DIFFERENCES IN CLINICAL FEATURES BETWEEN CHILDREN AND ADULTS WITH DENGUE HEMORRHAGIC FEVER/DENGUE SHOCK SYNDROME

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Abstract. This retrospective study was conducted to assess the differences in clinical features between children and adults with dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) admitted to Ratchaburi Hospital, Ratchaburi Province, Thailand. A total of 273 patients with DHF/DSS admitted to Ratchaburi Hospital during January 2007 to May 2008 were included in the study. The median age (range) of studied subjects was 16 years (6 months to 62 years) and the ratio of adults to children was 1.6:1. Forty-eight percent of subjects were 16-30 years old. The common signs, symptoms and clinical features were: nausea/vomiting (74.0%), a positive tourniquet test (73.0%), anorexia (67.0%), hemoconcentration (58.0%), headache (54.0%), abdominal tenderness (43.0%), myalgia (39.0%) and pleural effusion (20.0%). Children had anorexia, a positive tourniquet test, abdominal tenderness and a convalescent rash more frequently than adults. Children also had significantly more prominent plasma leakage as shown by lower serum albumin and sodium and a higher prevalence of pleural effusion, ascites and shock. Although not statistically significant, the prevalence of bleeding in children was higher than in adults but more adults needed blood transfusion. This study provides additional insight into the clinical picture of DHF/DSS in adults and children and may be beneficial for clinicians caring for these adults and children.

Keywords: dengue hemorrhagic fever, clinical feature, children, adult

INTRODUCTION

Dengue infection is one of the most important mosquito-borne viral diseases in tropical and subtropical regions of the world. The World Health Organization (WHO) has estimated 2.5 billion people, two-fifths of the world's population, are at risk for dengue and there may be 50 million dengue infections worldwide every year (WHO, 2009). The clinical spectrum of dengue infection includes asymptomatic infection, undifferentiated fever (UF), dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) (WHO, 1997).

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Dengue infection has been previously thought of as a disease mainly of children (Nimmannitya, 1987). However, recent reports have shown the age distribution of this disease has shifted toward adults (Guzmán *et al*, 1990; Rigau-Pérez *et al*, 2001; Gupta *et al*, 2006). It is important that clinicians caring for adults be familiar with this disease. Unfortunately, information about the clinical features of dengue in adults and age-related differences are limited. There are only a few reports on the clinical features of dengue infection in adults (Wichmann *et al*, 2004; Kularatne *et al*, 2005; Hammond *et al*, 2005; Kittigul *et al*, 2007; Hanafusa *et al*, 2008; Binh *et al*, 2009; Wang *et al*, 2009). Some papers have compared the clinical features and disease severity between adults and children (Wichmann *et al*, 2004; Hammond *et al*, 2005; Kittigul *et al*, 2007; Hanafusa *et al*, 2008; Binh *et al*, 2009; Wang *et al*, 2009). Nearly all these papers describe dengue infection as a combination of DF and DHF/DSS. Since DHF/DSS is more severe than DF, it should be more useful to describe DHF/DSS in adults. This study was carried out to determine the clinical features of DHF/DSS in children and adults and compare the differences between adults and children.

MATERIALS AND METHODS

We conducted this retrospective study at Ratchaburi Hospital (RH), Ratchaburi Province, Thailand. RH is a regional hospital, providing tertiary medical care. It is located approximately 100 km southwest of Bangkok, the capital of Thailand, and has approximately 800 beds, including 90 pediatric beds.

The medical records of patients, both adults (aged > 15 years) and children, admitted to RH between January 2007 and May 2008 with a clinical diagnosis of DHF/DSS were retrieved. Patients who had no evidence of other infections and who met WHO criteria for DHF (WHO, 1997), such as fever, hemorrhagic tendencies, thrombocytopenia and evidence of plasma leakage, were recruited. DHF patients who had signs of circulatory failure were classified as having dengue shock syndrome (DSS).

The sample size of the study population was calculated using the formula for a case-control study based on the data from a study by Hammond *et al* (2005) who found the incidence of clinical shock was 12% in adults and 35% in children. With a 95% confidence level and 95% power, the sample size for children and adults should be 92 for each age group. However, to study the actual proportion of the disease in each age group, we collected all cases presenting during the study period.

