Original Article

Clinical profile of dengue fever infection in King Abdul Aziz University Hospital Saudi Arabia

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Abstract

Background: The study aimed to compare the clinical profile of all patients diagnosed with dengue viral infection at King Abdul Aziz University Hospital (KAAUH), during 2005-2008.

Methodology: This retrospective study included 147 patients infected with dengue virus, age ≤ 16 years. Laboratory and haematological data were included.

Results: Two peaks of infection occurred during 2006 and another two in 2008. Common clinical symptoms were fever, vomiting, and abdominal pain. Common haematological abnormalities were thrombocytopenia and leucopoenia. Differences existed between the years in the percentage of patients with fever, elevated alanine aminotransferase (ALT), direct bilirubin, lactate dehydrogenase (LDH), fibrin degradation products (FDPs), and haemoglobin (Hb) levels. Differences were found in nationalities between the years, but patient nationality had no effect on disease incidence. Differences were noted in the percentages of patients' immunoglobulin M (IgM) and polymerase chain reaction (PCR) positive. There was a slight inverse correlation of IgM positive with patient age. PCR, fever, ALT, direct bilirubin, LDH, FDPs, Hb, blood transfusion, and platelet transfusion showed no correlation with age or nationality. In 2005, all the patients survived, but there were 4.55%, 25%, and 2.7% deaths during 2006-2008.

Conclusions: Significant differences in the clinical presentation of dengue virus (DENV) infection, indicative of a variation in disease severity from dengue fever (DF) to dengue hemhorrhagic fever (DHF)/dengue shock syndrome (DSS), were noted over the years. Possible reasons are infection with different serotypes, concurrent/sequential infection of more than one serotype, and differences in host immune responses associated with host genetic variations.

Key words: dengue fever, thrombocytopenia, leucopoenia, Saudi Arabia

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Introduction

Dengue is a mosquito-borne viral illness caused by one of the four serotypes of the dengue virus (DENV; (DENV-1 to DENV-4) belonging to the family Flaviviridae. The virus serotypes are closely related but antigenically distinct. Dengue infections can result in a wide spectrum of disease severity ranging from an influenza-like illness (dengue fever; DF) to the life-threatening dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS). In recent decades, the incidence of dengue infection has increased around the world and has become a major international public health concern. The disease is now endemic in more than 100 tropical and sub-tropical countries. The World Health Organization (WHO) estimates that there may be 50 million dengue infections worldwide every year [1,2].

Infection with one serotype of DENV provides lifelong immunity to that serotype, but results only in partial and transient protection against subsequent infection by the other three serotypes. It is possible for a person to be infected as many as four times, once with each serotype. It is well documented that sequential infection with different DENV serotypes increases the risk of developing DHF. Ninety percent of DHF infections occur in children less than 15 years of age. There is currently no specific treatment for DENV infection, although several potential vaccines are in development; therefore, the only method of preventing DENV transmission is vector (mosquito) control [1,3].

DF is endemic in Saudi Arabia, especially in the western and southern regions [4]. Millions of pilgrims travel to Jeddah every year via air or sea to go to Makah (Mecca), the holy city of Islam, for about 20 days; for example, Jeddah received 1,557,447 visitors for Hajj in 2005 [5]. In addition to

this figure, pilgrims regularly visit Makah during the year.

Early clinical features of dengue infection are variable among patients, and initial symptoms are often non-specific; therefore, specific laboratory tests are necessary for an accurate diagnosis [7,8]. According to the US Centers for Disease Control and Prevention (CDC) and the WHO dengue guidelines [8], the clinical features of DF and DHF are sudden onset of fever, severe headache, myalgias and arthralgias, leucopoenia, thrombocytopenia, and hemorrhagic manifestations. It occasionally produces shock and haemorrhage, leading to death. Classic DF symptoms include fever, headache, retro-orbital pain, myalgias and arthralgias nausea, vomiting, and often a rash. Some DF patients develop the more serious form of the disease DHF with symptoms that include a decline in fever and presentation of hemorrhagic manifestations, such as microscopic hematuria, bleeding gums, epistaxis, hematemesis, melina, and ecchymosis. DHF patients develop thrombocytopenia and hemoconcentration; the latter is due to an increase in the concentration of blood cells resulting from the leakage of plasma from the bloodstream. These patients may progress into DSS, which can lead to profound shock and death if not treated. Advance clinical symptoms of DSS include severe abdominal pain, protracted vomiting, and a notable change in temperature from fever to hypothermia [2].

