Dengue fever in a tertiary hospital in Makkah, Saudi Arabia

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Abstract

Dengue fever is endemic in the western part of Saudi Arabia. This study aimed at describing the clinical and laboratory profiles of dengue fever patients admitted to a tertiary hospital in Makkah, Saudi Arabia, from 2006 to 2008.

A total of 159 dengue fever patients were admitted during the spring and early summer. Their mean age was 25.6 ± 16.1 years. Males outnumbered females by a ratio of 2:1. Of them, 143 patients (89.9%) had classic dengue fever and 16 patients (10.1%) had dengue haemorrhagic fever (DHF); one of them developed severe dengue shock syndrome (DSS) and died (0.6%). The common symptoms were high-grade fever, headache and body aches (100%), nausea and vomiting (27%), retro-orbital pain (25%), skin rash (16.4%), dry cough (8.2%) and haemorrhagic manifestations (3.14%). The main laboratory abnormalities were leukopenia (WBCs less than 4000/cmm) in 53.7% of patients, thrombocytopenia (platelet count less than 100 000/cmm) in 36.2% of patients and prolonged partial thromboplastin time (PTT) (>1.5 times of control value) in 33% of patients. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were elevated more than five-fold in 35.2% of patients. The mean AST/ALT were 226.7/164 U in DF while in DHF these were 555/314 U. Twenty-six patients (16.4%) developed skin rash and had a significantly lower ALT value and a higher platelet count than those without rash.

Keywords: Dengue virus; dengue haemorrhagic fever; Makkah; Saudi Arabia; clinical symptoms; AST/ALT ratio.

Introduction

Dengue fever (DF) is one of the world’s major re-emerging infections. In recent decades, there has been an expanded geographical distribution of the virus and the mosquito vector, increased epidemic activity, and the emergence of dengue haemorrhagic fever (DHF) in new geographical regions. The disease is endemic in more than 100 countries and around 2500 million people are at risk. WHO estimates that there may be 50 million cases of dengue infection worldwide.
every year.\cite{2,3} The reasons for the emergence of dengue haemorrhagic fever are complex and not fully understood but demographic, social and public health infrastructure changes in the past decades have contributed greatly to this phenomenon.\cite{4}

Dengue virus belongs to the genus *Flavivirus*, family *Flaviviridae*. It is composed of single-stranded RNA and has four antigenically-related but distinct serotypes (DENV-1, DENV-2, DENV-3 and DENV-4). It is transmitted by the bite of *Aedes aegypti* mosquito.\cite{5} According to WHO, dengue virus can cause classic dengue fever, dengue haemorrhagic fever and dengue shock syndrome (DSS).\cite{6} Outbreaks have been more common in West Asia in the 1990s, with a major epidemic occurring in Jeddah, Saudi Arabia, in 1994.\cite{7} A few reports on the epidemic were published after 2001.\cite{8,9,10} Many factors contribute to the recognition of such outbreaks, which include increased awareness on the part of medical authorities and more exposure of populations to the mosquito vector, especially in low-standard areas and in the peripheral region of towns where solid waste disposal is suboptimal.

This study aimed at reporting the demographic, clinical and laboratory data along with the disease outcome of all dengue patients admitted to Al Noor Specialist Hospital, Makkah, during the period 2006–2008, and comparing the characteristics between those with simple and complicated disease, which may aid in improved recognition of the disease in the area.

**Materials and methods**

**Study site and population**

This study was conducted on 159 patients admitted with diagnosis of dengue infection to Al Noor Specialist Hospital, Makkah, from 2006 to 2008. Makkah is a holy city for Muslims from all over the world. It is located in the western province of Saudi Arabia, about 70 km from the Red Sea (Jeddah city). It is the third largest city in Saudi Arabia after Riyadh and Jeddah. It has a population of about 3 million and receives about four million visitors a year. Al Noor Specialist Hospital is a 600-bed, well-equipped, tertiary-level hospital. It is the main hospital in Makkah. It actually serves the entire local community as well as visitors as it is only 3 km away from the holy mosque. All age groups, including paediatric patients, are admitted there.

**Study design**

All patients presented to the emergency room with high fever, bone pains and bicytopenia were admitted as cases of “fever and bicytopenia for investigation” and were fully investigated. The diagnosis was revised on discharge and the final diagnosis was implemented on the Hospital Information System (HIS) according to the disease coding system ICD-10 AM (International Classification of Disease-10, Australian Modification), version 2006. Data were collected retrospectively by reviewing the HIS and the patient discharge summary.