The demographic data and clinical features of patients with DHF/DSS were collected. Descriptive statistics were used to describe these data. Comparisons of these data between children and adults were conducted using a chi-square or Fisher's exact test for the categorical variables. The Student's *t*-test was used for continuous variables that were normally distributed and the Mann-Whitney *U* test was used for the data that were not normally distributed. All the analyses were calculated using a 2-tailed p-value < 0.05 as the statistically significant cut-off point.

This study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University.

RESULTS

A total of 273 patients were included in the study, 105(38.5%) were children and 168 (61.5%) were adults. The age of

Table 1
Frequency (%) of primary and secondary dengue infections in children and adults with DHF/DSS.

Serologic result	Children	Adults	Total	*p*-value [a]
Primary dengue infection	2 (25.0)	4 (25.0)	6 (25.0)	1.000
Secondary dengue infection	6 (75.0)	12 (75.0)	18 (75.0)	
Total	8 (100)	16 (100)	24 (100)	

[a]Fisher's exact test

Table 2
Frequency (%) of clinical symptoms in children and adults with DHF/DSS.

Symptom	Children *n*=105	Adults *n*=168	Total *n*=273	*p*-value[a]
Nausea/vomiting	83 (79.0)	118 (70.2)	201 (74.0)	0.11
Anorexia	85 (81.0)	97 (58.0)	182 (67.0)	<0.001
Headache	54 (51.4)	93 (55.4)	147 (54.0)	0.53
Myalgia	24 (23.0)	81 (48.2)	105 (39.0)	<0.001
Abnormal vaginal bleeding	5/42 (11.9)	13/75 (17.3)	18/117 (15.4)	0.61
Hematemesis	16 (15.2)	15 (9.0)	31 (11.4)	0.11
Epistaxis	15 (14.3)	12 (7.1)	27 (10.0)	0.054
Gum bleeding	9 (9.0)	10 (6)	19 (7.0)	0.41
Melena	8 (8.0)	7 (4.2)	15 (6.0)	0.22
Need for blood transfusion	4 (4.0)	12 (7.1)	16 (6.0)	0.25
Retro-orbital pain	8 (8.0)	7 (4.2)	15 (6.0)	0.22
Arthralgia	4 (4.0)	7 (4.2)	11 (4.0)	1.00[b]

[a]Chi-square test; [b]Fisher's exact test

the subjects ranged from 6 months to 62 years. Most of the subjects (48.0%) were 16-30 years old. The median ages of the children, adults and total study population were 11, 22 and 16 years, respectively. In the children's group, 63 (60.0%) were male and 42 (40.0%) were female (male to female ratio of 1.5:1). In the adults' group, 93 (55.4%) were male and 75 (44.6%) were female (male to female ratio of 1.2:1).

A serologic diagnosis using enzyme-linked immunosorbent assay was performed in only 8 children (7.6%) and 16 adults (9.5%) and primary infection was found in 25% of both children and adults (Table 1).

Nausea/vomiting, anorexia, headache and myalgia were the common symptoms found in both children and adults (Table 2). Unfortunately, only some patients were examined for specific clinical signs. Hepatomegaly and abdominal tenderness, a positive tourniquet test and a convalescent rash were common. Most of the patients, both children and adults, had a peak fever >38°C and only 16% of patients had a fever for 8 days or longer. Among patients who had a positive tourniquet

Table 3
Frequency (%) of clinical signs in children and adults with DHF/DSS.

