Original Article

Impact of dengue fever on liver function tests and to relate liver function tests with severity of disease

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ABSTRACT:
Introduction: Dengue fever is an ancient disease. The earliest record found today is in a Chinese encyclopedia of disease symptoms and remedies, first published during Chin dynasty (265 to 420 AD). Severe Dengue was first recognized in the 1950s during dengue epidemics in the Philippines & Thailand,. has become a leading cause of hospitalization and death among children in these regions¹. Liver dysfunction as a result of dengue infection can be a direct viral effect on liver cells or an adverse consequence of dysregulated host immune response against the virus.

Material and methods
Hospital based prospective observational study conducted at Sri Venketeswara Ram NaraianRuia Government General Hospital, Tirupati included all NS₁ Ag positive or dengue Ig M positive cases in the age group of 6 months to 12 years.

Results:
Liver function tests AST, ALT and Alk phosphatase, bilirubin were deranged in children with severe dengue and dengue with warning signs compared to dengue without warning signs. Total bilirubin, AST, ALT and alkaline phophatase derangements were highly significant with p-value<0.001. Enzymes are elevated significantly in severe dengue compared to dengue with and without warning signs.

Conclusion:
All the liver function tests (Total bilirubin, AST, ALT and Alk phosphatase) were higher in children with severe dengue compared to dengue fever with warning signs and dengue fever without warning signs. The mean AST and ALT levels were 231.31 and 201.14 U/L respectively. This differs from the pattern in viral hepatitis.

INTRODUCTION:
Dengue is a mosquito borne infection found in tropical and sub-tropical regions around the world. In recent years, transmission has increased predominantly in urban areas and has become a major international public health concern.¹ The incidence of Dengue has grown dramatically around the world in recent decades. Over 25 billion people (40% of the world’s population) are now at risk from Dengue. WHO currently estimates, there may
be 50-100 million dengue infections worldwide every year.\(^2\)

Unusual clinical manifestations of dengue fever have become more common in the last few years\(^3\). Although the liver is not a major target organ, hepatic dysfunction is a well recognized feature, often characterized by acute hepatitis, with pain in the righthypochondrium, hepatomegaly, jaundice and raised aminotransferase levels\(^4\).

Liver dysfunction as a result of dengue infection can be a direct viral effect on liver cells or an adverse consequence of dysregulated host immune response against the virus.\(^6\)

Dengue fever is known to involve multiple systems sometimes resulting in multi organ dysfunction. Liver involvement is known to occur and of late there have been multiple reports of fulminant hepatitis in children with dengue fever.\(^7\) Hence the following prospective observational study in 100 consecutive patients with dengue fever was conducted to find out the profile of liver involvement in children with dengue viral infection.\(^8\)

**MATERIAL AND METHODS**

The present study was conducted at Sri Venketeswara Ram NaraianRuia Government General Hospital, Tirupati

**INCLUSION CRITERIA**

All NS\(_1\) Ag positive or dengue Ig M positive cases in the age group of 6 months to 12 years irrespective of sex admitted in Department of Pediatrics, Sri VenketeswaraRamnaraianRuia Government General Hospital, Tirupati.

**STUDY DESIGN**

Hospital based prospective observational study. All children included in the study will be investigated for complete blood count, NS1antigen, serum dengue IgM or IgG antibodies. Liver function tests namely serum total bilirubin, total protein, serum albumin, aspartate transaminase, alanine transaminase, alkaline phosphatase, prothrombin time, international normalized ratio. Other tests like activated partial thromboplastin time, bleeding time, clotting time and treated as per WHO protocol.

**OBSERVATION AND RESULTS**

**Table 1: Age distribution of Patients with Dengue Fever**

<table>
<thead>
<tr>
<th>Age (Year)</th>
<th>Dengue without warning signs (n=21)</th>
<th>Dengue with warning signs (n=54)</th>
<th>Severe Dengue (n=25)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>0 (0%)</td>
<td>2 (3.7%)</td>
<td>8</td>
<td>10 (10.0%)</td>
</tr>
<tr>
<td>1-5</td>
<td>9 (42.8%)</td>
<td>23 (42.5%)</td>
<td>12</td>
<td>44 (44.0%)</td>
</tr>
<tr>
<td>6-12</td>
<td>12 (58.2%)</td>
<td>29 (53.7%)</td>
<td>5</td>
<td>46 (46.0%)</td>
</tr>
</tbody>
</table>

In the present study 8 out of 10 children whose age is less than one year presented with severe dengue. Remaining two children presented with warning signs. In the age group of one to five years, 9 children presented without warning signs, 23 children are with warning signs and 12 had severe dengue. In children between 6 to 12 years 12 children had dengue without warning signs, 29 children presented with warning signs and 5 children with severe dengue.

