Clinical, Hematological and Immunological Correlation in Children with Dengue Infection

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Authors' contributions
This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Mortality rate caused by dengue in tropical urban life by a vector mosquito possess severe effects including children. This is an observational study carried out in a tertiary care hospital in Navi Mumbai, from June 2006 to August 2008 area which is endemic for vector borne diseases. The clinical signs, symptoms, hematological parameters and serological correlation in 100 serologically positive for IgM and IgG children confirmed by Mac ELISA were studied. Chi-square test of significance was applied between the selected laboratory and clinical parameters. The outcomes of the study were provided with a high incidence of infection was seen in the age group of 6-10 years (50%), with a male (63%) predominance affection. Fever (100%), along with Vomiting (89%), myalgia (45%) and abdominal pain (27%) are the most common symptoms associated with dengue. Other symptoms found in childrens affected by dengue shows hemorrhagic manifestation (25%), hepatomegaly (78%), as cites and effusion (50%), hem concentration (31%), leucopenia (38%), and raised serum transaminases (67%). These findings were correlated with the severity of the infection and the parameters which were statistically significant were hemorrhagic manifestation, plasma leakage with as cites and effusion, hepatomegaly, hem concentration and leucopenia. The findings would be useful in early detection and prompt management and referral of cases for preventing mortality rate in children.
Keywords: Dengue fever; dengue hemorrhagic fever; dengue shock syndrome; IgM and IgG Mac ELISA; Thrombocytopenia.

1. INTRODUCTION

Dengue has been caused by Flavivirus, a disease spread by the vector mosquitoes that has been transferred to man. In tropical urban life, this illness with vectors has become a worldwide burden of sickness and death. About 500,000 serious dengue cases, occurring primarily in children, are hospitalized across the world [1]. In most of the world and more frequently in the tropical belt, the illness is currently endemic.

The dengue viral strain belongs to the family of flaviviridus. It has been found that four serotypes of the virus, 1, 2, 3 and 4 generate cross immunity. This cross-immunity can cause up to four people's illnesses in a lifetime.

Aedes aegypti, the principal vector is, highly domesticated daytime biting mosquito. This vector breeds in artificial containers commonly found in and around homes, in flower vases, old automobile tyres, earthenware jars, tin cans, etc. The female Aedes aegypti, transmits the virus to other uninfected person; with an extrinsic incubation period of 8-10 days, when the virus multiplies in its salivary glands [2]. Other Aedes species causing dengue outbreaks are Aedes albopictus, Aedes polysinensis and some species of the Aedes scutellaris complex.

Children affected are generally with a previous dengue infection or infants with waning anibody levels.

Human infection occurs when man intrudes into the zoonotic cycle and is bitten by a zoophilic vector.

There is acute onset of fever seen after an incubation period of 3-14 days accompanied by a variety of clinical signs and symptoms [3].

1.1 Dengue Fever (DF)

Dengue infection presents with fever accompanied by headache, bodyache, retro-orbital pain, myalgia, arthralgia, nausea, vomiting and rash which is seen in more older children and adults. Patient may experience mild sore throat associated with altered taste and anorexia. Pharyngeal inflammation and conjunctiva injection are also seen [4]. Lymphadenopathy is also commonly noted.

Fever may be high grade with temperature rising upto 102-104° Farenheit, and lasting for 2-7 days. Gradually the fever decreases and reappears 12-24 hours later-Saddle back fever.

Rash is seen in 1-2 days after fever in about 50% of the cases. Centrifugal spread of rash i.e. truncal appearance and spreading to the face and extremities. The rash may become confluent with sparing of small round areas of normal skin.

Hemorrhagic manifestations like petechiae and purpura are the common symptoms. Other bleeding manifestations seen commonly are gum bleeding, menorrhagia, epistaxis and GI hemorrhage. In only one third of patients with DF, tourniquet test is seen to be positive [5].

At the end of febrile phase of illness, petechiae may appear either scattered or confluent followed by desquamation on the palm and soles along with pruritus.