In this study, we analyzed the variation in clinical features of DENV-infected patients at King Abdul Aziz University Hospital (KAAUH) from 2005 to 2008. The clinical presentations were also compared with the US CDC definition.

Materials and methods

Patients diagnosed with dengue viral infection (n = 147, 46 females and 101 males), aged 16 years old or less at the KAAUH from 2005 to 2008, were included in the study. The mean ages of the patients were 3.67 ± 1.15, 4.03 ± 1.78, 5.25 ± 1.26, and 4.68 ± 1.79 years (± SD) for 2005-2008. In 2005, all the patients were Saudis. In 2007, 25% were other Arabs and 75% were Yemenis. During 2006 and 2008, patient nationalities included Saudis, Africans, other Arabs, Asians, Egyptians, and Yemenis. Other data collected included clinical, laboratory and haematological patient profiles; time of infection (month and year); days of hospitalization; and mortality rate.

Laboratory Profile

The PCR based assay described by Griffais R *et al.* [9] was carried out. Additionally, the dengue virus IgG/IgM ELISA test with 99% sensitivity and specificity was performed using commercial kits provided from BIO-QUANT INC San Diego, CA, United States. Liver function tests (LFTs) including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total, indirect and direct bilirubin, and LDH, as well as the FDP test were performed on Dimension XL (Dade Behring, Marburg, Germany).

Haematological profile

Haematological parameters evaluated were platelet count, prothrombin time (PT), partial thromboplastin time (PTT), Hb and hematocrit (HCT) levels, complete blood count (CBC), and white blood cell count (WBC). Blood and platelet transfusions conducted were also recorded.

Statistical Analysis

Data analysis was performed by using NCSS statistical software version 07.1.8, Kaysville, Utah, United States. All categorical variables were grouped and tested using the chi-square test to evaluate the differences from one year to another. Continuous variables were analyzed using descriptive statistics. All variables were tested using logistic regression against age and nationality. Odds ratios were calculated and tested using the Wald test.

Results

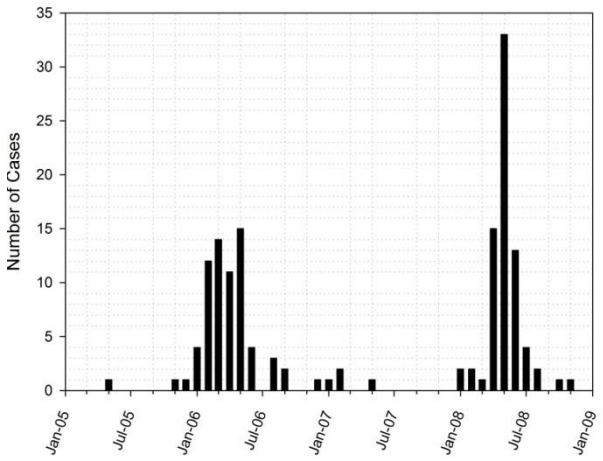
Seasonal distribution

The first case of DENV infection detected by positive PCR in 2005 was in May. Only three and four cases were reported during 2005 and 2007, respectively. Two peaks of infection occurred during 2006 (66 cases) and 2008 (74 cases). The peak of 2006 started in February and ended in July. The peak of 2008 started in April and also ended in July. Figure 1 shows the months when peak infection occurred during each year.