The data studied included age, sex, nationality and the presence of fever, constitutional symptoms, skin rashes and bleeding tendency. Investigations included complete blood count, liver function tests and coagulation profile (PT, PTT and INR). Tests for fever of unknown origin were conducted and these included: bacterial cultures, serology for *Salmonella* and *Brucella* and serology for viruses (hepatitis viruses A, B and C, cytomegalovirus and infectious mononucleosis virus). Thin and thick blood films were examined for malaria parasites.
Sera from all suspected cases were tested in the Central Laboratory of the Ministry of Health in Jeddah for anti-dengue immunoglobulins (IgM) by enzyme-linked immunoassay (ELISA) and for the dengue virus RNA by polymerase chain reaction (RT-PCR). The results were either positive or negative for dengue fever. It must, however, be mentioned that serotyping was not done in this study.

The diagnosis of dengue fever depended on the clinical and laboratory findings and positive serology according to WHO criteria.[6]

Statistical analysis

All data were entered and analysed using Microsoft Office Excel 2007.

Results

All patients tested positive for anti-dengue immunoglobulins (IgM-ELISA) and/or dengue virus RNA by polymerase chain reaction (RT-PCR). They had negative cultures and negative serology for *Salmonella*, *Brucella*, viral hepatitis, cytomegalovirus and infectious mononucleosis virus infections. Also, thin and thick blood films for malaria were negative.

Seasonality

Thirty nine patients were admitted during 2006, 97 during 2007 and 23 during 2008. Most of the patients were admitted during the spring and early summer (April, May and June) (123/159, 77.4%) (see Figure).

Figure: Monthly distribution of dengue fever patients admitted during 2006–2008
Two thirds of the patients were Saudi (67%), only two patients were visitors (pilgrims for Hajj), while all others were residents of Makkah. The mean age was 25.6±16.1 years (range 4 to 81 years). All age groups, including children, were admitted; the percentage of children below the age of 12 years was only 24%. The age distribution is shown in Table 1. The male to female ratio was 2:1 (107 M:52 F).

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Number of patients (%) (Total =159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 12</td>
<td>38 (24.0%)</td>
</tr>
<tr>
<td>13–20</td>
<td>47 (30.0%)</td>
</tr>
<tr>
<td>21–30</td>
<td>32 (20.0%)</td>
</tr>
<tr>
<td>31–40</td>
<td>17 (10.5%)</td>
</tr>
<tr>
<td>41–50</td>
<td>17 (10.5%)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>8 (5.0%)</td>
</tr>
</tbody>
</table>

According to WHO criteria,[6] 143 patients (89.9%) were diagnosed as classic DF and 16 patients as DHF (10.1%), five of them had clinically significant bleeding (3.1%) and one patient died because of severe DSS (0.6%). Plasma leakage, which is the hallmark of DHF, could not be fully assessed since it is a retrospective study and no routine serial follow-up of complete blood count (CBC), chest X-ray (CXR) or ultrasound to document plasma leakage was undertaken unless it was clinically significant.

Clinical manifestations

All patients had headache, bodyaches and high-grade fever. Fever was more than 38.5 °C for an average of 4.83±2.48 days before admission (range: 1 to 14 days). Two male patients presented with fever and coma on top of chronic liver disease and were diagnosed as hepatic encephalopathy and dengue fever; they improved on supportive treatment. One patient presented with shock and gastrointestinal bleeding; the endoscopy showed haemorrhagic gastritis and the mucosa was oozing blood. This patient died after two days in the intensive care unit because of irreversible shock (Table 2).

It is not possible to revise the clinical data according to the new WHO guidelines (2009)[11] for severe and non-severe dengue as these were published after the end of the study.

Laboratory investigations

The haematological abnormalities were thrombocytopenia and leukopenia. Platelet count less than 100 000/cmm was seen in 36.2% of patients and less than 50 000/cmm in 6.9% of patients. The white blood cell count was less than 4000/cmm in 53.7% of patients and less than 2000/cmm in 9.3% of patients. Partial thromboplastin time was 1.5-fold higher than the upper normal level in 33.3% of patients, while prothrombin time and INR were normal in all patients. The AST and ALT values were five-fold more than the upper normal levels in 56 patients (35.2%). The AST value was ten-fold more than the upper normal level in 23 patients (14.5%), while ALT value was ten-fold more than the upper normal level in 14 patients (8.8%), and AST/ALT ratio was 1.38:1.