In the laboratory picture, neutropenia followed by a lymphocytosis is seen which is often marked by atypical lymphocytes. Mild elevation in liver enzyme levels in the serum may be noted. At this stage, thrombocytopenia is also commonly noted [6].

1.2 Dengue Fever (DF): Case Definition

Fever accompanied with two or more clinical signs and symptoms such as headache, body ache, retro-orbital pain, rash and skin and mucosal bleeds and finding of leucopenia [7].

and

The Supportive serology tests of IgM and IgG antibodies by ELISA or hem agglutinin-inhibition antibody titer.

1.3 Dengue Hemorrhagic Fever (DHF)

DHF is characterized by 4 major clinical manifestations:

1) High fever 2) bleeding manifestations 3) Hepatomegaly and 4) Evidence of plasma leakage
Plasma leakage is manifested by elevated hematocrit, serious effusion and hypoproteinemia.

The patients with DHF commonly present with high grade fever (>39°C), facial flush, anorexia, vomiting, headache, arthralgia, sore throat, mild conjunctival injection, generalized abdominal pain with tenderness at right costal margin and epigastric region [8].

In the early phase of fever, the liver is usually palpable. Liver enlargement is commonly found, but is not a constant finding in all cases. However, elevated liver enzymes may be seen.

Scattered petechiae may be seen on the extremities. Some patients may bleed at venepuncture site. GI haemorrhage is seen in more severely affected patients. Hematemesis with vomitus (coffee ground colour) and melena are seen in impending or shock state [9]. Epistaxis and gingival bleeding may occur. The defervescence phase is followed by signs of circulatory failure. There may be sweating, cold peripheral extremities, restless and weak pulse and hypotension.

Children with severe dengue present in a state of shock; comatose have facial blanching rash along with perioral cyanosis [10]. Thrombocytopenia and hemoconcentration are usually detectable before the fever subsides and the beginning of shock.

The warning signs that DSS is impending include:

1) Abdominal pain more in the epigastric and right hypochondriac region.
2) Vomiting (frank hematemesis or coffee ground)
3) Altered sensorium (irritability or somnolence)
4) Change from fever to hypothermia
5) A sudden decrease in platelet count

1.4 Dengue Shock Syndrome (DSS)

Dengue Shock Syndrome is defined as signs of circulatory failure, including narrow pulse pressure (≤20 mm Hg), hypotension, or frank shock.

As the severity progresses, fever and non-specific constitutional signs and symptoms are followed by sudden deterioration [11]. During the febrile phase, or after the temperature recedes, patients skin may become congested with circumoral cyanosis. The pulse becomes rapid and weak and low blood pressure noted as the patient reaches a phase of shock. Acute abdominal pain is usually seen shortly before the onset of shock.

1.5 Central Nervous System Manifestations

Neurological manifestations have been reported in dengue fever and more in the severe cases. Child may have altered sensorium, convulsions and coma have been ascribed to an encephalopathy secondary to prolonged DHF/DSS, resulting from the leakage of plasma into serous spaces, shock, hemorrhage, and metabolic disturbance [12].

Unusual neurological presentations include mononeuropathies, polyneuropathies, encephalitis, and transverse myelitis and Guillain Barre syndrome are also reported [13].

1.6 Hepatic Manifestations

Hepatocellular injury manifested by hepatomegaly, elevation of liver enzymes and mild coagulopathy are common in DHF and even in DF.

1.7 Dengue Serology

1.7.1 Primary dengue infection

IgM titers are high. It is seen in 50% of the patients, while they are still febrile, while in the remaining it appears after fever subsides. 80% of cases will have serum positive for antibodies by day 5 of illness [14]. After the appearance of antibodies, the levels peak by about 2 weeks after the onset of symptoms and decline slowly in 3-6 months [15].