**Table 2: Gender Wise distribution of Patients with Dengue Fever**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Dengue without warning signs (n=21)</th>
<th>Dengue with warning signs (n=54)</th>
<th>Severe Dengue (n=25)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>9 (42.8%)</td>
<td>31 (57.4%)</td>
<td>16</td>
<td>56 (56.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (57.2%)</td>
<td>23 (42.6%)</td>
<td>9</td>
<td>44 (44.0%)</td>
</tr>
</tbody>
</table>

In the present study 56% were males and 44% were females. The male: female sex ratio was 1.27:1.

**Table 3: Laboratory Parameters**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Min</td>
<td>Max</td>
</tr>
<tr>
<td>Hb</td>
<td>8.91</td>
<td>13.0</td>
</tr>
<tr>
<td>Hct</td>
<td>33.46</td>
<td>52.0</td>
</tr>
<tr>
<td>Platelet</td>
<td>10000</td>
<td>400000</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>1.082</td>
<td>2.3</td>
</tr>
<tr>
<td>Sr. Proteins</td>
<td>6.6</td>
<td>7.8</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.723</td>
<td>5.5</td>
</tr>
<tr>
<td>AST</td>
<td>231.3</td>
<td>922</td>
</tr>
<tr>
<td>ALT</td>
<td>201.1</td>
<td>766.0</td>
</tr>
<tr>
<td>Alk.phosp</td>
<td>145.1</td>
<td>290.0</td>
</tr>
<tr>
<td>PT</td>
<td>16.06</td>
<td>38.0</td>
</tr>
<tr>
<td>APTT</td>
<td>32.73</td>
<td>52.0</td>
</tr>
<tr>
<td>INR</td>
<td>1.429</td>
<td>4.4</td>
</tr>
<tr>
<td>BT</td>
<td>4.84</td>
<td>9.3</td>
</tr>
<tr>
<td>CT</td>
<td>4.409</td>
<td>8.5</td>
</tr>
</tbody>
</table>
The mean hemoglobin, hematocrit and platelet counts at presentation were 8.91 g/dl, 33.46 and 46654 respectively. The mean total bilirubin, albumin, AST, ALT, Alk phosphatase level were 1.082, 4.723g/dl, 231.3 U/L, 201.1 U/L and 145.1 U/L respectively. The mean PT, aPTT, INR, BT and CT were 16.06, 32.73s, 1.429, 4.84 mins and 4.409 mins respectively.

**Table 4:** Comparison of Liver Function Test Derangements in Patients with Dengue Fever

Liver function tests AST, ALT and Alk phosphatase, bilirubin were deranged in children with severe dengue and dengue with warning signs compared to dengue without warning signs. Total bilirubin, AST, ALT and alkaline phosphatase derangements were highly significant with p-value0.001. Enzymes are elevated significantly in severe dengue compared to dengue with and without warning signs.

**Table 5:** Comparison of Coagulation Test Derangements in Patients with Dengue Fever

The mean Prothrombin time (PT), mean activated partial thromboplastin time (APTT), and international normalized ratio were significantly higher in severe dengue compared to dengue with warning signs and dengue without warning signs.

**DISCUSSION**

- In present study the mean age of presentation in children with severe dengue is 3.31 years. Mean age of presentation in children with warning signs is 5.85 years and mean age of presentation in children without warning signs is 6.42 years. Overall mean age of presentation is 5.6 years. It is comparable with studies done by Cam et al, and Pancharoen et al.

- Hepatomegaly was seen in 90% of cases which is comparable to study done by Narayanappa et al which had an incidence of 90%. Although liver size does not correlate with disease severity or abnormal liver function tests, presence of an enlarged liver is observed more frequently in severe dengue and dengue with warning signs compared to dengue without warning signs with a p-value of 0.026 . The hepatic involvement may be due to direct infection of the dengue virus or due to immune mediated hepatocyte injury or various other mechanisms as mentioned earlier.

- Pain abdomen in dengue fever can be due to mesenteric lymphadenitis, hepatic enlargement or bowel wall ischemia secondary to shock. Pain abdomen was
more common in children with severe dengue as compared to children with dengue with warning signs. Pain abdomen was seen in 50% of our cases which is comparable to earlier studies which had an incidence of 40 to 50%.

- Rash was seen in 52% of the cases which is comparable to earlier studies by Saba Ahmed et al. Incidence is more in children with severe dengue compared to children with dengue with warning signs and dengue without warning signs with a p-value of 0.001.

- Icterus was seen in 2 cases. It was seen only in children with severe dengue.