Clinical profile

Clinical features observed were fever, headache, vomiting, rash, ecchymosis, melina, hematemesis, and other hemorrhagic manifestations, retro-orbital pain, and abdominal pain (Figure 2). The most

Figure 1. The number of infected cases per month for each year



common clinical presentations were fever (66.67%, 84.58%, 50%, and 62.16%), vomiting (66.67%, 45.45%, 25%, and 40.54%) (2005-2008), and abdominal pain (33.33%, 36.36%, and 27.03%) during 2005, 2006, and 2008, respectively. None of the patients reported any abdominal pain in 2007 (Figure 2).

Relatively less common clinical features were hemorrhagic manifestations, headaches, rash, and retro-orbital pain. During 2005 and 2007, none of the patients experienced headaches or hemorrhagic manifestations. In comparison, 12.12% and 5.41% of patients presented with hemorrhagic manifestations (not including ecchymosis, melina and hematemesis) during 2006 and 2008, respectively; additionally, 34.85% of patients reported headaches in 2006 and 22.97 % in 2008. None of the patients presented with ecchymosis or melina during 2005, 2007, and 2008, compared to only 4.55% of patients who had both symptoms during 2006. Hematemesis was also rare; it was not reported in any patients during 2005 or 2007, and was reported in only 6.06% and 1.35% of the patients during 2006 and 2008, respectively. In addition, 18.18% and 13.51% of the patients developed a rash and 6.06% and 8.11% reported retro-orbital pain during 2006 and 2008, respectively. However, none of the patients during 2005 or 2007 reported a rash or retro-orbital pain (Figure 2). Table 1 shows patient details including age, nationality, clinical and laboratory profiles, days of hospital admission, and mortality rate.

Most of the hospitalized patients remained in hospital up to ten days (66.66%, 63.63%, 75%, and 45.95% for 2005-2008). All the patients survived during 2005, but 4.55%, 25%, and 2.7% of the patients died during 2006-2008 (Table 1). Table 2 shows the haematological profile of the patients.

Haematological profile

Thrombocytopenia (< l00,000 platelets/μL) was one of the most common haematological abnormalities, observed in 66.67%, 68.76%, 100%, and 67.58% of patients in 2005-2008. Leucopoenia (< 4.3 - 10.8 x 10^9 cells/L) was also common; 100%, 65.63%, 50%, and 68.93% of patients had a WBC of < 4.0 x 10^9/L in 2005-2008 (Table 2).

The clinical presentation of disease varied significantly from one year to another in the percentage of patients with fever ($p = 0.018714$), elevated ALT ($p = 0.015764$), direct bilirubin ($p = 0.01613$), LDH ($p = 0.040767$), and FDPs ($p = 0.04297$). Significant differences were also noted in the percentage of patients who were IgM and PCR positive at $p < 0.00001$ and $p = 0.000006$, respectively. There were no significant differences in the percentage of IgG positive patients. Although there was a significant difference in nationalities from one year to another ($p = 0.013286$), patient nationality had no effect on the incidence of disease (Table 1).