1.7.2 Secondary dengue infection

Has high levels of IgG, and low levels of IgM. After 2-3 days of fever onset IgG begins to rise. In primary or secondary dengue infections, MAC-ELISA detects a rise in dengue specific IgM antibodies, in day-1 today-2 intervals serum samples, in the acute phase. Most cases (93%) develop detectable IgM antibodies by average of 7 days after onset of illness, and most (99%) patients tested between 14 days(average) had detectable IgM antibodies [16].
MAC-ELISA has a sensitivity of 70%-80% and a specificity of 85%-95%. The best distinction between primary and secondary dengue was observed when an IgG cut off value of 3.0 was used [17].

2. MATERIALS AND METHODS

This was a prospective observational study conducted from July 2006 to August 2008 in the pediatric department of a general tertiary care hospital in Navi Mumbai.

This study was carried out in Navi Mumbai (Raigad district), where there is rapid widespread dengue epidemic affecting all age groups but commonly hospitalization and deaths are seen in children. This area of the study population contains large slums where sanitary and vector control activities are still deficient.

Despite effective vector control measures being taken in this area, there are 50-100 cases reported each year, and hence it is important to study the clinical presentations, the natural course of illness, the management and the outcome of the disease.

2.1 Inclusion Criteria

All infants and children (0-18 years), with a history of fever and other signs and symptoms as mentioned by the WHO criteria, and the cases admitted in the pediatric ward with any of the given below criteria laid down by the WHO with a positive IgM and IgG serology with capture ELISA. NS1 criteria was not considered in the study as people with negative NS1 results should be tested for the presence of dengue IgM antibodies to determine possible recent dengue exposure. So antibody test was conducted in 100 pediatric cases from 0-18 years.

The criteria to define dengue are:

2.1.1 Dengue fever

Fever with two or more of the following; headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestation (g) leukopenia and supporting ELISA antibody test.

2.1.2 Dengue hemorrhagic fever

Fever for more than 2-7 days, with hemorrhagic manifestations of either a positive tourniquet test, or epistaxis, malena, hematemesis, skin bleeds in the form of petechiae/purpura, thrombocytopenia and evidence of plasma leak by a rise in the hematocrit ≥ 20% of that normal for age and sex.

2.1.3 Dengue shock syndrome (DSS)

Signs of circulatory failure, with hypovolemia or frank state of shock are a symptom of DSS. The special test: IgM and IgG capture ELISA was done in each patient after a written informed consent.

Data was collected, tabulated, and analyzed statistically and the test of significance was used when a frequency distribution was studied; was the Karl Pearson Chi-Square test. The actual P values shown in the test were calculated using the SPSS version 17.0. The P value of taken to show significant association between two parameters is < 0.05.

3. RESULTS AND DISCUSSION

This study was carried out in a tertiary care hospital, Navi Mumbai, from June 2006 to December 2008, 100 patients (age group 0-18 years) with dengue fever in the Pediatric department were studied and the following observations were made.

The Table 1 shows that, most of the patients in the present studies were between the age group of 6 – 10 years (50%); maximum incidence. Mean age of affection in this study was seen to be 6.6 years. Males are seen to be affected more than females with a ratio of 1.7:1.

The commonly affected age group is 6-10 years where 40% of the cases in these groups show symptoms with DHF as these groups of children are exposed to the areas of open grounds and their playful activities with stagnant water provides the vectors to identify the suitable host to spread the infection. The age affection in correlation to the severity of infection is not significant (P value is > 0.05).

Severe dengue infection was seen predominantly in two age groups commonly in infancy and in children 5-9 years old (58%). The mean age of presentation was 4.9 years. In infants less than 1 year, passively transferred maternal antibodies predispose these infants to severe dengue infection.
Table 2 shows that fever was the most common symptom which is present in 100% of the patients. Symptoms such as vomiting are seen in age group of 4 years and above (89%). Nausea, vomiting, headache, myalgia and arthralgia was seen in children with a age group of 7 years and above, and other studies for Dengue and associated diseases showed similar clinical signs and symptoms. Rash was seen in 20% of the cases. Myalgia and headache were symptoms which were commonly described by older children and adults. Similar findings were mentioned by Rothman and Potts JA (2007).