Five patients presented with DHF and with clinically significant levels of bleeding; they were four males and one female and all were non-Saudi, the average age being 20.8±9.8 (8 to 37). Haemoglobin was lower than 12 gm/dl.
and WBC count was above 4000/cmm in all patients. The platelet count was below 100 000/cmm in three patients (60%) and PTT was above normal in all patients. In all patients, ALT was above five-fold, and AST was above ten-fold. Table 3 shows that the patients presented with bleeding had less platelet count and more prolonged PTT, and significantly higher WBCs, AST and ALT values.

Table 2: Clinical manifestations of patients with dengue fever

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>159 (100%)</td>
</tr>
<tr>
<td>Headache/bodyache</td>
<td>159 (100%)</td>
</tr>
<tr>
<td>Retro-orbital pain</td>
<td>40 (25%)</td>
</tr>
<tr>
<td>Chills and rigours</td>
<td>34 (21.4%)</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td></td>
</tr>
<tr>
<td>Upper Nausea and vomiting</td>
<td>43 (27.0%)</td>
</tr>
<tr>
<td>Lower Abdominal pain and diarrhoea</td>
<td>39 (24.5%)</td>
</tr>
<tr>
<td>Skin rash: Total</td>
<td>26 (16.4%)</td>
</tr>
<tr>
<td>Morbilliform</td>
<td>15/26 (57.7%)</td>
</tr>
<tr>
<td>White islands in a sea of red</td>
<td>8/26 (30.8%)</td>
</tr>
<tr>
<td>Sunburn-like erythema of the face</td>
<td>3/26 (11.5%)</td>
</tr>
<tr>
<td>Respiratory symptoms (dry cough and sore throat)</td>
<td>13 (8.2%)</td>
</tr>
<tr>
<td>Haemorrhagic manifestations (five patients)</td>
<td>5 (3.14%)</td>
</tr>
<tr>
<td>Haematemesis and melena</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Epistaxis and hemoptysis</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Haematuria</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Puerperal haemorrhage</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Others (hepatic encephalopathy)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Mortality (one patient)</td>
<td>1 (0.6%)</td>
</tr>
</tbody>
</table>

n=number of patients (159)
%=percentage of patients with studied clinical manifestation to the total number of patients and the group.

Twenty-six patients had skin rashes and dengue fever; the skin rash ranged from morbilliform (15 patients), white islands in a sea of red (eight patients) to sunburn-like erythema of the face (three patients) (Table 2). It was found that the patients who presented with rash had a statistically insignificant lower WBCs count and AST values while the platelet count was significantly higher and ALT value was significantly lower (Table 4).
### Table 3: Comparison of laboratory findings between DF and DHF patients presented with bleeding

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF patients Mean±SD (range)</th>
<th>DHF patients with bleeding (5 patients) Mean±SD (range)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets (150–400x10^3/cumm)</td>
<td>124±72.8x10^3 (6–340)</td>
<td>101±54 (45–161)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>WBCs (4–11x10^3/cumm)</td>
<td>3.94±2.05x10^3 (0.9–9.9)</td>
<td>8±2.6 (5.2–11.3)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PTT (28.6–38.2 sec)</td>
<td>45.69±9.6 (32–71)</td>
<td>47.6±8.2 (39.3–55.6)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>AST (15–37 IU/L)</td>
<td>226.7±190 (45–980)</td>
<td>555±183 (425–685)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ALT (17–41 IU/L)</td>
<td>164±119.5 (31–458)</td>
<td>314±26 (295–333)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

SD=standard deviation  
ALT=alanine aminotransferase  
AST=aspartate aminotransferase  
PTT=partial thromboplastin time  
WBCs=white blood cells

### Table 4: Comparison between laboratory results in dengue fever patients with and without skin rash

<table>
<thead>
<tr>
<th>Without skin rash (133) Mean±SD (range)</th>
<th>With skin rash (26) Mean±SD (range)</th>
<th>Parameter</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.15±2.13 (0.9–9.9)</td>
<td>3.9±2.29 (1.9 to 9.9)</td>
<td>WBCs (4–11x10^3/cumm)</td>
<td>&gt;0.05 (0.717)</td>
</tr>
<tr>
<td>112.34±65.5 (6–340)</td>
<td>171±86.3 (6–330)</td>
<td>Platelets (150–400x10^3/cumm)</td>
<td>&lt;0.05 (0.010)</td>
</tr>
<tr>
<td>257.96±207 (47–980)</td>
<td>119±25.49 (45–165)</td>
<td>AST (15–37 IU/L)</td>
<td>&gt;0.05 (0.072)</td>
</tr>
<tr>
<td>180±126.5 (31–458)</td>
<td>84.2±45.1 (22–182)</td>
<td>ALT (17–41 IU/L)</td>
<td>&lt;0.05 (0.026)</td>
</tr>
</tbody>
</table>