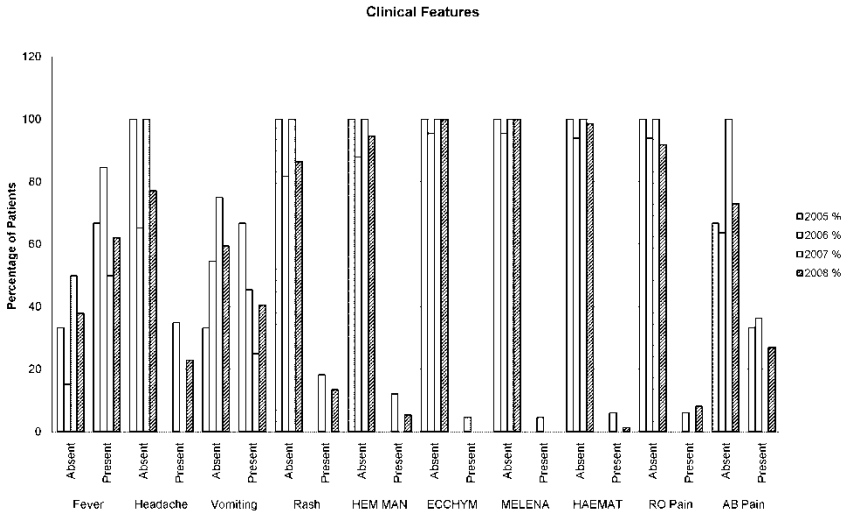
There was a slight inverse correlation of IgM positive patients with patient age. This tendency scored an odds ratio of 0.63593 and a $p = 0.00095$ using the Wald test. The remaining nine statistically significant variables (PCR, fever, ALT, direct bilirubin, LDH, FDPs (Table 1), Hb, blood transfusion, and platelet transfusion (Table 2)), showed no correlation with patient age or nationality. Significant differences were also recorded for Hb levels ($p = 0.006519$) and the percentage of patients who received blood ($p = 0.047119$) and platelet transfusions ($p = 0.044971$) (Table 2). Other signs and symptoms varied between the years but the differences were not significant (Tables 1 and 2).

Discussion

Seasonal distribution

The main peaks of infection during 2006 (February to July) and 2008 (April to July) included the summer. The reason for this is unclear because Jeddah has a hot climate with limited rainfall. A possible explanation could be increased travel due to the annual vacation of children [10]. The peak of

Figure 2. Clinical features



infection beginning before the summer may be due to the fact that Jeddah receives millions of pilgrims throughout the year who are en route to Makah.

Clinical features compared to US CDC definition

The most common clinical presentations were fever, vomiting, and abdominal pain, which were also common symptoms during the first outbreak of dengue in Makah in 2004 [4]. Fever and vomiting are symptoms associated with DF; however, protracted vomiting and severe abdominal pain may also result in the subsequent development of DSS. The main haematological abnormalities were leucopoenia and thrombocytopenia (associated with DHF), which are in agreement with the findings of another study in Jeddah, Saudi Arabia [10]. Coagulopathy is frequent in DENV-infected patients; for example, the bleeding disorder disseminated intravascular coagulation (DIC) is often seen in DF and DHF [10]. The presence of DIC may therefore explain the prolonged PTT observed in 31.82%, 25%, and 27.03% of patients in 2006-2008. Due to the nature of the study design, no other details could be explained about DIC.

In this study, we found many symptoms according to the US CDC definition of DENV infection that were either absent or present in low numbers**.** The relatively fewer common clinical features were hemorrhagic manifestations (associated with DHF) headaches, rash, and retro-orbital pain. Rash and hemorrhagic manifestations were also relatively uncommon in another study conducted in Jeddah [10]. None of the patients reported any myalgias or arthralgias in any year.

Comparison of the significant differences in clinical presentations from 2005-2008

Significant differences were observed between the years for the percentage of patients who were IgM positive, PCR positive (indicating the presence of DENV), presenting with fever, and showed liver dysfunction, (elevated ALT, direct bilirubin level, and LDH). Similarly, the percentage of patients with elevated FDPs (a sign of DIC), and requiring blood and platelet transfusions also showed significant variation, as did the Hb levels. Although there was a significant difference in nationalities from one year to another, patient nationality had no affect on the incidence of disease. No significant differences were noted between the years for the percentage of IgG positive patients, suggesting that there was no significant difference in the percentage of patients demonstrating a secondary antibody response.

Table 1. Comparison between years for patient demography, clinical, and laboratory profiles (n = 147).