Findings	Children	Adults	Total	*p*-value[a]
Liver size				
≤ 2 cm	32/41 (78.0)	13/13 (100.0)	45/54 (83.0)	0.09[b]
> 2 cm	9/41 (22.0)	0	9/54 (17.0)	
Positive tourniquet test	45/57 (79.0)	21/34 (62.0)	66/91 (73.0)	<0.001
Hemoconcentration (Hct increase ≥ 20%)	66/104 (63.5)	91/168 (54.2)	157/272 (58.0)	0.13
Abdominal tenderness	53/101 (52.0)	52/143 (36.4)	105/244 (43.0)	<0.001
Convalescent rash	31/58 (53.4)	11/62 (18.0)	42/120 (35.0)	<0.001
Day of positive tourniquet test				
≤ 3 days	19/47 (40.0)	8/23 (35.0)	27/70 (39.0)	0.65
≥ 4 days	28/47 (60.0)	15/23 (65.0)	43/70 (61.0)	
Pleural effusion	15/52 (29.0)	5/50 (10.0)	20/102 (20.0)	<0.001
Ascites	11/51 (22.0)	3/51 (6.0)	14/102 (14.0)	0.001
Petechiae	14/105 (13.3)	25/168 (15.0)	39/273 (14.3)	0.72
Drowsiness	11/105 (11.0)	4/168 (2.4)	15/273 (5.5)	0.004
Confusion	3/105 (3.0)	3/168 (2.0)	6/273 (2.2)	0.68[b]
Jaundice	2/105 (2.0)	2/168 (1.0)	4/273 (1.5)	0.64[b]
Ecchymosis	0	1/168 (1.0)	1/273 (0.4)	1.00[b]
Shock (DSS)	28/105 (26.7)	10/168 (6.0)	38/273 (13.9)	<0.001
Duration of fever				
≤ 7 days	89 (85.0)	141 (84.0)	230 (84.0)	0.85
≥ 8 days	16 (15.0)	27 (16.0)	43 (16.0)	
Peak fever				
≤ 38°C	22 (21.0)	51 (30.0)	73 (27.0)	0.09
> 38°C	83 (79.0)	117 (70.0)	200 (73.0)	

[a]Chi-square test; [b]Fisher's exact test

test, only 39% had a positive test before the fourth day of illness (Table 3). Children presented more frequently with anorexia, a positive tourniquet test, drowsiness, abdominal tenderness, a convalescent rash, a pleural effusion, ascites and shock while more adults had myalgia (Tables 2, 3). Although not statistically significant, children had a higher prevalence of bleeding but more adults needed a blood transfusion (Table 2).

Table 4 shows laboratory findings in the children and adults subjects. The comparison between children and adults revealed the adults had a significantly lower median platelet count. Children had a lower atypical lymphocyte count, a lower hematocrit, serum sodium, bicarbonate, creatinine, albumin and globulin levels than adults. Children also had higher potassium and AST levels and a longer prothrombin time.

Two cases in this study died. The overall case fatality rate was 0.73%. The first case that expired was an 8-month-old female who had fever for 7 days prior to admission. She presented to the district hospital with nausea/vomiting, epistaxis,

Table 4
Laboratory findings in children and adults with DHF/DSS.

Laboratory findings	Children	Adults	*p*-value[a]
Highest Hct (%)	45.0 (5.27)[c] *n*=105	46.2 (5.7)[c] *n*=168	0.07
Lowest Hct (%)	36.2 (4.22) [c] *n*=104	37.8 (5.35)[c] *n*=168	0.006
Lowest platelet count (cells/mm^3)	46,500 (6,000-153,000)[d] *n*=104	32,000 (2,900-99,000)[d] *n*=168	<0.001[b]
Lowest WBC count (cells/mm^3)	2,750 (1,030-8,300)[d] *n*=104	2,585 (890-8,300)[d] *n*=168	0.57[b]
Highest percent of atypical lymphocytes (%)	8.0 (0-52)[d] *n*=102	13.0 (1-44)[d] *n*=162	<0.001[b]
Serum sodium (mEq/l)	132.0 (5.66)[c] *n*=68	135.0 (3)[c] *n*=116	<0.001
Serum potassium (mEq/l)	3.7 (0.55)[c] *n*=68	3.5 (0.58)[c] *n*=116	0.005
Serum bicarbonate (mEq/l)	19.8 (3.9-107.7)[d] *n*=68	22.6 (9.9-104.5)[d] *n*=116	<0.001[b]
BUN (mg/dl)	12.7 (6.31)[c] *n*=29	11.5 (4.64)[c] *n*=98	0.34
Creatinine (mg/dl)	0.7 (0.2-1.3)[c] *n*=29	0.9 (0.1-9.2)[d] *n*=99	0.001[b]
Albumin (g/dl)	2.8 (0.67)[c] *n*=26	3.4 (0.58)[c] *n*=57	<0.001
Globulin (g/dl)	2.7 (1.2-4.1)[c] *n*=26	3.2 (2.3-4)[c] *n*=57	0.001[b]
AST (IU/l)	173.0 (37-7,480)[d] *n*=27	122.0 (15-10,841)[d] *n*=61	0.02[b]
ALT (IU/l)	87.0 (33-2,025)[d] *n*=27	77.0 (24-3,745)[d] *n*=61	0.26[b]
Prothrombin time (seconds)	13.0 (12-33.7)[d] *n*=10	11.7 (9-24.6)[d] *n*=22	0.002[b]
Partial thromboplastin time (seconds)	38.4 (25.2-73.3)[d] *n*=10	37.5 (27.6-56.4)[d] *n*=22	0.60[b]