- In the present study, the mean hemoglobin at presentation was 8.91 g/dl. Minimum hemoglobin in our study is 4 g/dl and maximum value of haemoglobin is 13 g/dl. In other studies, it ranged from 10.8 g/dl to 13.7 g/dl.

- In our study the mean haematocrit is 33.46. Minimum haematocrit value is 18 and maximum value of haemtocrit is 52.

- The mean value of platelet in present study is 46,654 and minimum value of platelet count is 10,000 and maximum value of platelet count is 4,00,000.

- We have found in our study that deranged liver functions are an important feature in patients with dengue infection. In children with dengue fever without warning signs 13 children had AST elevation 1-3 times the normal value and 8 children had AST elevation 4-10 times the normal value. In children with dengue with warning signs 19 children had AST elevation 1-3 times the normal value and 35 children had AST elevation 4-10 times the normal value. In children with severe dengue 9 children had AST elevation 4-10 times the normal value and 16 children had AST value above 10 times the normal value.

- AST elevation increased with severity of disease with a p-value of 0.001. The mean value of AST in children with dengue without warning signs is 108.19. The mean value of AST in children with dengue with warning signs is 168.05. The mean value of AST in severe dengue is 471.36.

- In children with dengue fever without warning signs 18 children had ALT elevation 1-3 times the normal value and 3 children had ALT elevation 4-10 times the normal value. In children with dengue fever with warning signs 18 children had ALT elevation 1-3 times the normal value and 3 children had ALT elevation 4-10 times the normal value.

- Elevation in ALT is directly proportional to severity of disease with a p-value of 0.001. The mean value in ALT children with dengue without warning signs is 96.23, in children with dengue with warning signs the mean value of ALT is 149.4, in children with severe dengue the mean value of ALT is 400.92.

- Alkaline phosphatase values increased with severity of disease with a p-value of 0.001. The mean value of alkaline phosphatase in children with dengue without warning signs is 119.904, in children with dengue with warning signs the mean value of alkaline phosphatase is 132.85, in children with severe dengue the mean value of alkaline phosphatase is 192.76.

- The mean total bilirubin level in the present study was 1.082 gm/dl. Other studies reported mean total bilirubin levels of 0.8 g/dl to 0.93 g/dl. In children with dengue without warning signs mean total bilirubin is 0.661. In children with dengue with warning signs mean total bilirubin is 1.17. In children with severe dengue mean total bilirubin is 1.228. Bilirubin elevation is more in children with severe dengue compared to dengue with warning signs and dengue without warning signs with a p-value of 0.001.

- In the present study the mean value of serum proteins is 6.6. In children with severe dengue the mean value of serum proteins is 6.712. In children with dengue with warning signs mean value of serum proteins is 6.707. In children with dengue
without warning signs mean value of serum proteins is 6.585. There is no variation in the value of serum proteins with severity of dengue with a p-value of 0.627.

- The mean albumin level was 4.723 g/dl.

### Table 6: Liver Function Tests Comparison Studies

<table>
<thead>
<tr>
<th>Tests</th>
<th>Chinna RS et al&lt;sup&gt;18&lt;/sup&gt;</th>
<th>Prakash Oet al&lt;sup&gt;16&lt;/sup&gt;</th>
<th>Wong M et al&lt;sup&gt;19&lt;/sup&gt;</th>
<th>Present study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin</td>
<td>0.93 mg/dl</td>
<td>0.8 mg/dl</td>
<td>1.62 mg/dl</td>
<td>1.082</td>
</tr>
<tr>
<td>Sr. Albumin</td>
<td>3.2 g/dl</td>
<td>3.89 g/dl</td>
<td>4.723 g/dl</td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>353.7 U/L</td>
<td>174 U/L</td>
<td>163.18 U/L</td>
<td>231.31 U/L</td>
</tr>
<tr>
<td>ALT</td>
<td>218.6 U/L</td>
<td>88.5</td>
<td>144.58 U/L</td>
<td>201.14 U/L</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>135.2 U/L</td>
<td>80 U/L</td>
<td>70.08 U/L</td>
<td>145.1 U/L</td>
</tr>
</tbody>
</table>

**LIMITATIONS OF PRESENT STUDY**

1. Small Sample Size
2. Repetition of liver function test not done.
3. There is no follow up of cases included in the study.

**What’s New:**

According to present study there is significant association between abnormality of liver function tests and severity of dengue fever. Although the present study shows statistically significant association between liver function tests and severity of dengue.

**REFERENCES**

1. WHO dengue and severe dengue fact sheet N 117; updated march 2014.WHO.
Impact of dengue fever on liver function tests and to relate liver function tests with severity of disease