Hemorrhagic manifestations are common in dengue infection and are seen more in adults. The commonest hemorrhagic manifestation in children was epistaxis.

Hepatomegaly was a common finding seen in dengue infections. It was seen in 78% of the cases. The finding of hepatomegaly were well correlated with the disease severity, P value is highly significant (P value is 0.001). It is seen 100% of the cases of DSS. Batra and others in 2004, in rural Maharashtra reported 56% cases with hepatomegaly.

Splenomegaly was seen in 61% of the cases diagnosed more on Ultrasonography did not correlate with the disease severity (P value >0.05). The incidence of splenomegaly was seen more in DHF and DSS than in dengue fever.

Shock (hypotension) on admission was seen in 40%. Lymphadenopathy is seen in 1% of the cases. Hemorrhagic manifestations are seen in 25% of the cases with dengue infection. Hematemesis was seen in 6% of the cases. The hemorrhagic manifestations correlated with disease severity (P value <0.05).

### Table 1. Demographic factor wise distribution of cases

<table>
<thead>
<tr>
<th>Age wise (years)</th>
<th>Number of cases</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 5 years</td>
<td>27 cases</td>
<td>27%</td>
</tr>
<tr>
<td>6 – 10 years</td>
<td>50 cases</td>
<td>50%</td>
</tr>
<tr>
<td>10 – 18 years</td>
<td>23 cases</td>
<td>23%</td>
</tr>
<tr>
<td>Gender</td>
<td>Number of cases</td>
<td>Percentage %</td>
</tr>
<tr>
<td>Male</td>
<td>63</td>
<td>63%</td>
</tr>
<tr>
<td>Female</td>
<td>37</td>
<td>37%</td>
</tr>
</tbody>
</table>

### Table 2. Clinical signs & symptomatology

<table>
<thead>
<tr>
<th>Clinical presentations</th>
<th>N=100</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td></td>
<td>100 %</td>
</tr>
<tr>
<td>Days before admission</td>
<td>100</td>
<td>17 %</td>
</tr>
<tr>
<td>0 – 3 days</td>
<td>17</td>
<td>70 %</td>
</tr>
<tr>
<td>4 – 7 days</td>
<td>70</td>
<td>13 %</td>
</tr>
<tr>
<td>&gt; 7 days</td>
<td>13</td>
<td>20 %</td>
</tr>
<tr>
<td>Rash</td>
<td>20</td>
<td>0 %</td>
</tr>
<tr>
<td>Retro-orbital pain</td>
<td>0</td>
<td>4 %</td>
</tr>
<tr>
<td>Headache/bodyache</td>
<td>4</td>
<td>45 %</td>
</tr>
<tr>
<td>Arthralgia/myalgia</td>
<td>45</td>
<td>10 %</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10</td>
<td>89 %</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>89</td>
<td>27 %</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>27</td>
<td>30 %</td>
</tr>
<tr>
<td>Conjunctival congestion</td>
<td>30</td>
<td>25 %</td>
</tr>
<tr>
<td>Bleeding manifestations</td>
<td>25</td>
<td>16 %</td>
</tr>
<tr>
<td>Edema/Ascites</td>
<td>16</td>
<td>31 %</td>
</tr>
<tr>
<td>Shock</td>
<td>31</td>
<td>1 %</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>1</td>
<td>78 %</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>78</td>
<td>46 %</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>46</td>
<td></td>
</tr>
</tbody>
</table>
Hematological and biochemical parameter alterations are seen in dengue fever; (Table 3). The mean hemoglobin on admission in Dengue fever was 10.8 gm/dl, 9.9gm/dl in DHF and 11.9 in DSS.

Hemoconcentration was seen in 31% of the total cases and in 66% of the DSS cases. Hence, hemoconcentration is well correlated with the disease severity (P value <0.01).

Leukopenia, white cell count less than 4000/cumm was observed in 38% of the cases and is commonly seen in the age group of 0-5 years. In the present study leukopenia well correlated with the degree of severity of infection (P value is 0.003).