		2005 (n = 3)	2006 (n = 66)	2007 (n = 4)	2008 (n = 74)	[+] P-value
Nationality	Saudi	100	53.03	0	31.08	**0.013286**
	African	0	7.58	0	13.51	
	Other Arab	0	1.52	25	5.41	
	Asian	0	9.09	0	21.62	
	Egyptian	0	10.61	0	4.05	
	Yemeni	0	18.18	75	24.32	
Age (Years)	Mean±SD	3.67±1.15	4.03±1.78	5.25±1.26	4.68±1.79	
IgG	Positive	33.33	33.33	0	45.95	0.149204
IgM	Positive	100	89.39	75	75.68	**<0.00001**
PCR	Equivocal	0	1.52	0	0	**0.000006**
	Positive	33.33	15.15	0	40.54	
Fever	Present	66.67	84.58	50	62.16	**0.018714**
Headache	Present	0	34.85	0	22.97	0.155602
Vomiting	Present	66.67	45.45	25	40.54	0.668663
Rash	Present	0	18.18	0	13.51	0.595334
Hemorrhagic Manifestations	Present	0	12.12	0	5.41	0.431446
Ecchymosis	Present	0	4.55	0	0	0.288748
Melena	Present	0	4.55	0	0	0.288748
Hematemesis	Present	0	6.06	0	1.35	0.455134
Retro-orbital Pain	Present	0	6.06	0	8.11	0.857301
Abdominal Pain	Present	33.33	36.36	0	27.03	0.354553
ALT	1-2x	66.67	33.33	50	32.43	**0.015764**
	3-4x	0	7.58	50	28.38	
	>4	100	25.76	0	13.51	
AST	1-2x	33.33	28.79	0	39.19	0.143608
	3-4x	33.33	16.67	25	27.03	
	>4	33.33	27.27	25	12.16	
Total bilirubin	elevated	0	9.09	50	13.51	0.102232
Direct bilirubin	elevated	0	4.62	50	5.41	**0.01613**
Indirect bilirubin	elevated	0	4.55	0	4.05	0.967618
LDH	elevated	33.33	16.67	0	4.05	**0.040767**
FDPs	elevated	0	12.12	25	0	**0.04297**
Mortality rate	survived	100	95.45	75	97.3	0.172232
	died	0	4.55	25	2.7	
Days of Hospital Admission	0	33.33	24.24	25	48.65	0.311197
	<5	33.33	45.45	75	29.73	
	5--10	33.33	18.18	0	16.22	
	10--20	0	10.61	0	5.41	
	>30	0	1.52	0	0	

Numbers are percentage of patients.
[+]Chi-square test. Values of $p < 0.05$ are considered to be statistically significant (shown in bold).

Table 2. Comparison of the haematological profile of patients between years (n = 147).

		2005 (n = 3)	**2006 (n = 66)**	**2007 (n = 4)**	**2008 (n = 74)**	**[+] P-value**
Platelet Count ($x10^3/\mu L$)	<10	0	3.13	0	1.35	0.258158
	11-20	0	3.13	50	5.41	
	21-30	0	1.56	0	5.41	
	31-40	0	6.25	0	6.76	
	41-50	0	4.69	25	6.76	
	51-100	66.67	50	25	41.89	
	101-150	0	18.75	0	18.92	
	>150	33.33	12.5	0	13.51	
PT	Prolonged	0	4.55	0	8.11	0.592081
PTT	Prolonged	0	31.82	25	27.03	0.63652
Hb (g/dL)	<5	0	1.56	25	0	**0.006519**
	5-10	0	6.25	0	5.41	
	>10	100	92.19	75	94.59	
HCT (%)	<30	0	9.38	25	8.11	0.884556
	31-50	100	87.5	75	86.49	
	>50	0	3.13	0	5.41	
WBC ($x\ 10^9/L$)	0.1-1.0	0	1.56	0	1.35	0.793028
	1.1-2.0	66.67	21.88	25	16.22	
	2.1-3.0	33.33	32.81	25	35.14	
	3.1-4	0	9.38	0	16.22	
	>4	0	34.38	50	31.08	
Blood Transfusion	received	0	1.52	25	2.7	**0.047119**
Platelet Transfusion	received	0	3.03	25	1.35	**0.044971**

Numbers are percentage of patients.
[+]Chi-square test. Values of $p < 0.05$ are considered to be statistically significant (shown in bold).