SD=standard deviation  
ALT=alanine aminotransferase  
AST=aspartate aminotransferase  
PTT=partial thromboplastin time  
WBCs=white blood cells
Course of the illness

All patients were treated symptomatically with intravenous fluids and analgesics. Fresh frozen plasma, platelet and blood transfusion were given only when needed, according to WHO criteria. The length of stay in the hospital varied from one to nine days with an average of 4.07±1.48 days. All patients improved, except one male, non-Saudi patient, who developed severe DSS and died. Patients were discharged from hospital, according to WHO criteria for discharging patients which include: absence of fever for at least 24 hours without the use of anti-fever therapy, return of appetite, visible clinical improvement, good urine output, minimum of three days after recovery from shock, no respiratory distress from pleural effusion, and no ascites and platelet count of more than 50 000/cmm.[6]

Discussion

This study signifies the special pattern of dengue fever in the western part of Saudi Arabia, which is different from other parts of Asia; it happens more in adults and males, has different seasonality, has less morbidity and mortality, and does not constitute a major health problem for visitors to holy places.

Epidemics of dengue fever have been reported from the Arabian Peninsula since the late 19th century, affecting many major cities such as Aden, Jeddah, Makkah and Madinah.[7] Dengue fever virus was first isolated in Jeddah in 1994 from a fatal case of DHF; since that time, medical personnel in the area were alerted and a surveillance system was established by the Ministry of Health. From 1994 to 1999, a total of 207 cases of dengue fever were reported,[8] since then, sporadic cases have continued to be reported from Jeddah and Makkah.

In the present study, most of the cases were admitted in the spring and early summer (77%); cases were also reported from Jeddah.[10] While in tropical areas most of the epidemics happen in the post-rainy season in the autumn months,[12] it is important to mention that it seldom rains in Makkah and Jeddah but there are swamps and inadequate sanitary facilities in some areas. While dengue fever is an important health problem for travellers to all endemic areas, including Makkah, only two of the patients were visitors (for Hajj) and the others were non-Saudi patients resident in Makkah. The reason for a lesser number of Hajj patients could be because of good sanitation and mosquito control in Hajj residency areas. (The risk of exposure to dengue fever can be minimized in modern, air-conditioned hotels with well-kept grounds.[13])

The mean age of patients was 25.6±16.1 years and the percentage of infected children was 24%; in Jeddah the mean age was 27.6±11.2 years and the percentage of children was 6%.[10] Internationally, dengue fever is an infectious disease of children. Reports from India, Sri Lanka, Indonesia and Thailand indicate that children may constitute up to 95% of cases and the peak age of contracting dengue infection is between 5 and 10 years.[14-18]

It is clear that the age pattern of dengue fever infection in Saudi Arabia is different from that of South-East Asia, and is closer to the age pattern of dengue fever infection in Brazil, where it is the highest in adults. This may be related to the genotypes present. The reports from Brazil indicate that DENV-1 and DENV-2 viruses happen more in adults,[19,20] and in Jeddah, DENV-1 and DENV-2 viruses constitute 93% of the cases[9]. Males are affected more than females (ratio of 2 to 1); the same is the case in Jeddah[10] while reports from other endemic areas show that males and
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females are affected equally.\cite{16,17,21} The less number of females affected in Saudi Arabia may be due to their limited outdoor exposure (for social reasons) and to their wearing the veil (hijab) outdoors when the whole body is covered.

