dengue patients. The first is immune enhancement hypothesis. In 2004, a strong correlation was found between T-cell activation and hepatic cellular infiltration in immune-competent mice infected with dengue virus. It was noted that the kinetics of liver enzyme elevation was also correlated with that of T-cell activation, which suggested a relationship between T-cell infiltration and elevation of liver enzymes. One of the studies detected the appearance of different helper cells and cytokines in human white blood cell cultures, infected in vitro with dengue virus type 2. They reported that during dengue infection; monocytes, B-cells, T-cells and mast cells produce large amounts of cytokines. Despite all this, the role of host immunity in dengue infection is still very unclear. Unregulated host immune response may play some part in severity of dengue infection, therefore, by modifying the immune response, severe infection can be prevented.

The second hypothesis relates the damage in the liver to direct virulence of the virus. According to these studies, we hypothesized the same mechanism responsible for the liver damage which occurred in our patients.
Liver damage with elevation of aminotransferases and reactive hepatitis was a common complication of dengue virus infection. Hence, measurement of AST and ALT is mandatory to see the liver involvement.\textsuperscript{14}

The SGOT/AST levels in dengue infection tend to be greater than SGPT/ALT levels.\textsuperscript{15,16} In our study too, aspartate aminotransferase levels (171.27 ± 190.03) tend to be greater than alanine aminotransferase levels (144.71 ± 162.77). This pattern is similar to that we see in alcoholic hepatitis but differs from that seen in other viral hepatitis. The exact cause of this is uncertain, but it has been suggested that it may be due to excessive release of AST from damaged myocytes during dengue infection.\textsuperscript{17} This preferential elevation of liver enzymes, with AST being significantly higher than ALT was also noted in other study.\textsuperscript{18} This abnormality may act as an early indicator of dengue infection.

In our study, we noticed high correlation between the degree of liver damage and presence of the complications. In 77% of the patients having dengue hemorrhage, severe

\textbf{Graph 3: Grading of liver injury according to diagnosis}
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degree of liver damage occurs (Grades 2 and 3). We suggest a significant role of deranged liver functions in the causation of bleeding in addition to thrombocytopenia. Severe degree of liver injury (Grades 2 and 3) was also found in 80% of dengue shock syndrome cases. All the patients having encephalopathy had grade 4 liver damage. Encephalopathy in our patients may be due to fulminant hepatic failure or a high level of the virus that directly damages the brain. Involvement of the kidneys was also related to the severity of liver damage (Grade 4). Again, this may be a part of hepato-renal syndrome or direct virus virulence.

Similar results to our work were seen in other countries. In Saudi Arabia, Khan et al (2008) had made an association between high AST level and complications of dengue virus. In Taiwan,17 has reported higher bleeding episodes in those who had high levels of AST, ALT and GGT. In Vietnam,20 reported that DHF may cause mild episodes in those who had high levels of AST, ALT and with hepatitis and encephalopathy.17,19-21

CONCLUSION

Mild elevation of the liver enzymes is a common feature of dengue infection. On the other hand, this could be severe to a degree of acute hepatitis or even to fulminant hepatic failure. There is a high correlation between the degree of liver damage and the appearance of the complications. At least, the levels of SGOT/SGPT should be assessed in the first visit, and the follow-up of all dengue infected patients. Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) can be a useful surrogate marker to predict disease severity, and bleeding outcome in dengue infection. The level of the other liver enzymes, PT, creatinine, and electrolytes should be assessed in all severe cases of dengue infection.

REFERENCES