There was a slight inverse correlation of IgM positivity with patient age leading to the conclusion that the younger the patient, the greater the likelihood of a primary antibody response; however, there was no correlation between PCR, fever, ALT, direct bilirubin, LDH, FDPs, Hb, blood and platelet transfusion, and patient age or nationality.

From 2005-2008, a wide spectrum of clinical features were reported ranging from DF to DHF/DSS symptoms. Most of the patients who were hospitalized remained in hospital up to ten days. All the patients survived during 2005, but 4.55%, 25%, and 2.7% of patients died during 2006-2008. Therefore, the highest mortality rate (25%) occurred during 2007, when 25% of patients had Hb levels < 5g/dL, and 50% had severe thrombocytopenia (11-20,000 platelets/μL). Consequently, 25% of patients required blood and platelet transfusions. The pathogenesis of DENV is poorly understood. A complex interaction between immunopathologic, viral, and human genetic factors results in a varied DENV disease outcome [11], which may explain the varied range of clinical presentations observed in this retrospective analysis. It cannot, however, explain the high mortality rate during 2007. In our retrospective registry, no explanation was found for the increase in mortality during 2007.

A possible reason for the significant differences seen in the clinical expression of the disease between the years may be due to infection with different DENV serotypes [12] and the possibility of concurrent infections with more than one serotype. Co-circulation of multiple DENV serotypes has been reported from many parts of the world, including India during an outbreak of DHF/DSS in 2006. Co-circulation of multiple DENV serotypes would result in an increased risk of concurrent infections. There is, however, limited documentation describing concurrent infections with more than one serotype in the same individual [13,14]. Furthermore, as already alluded to, sequential infection with more than one

serotype is thought to be a major factor for the emergence of DHF [1].

Two studies conducted in Jeddah and nearby Makah support the possibility that there were multiple serotypes in co-circulation in Jeddah from 2005 to 2008. Three of the four dengue serotypes (DENV-1, DENV-2, and DENV-3) were circulating in Jeddah in the summer of 2004, and an outbreak from the summer of 2005 until early 2006 was caused by a DENV-1 strain from genotype Asia (lineage Asia-2) [15]. In addition, DENV-1 and DENV-2 were also identified in Makah during 2004 [4]. Co-circulation of multiple DENV serotypes would not be unexpected given the unique population dynamics of Jeddah; specifically, it receives millions of pilgrims annually from all over the world, as seen in this study with a highly significant difference in nationalities of patients during 2005-2008. International travel has had the most impact on the spread of dengue viral infection around the world [16].

Both primary and secondary infection by any of the four DENV serotypes can cause DF and DHF; however, virus virulence is not the only factor to explain differences in host susceptibility to the disease and disease severity. Host immune response variations have been associated with polymorphism in the human genome, which may help explain why some patients develop end-stage complications in dengue disease and others only experience a mild form of the disease [17]. In another study of children with DENV infection, host genetic differences were shown to affect the immune response and consequently, influence disease outcome [18].

Conclusion

Between 2005 and 2008, we observed significant differences in the clinical presentation of DENV infection ranging from DF to DHF/DSS symptoms. Dengue viral infection is a complicated disease and many factors may be attributed to the differences seen, such as infection with different serotypes or infection with more than one serotype, either sequentially or concurrently. Differences in host genetics and immune responses may also play a role in the severity of infection.

Dengue infection can have potentially fatal consequences, and to date, vector control methods to prevent the spread of the virus have been unsuccessful [19]. Although there are promising vaccine candidates in development, further studies are required for a greater understanding of the humoral immune responses to DENV infection and disease pathogenesis [20].

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