As regards the patients’ symptoms, high-grade fever, headache and bone pains were the most common symptoms, followed by gastrointestinal complications, chills and rigours, skin rash and respiratory problems. Similar findings have been reported by national\cite{10} and international researchers.\cite{22} Haemorrhagic manifestations happened in five patients (3.14%), similar to other reports in Saudi Arabia and internationally.\cite{10,23} In a study from Indonesia, out of 1300 cases severe bleeding was recorded in 76 of the dengue cases (6%) and included haematemesis (58%), melena (21%), haematemesis-melena (16%) and DIC (5%).\cite{20} Two patients presented with hepatic encephalopathy (1.3%), and both had chronic liver disease. A report from Thailand shows that hepatic encephalopathy was considered an unusual manifestation of dengue fever and they attributed this to toxic substance, drugs or underlying liver conditions.\cite{24} In rare cases dengue fever may present as an acute liver failure.\cite{25} One patient presented with DSS and GI bleeding and died (0.6%). In the Indonesian study, out of 1300 patients, 102 patients (8%) had DSS and 17 patients died (1.3%).\cite{20} About 36.2% of patients had a platelet count of less than 100 000/cmm, which is less than the international figure (58%).\cite{26} The lower percentage of DSS and thrombocytopenia in this study compared to the international figures perhaps because of the limited number of cases; also, it is necessary to do more frequent investigations to detect early and mild cases of plasma leakage (such as CBC, abdominal ultrasound and CXR).

Patients who developed bleeding were not necessarily those who had the lowest platelet number, which means that bleeding is a multifactorial process; bleeding may result from a combination of factors such as thrombocytopenia, coagulation defects and vasculopathy.\cite{20} The average number of white cell count was 3940±2050 and 53.7% of the patients had WBCs less than 4000/cmm; this was close to a local study\cite{10} where 48.72% of patients had WBC below 4000/cmm. Also, in a study from South-East Asia, the mean WBCs was 3834±2216 and the percentage of leukopenia below 5000/cmm was 89.77%.\cite{26} Prolonged PTT more than 1.5-fold the upper normal limit was found in one third of the patients; this was similar to reports from Jeddah, Thailand and India.\cite{10,15,22}

The liver is a target organ of dengue infection; hepatic involvement ranged from mildly elevated aminotransferases to fulminant hepatic failure leading to death.\cite{27-30} The pathology included severe, diffuse hepatitis, focal necrosis of hepatic cells and hyaline necrosis of Kupffer cells.\cite{31,32,33} Liver function tests showed elevated liver enzymes with normal bilirubin and alkaline phosphatase, liver enzymes were higher than five-fold the upper normal limit in 56 patients (35.2%); it was also elevated as reported from Saudi Arabia and Thailand in 66.7%, 63%, 67% and 34.2% of patients.\cite{10,27,34,35} It is worth noting that the level of AST elevation was higher than that of ALT (ALT/AST ratio of 1:1.38) in contrast to acute viral hepatitis; this finding was also reported from South-East Asia.\cite{24}

Sixteen patients had DHF (10.1%), five of them presented with overt bleeding; the average age was 20.8±9.8 (8 to 37), similar to reports from Brazil\cite{20} but different from South-East Asian patients where most of them were children.\cite{18} Liver enzymes were higher than those with classic dengue fever and the
AST/ALT ratio was higher at 1.77:1 while it was 1.38:1 in dengue fever patients. In South-East Asia, 92% of patients with DHF had AST more than 60U, and in patients who presented with encephalopathy, AST and ALT values usually exceeded 200U. The frequency of hepatic dysfunction depends on dengue fever disease severity. There was a correlation between liver enzymes and the severity of dengue infection. The appearance of rash may be associated with the milder illness of classic DF.

The prevalence of dengue fever in Saudi Arabia is not unique. WHO has described the presence of dengue in other areas of the Eastern Mediterranean Region – in Egypt as early as in 1979, in Sudan (1985) and in Djibouti (1991). In Saudi Arabia, three major epidemics have been reported: a DENV-2 epidemic in 1994 with 469 cases of dengue, 23 cases of DHF, two cases of DSS and two deaths; a DENV-1 epidemic in 2006 with 1269 cases of dengue, 27 cases of DHF, 12 cases of DSS and six deaths; and a DENV-3 epidemic in 2008 with 775 cases of dengue, nine cases of DHF, four cases of DSS and four deaths.

The limitations of this study are due mainly to its retrospective type, limited number of cases, inability to know the total number of suspected cases, and lack of frequent investigations to pick up early cases of plasma leakage. These issues should be taken into consideration in later studies.

In conclusion, dengue fever is an endemic disease in Makkah, the holy city for Muslims. It is rare in visitors who come to Makkah for the Hajj pilgrimage, but all measures to prevent the spread of the disease should be taken.

References