Thrombocytopenia was seen in all patients of DHF in the present study and only 3 cases had a platelet count less 20000/cumm on admission. Severe thrombocytopenia (platelet count of <50,000/cumm), was seen in the Indian study data also. There was no statistical significance between the degree of thrombocytopenia and grade of severity in the present study. Oxidative stress in viral infection for thrombocytopenia in dengue infection was related to the extent of lipid peroxidation.

The affection of the liver enzymes is a common finding in dengue and so is in the present study. 67% of the cases showed an increase in the serum transaminases levels (SGOT/SGPT) and showed the high incidence of hepatitis associated with dengue infection and also affection of other organs and heart. Affection of liver enzymes did not correlate with the disease severity (P value >0.05).

Studies from others countries showed higher incidence of liver involvement and raised transaminases. In the present study, the raised serum transaminases particularly SGPT did not correlate with the disease severity (P value >0.05).

Prothrombin time was seen raised in 12% of the cases of dengue infection and was noted only in the cases of severe infection like DHF/ DSS. The prothrombin time however did not correlate with the disease severity in the present study (P value is >0.05).

Radiological findings such as chest X-ray and ultrasonography are very sensitive for diagnosis of dengue cases with DHF infection. Pleural effusion was seen 42% of the cases (right sided effusion seen more than left). Bilateral pleural effusion was seen in 4% of the cases. Ascites was seen in only 50% of the cases. Gall bladder wall pseudo-thickening was seen 50% of the cases and more in DHF and DSS.

The finding of ascites and effusion as a result of plasma leakage in dengue is seen correlating with the disease severity (P value <0.05). The other USG findings which were suggestive of dengue infection were pseudo-thickening of the gall bladder wall, hepatomegaly and splenomegaly.

Various types of effusions like pericardial effusions are also reported in DHF. Dengue virus is also known to cause viral myocarditis. In the present study from the selected patients, one case had myocarditis on the 7th day of illness and admission in hospital for the infection of DHF.

Coinfection of the patients with dengue fever with malaria is also reported. This is likely as epidemiology of both infections is similar, being transmitted through mosquitoes.

In the present study 94% of the patients were discharged. Mortality was noted in only 3% of the cases with severe shock syndrome and encephalopathy.

Table 3. Laboratory findings

<table>
<thead>
<tr>
<th>Hematological and biochemical parameters</th>
<th>Number of cases (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoconcentration (≥20% rise in hematocrit more than normal for age and sex)</td>
<td>31 %</td>
</tr>
<tr>
<td>Leukopenia (&lt;4000/cumm)</td>
<td>38 %</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;100000/cumm)</td>
<td>58 %</td>
</tr>
<tr>
<td>Severe thrombocytopenia (&lt;50,000)</td>
<td>18 %</td>
</tr>
<tr>
<td>Hypoalbuminemia (&lt;2.5 g/dl)</td>
<td>15 %</td>
</tr>
<tr>
<td>Raised serum transaminases (SGOT/SGPT levels) (&gt;35 U/l)</td>
<td>67 %</td>
</tr>
<tr>
<td>Abnormal RFT (Raised Sr. Creatinine levels)</td>
<td>3 %</td>
</tr>
<tr>
<td>Abnormal Prothrombin Time (PT)</td>
<td>12 %</td>
</tr>
</tbody>
</table>
4. CONCLUSIONS

In country like India the severe morbidity and mortality rate caused by Dengue is currently high. Children with age group of 6 to 10 years are highly infected and the symptoms caused by dengue is similar in children and in adults and the Immunological response as evidenced by the IgM and IgG titres did not show significant correlation with disease severity. Poor prognosticating factors were younger age of presentation, delayed admission of shock cases, presence of bleeding and associated complications. Proper identification of cases, prompt treatment, early detection of complications and proper referral of cases will aid in bringing down the morbidity and mortality rate of dengue infection in children.

CONSENT AND ETHICAL APPROVAL

Written informed consent was taken prior to investigations. The Study was approved by the ethical committee of the college.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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