[a]Chi-square test; [b]Mann-Whitney *U* test; [c]Mean (standard deviation); [d]Median (range)

gum bleeding, petechiae, hematemesis and drowsiness. On admission, her hematocrit was 35%, her platelet count was 140,000 cells/mm^3, her WBC was 3,600 cells/mm^3 and her atypical lymphocyte count was 5%. She was then referred to RH. Forty-five minutes after admission to RH, the child developed cardiac arrest. Resuscitation was performed but was not successful. She died one hour after admission due to massive upper gastrointestinal bleeding.

The second case was a 15-year-old male who presented with fever for 4 days,

headache, nausea/vomiting, anorexia, myalgia, epistaxis, petechiae, hematemesis, melena, abdominal tenderness, confusion and drowsiness. On admission, his highest hematocrit was 53.5%, his lowest hematocrit was 42%, his lowest platelet count was 11,000 cells/mm^3, his lowest WBC count was 5,670 cells/mm^3, his highest atypical lymphocyte count was 11%, his AST level was 10,841 IU/l, ALT 3,745 IU/l, prothrombin time was 24.6 seconds (control 12.6 seconds), partial thromboplastin time was 53.7seconds (control 25 seconds), serum sodium was 136.8 mEq/l, potassium was 7.28 mEq/l, bicarbonate was 9.9 mEq/l, BUN was 21 mg/dl, creatinine was 2.2 mg/dl, albumin was 2.4 g/dl, globulin was 3.1 g/dl, blood glucose was 38 mg/dl, and the dengue IgM and IgG were both positive. He was given 3 units of fresh frozen plasma and 10 units of packed red blood cells. He developed metabolic acidosis, hepatic failure, renal failure, disseminated intravascular coagulation and massive upper gastrointestinal bleeding. He died 8 hours after admission.

DISCUSSION

This was a retrospective study describing the clinical features of DHF based on WHO's clinical criteria (WHO, 1997) because serologic and virologic testing to diagnose dengue infection are not available in most hospitals in Thailand; the WHO criteria are commonly used as the only diagnostic methods for DHF. Although these diagnostic criteria are not as accurate as virologic or serologic tests, their accuracy for diagnosing DHF is acceptable. A study conducted in Thailand (Srikiatkhachorn *et al*, 2010) to evaluate the sensitivity and specificity of the WHO criteria found the WHO criteria had good specificity for diagnosing severe dengue infection. Only 1% of non-dengue febrile illness cases met the definition of DHF. In a study from Vietnam by Phuong *et al* (2004), only 85 of 797 children (11%) clinically suspected of having dengue infection were proved to be seronegative. In this study, in addition to the WHO definition, we also excluded the patients who had evidence of another infection; therefore, we expect the accuracy for the diagnosis of DHF/DSS is high.

Although this was a hospital-based study, therefore the age-specific incidence of DHF cannot be calculated, it supports previous reports in the age of DHF patients is currently shifting to older age groups. However, the proportion of children to adults (1:1.6) is lower than a report from the Ratchaburi Provincial Health Office that revealed the age specific incidences of dengue infection in a population aged <15 years, 15-24 years and >24 years were 456.7, 202.6 and 33.9 per 100,000 population, respectively in the year 2007 and 1,210.7, 659.5 and 91.0 per 100,000 population, respectively, during the year 2008 (unpublished data).

In this study, we found nausea/vomiting, anorexia, headache and myalgia were the most common symptoms found among both children and adults with DHF/DSS. This finding is fairly consistent with other studies (Wichmann *et al*, 2004; Hammond *et al*, 2005; Kittigul *et al*, 2007; Hanafusa *et al*, 2008). We found myalgia was more common among adults and anorexia, a positive tourniquet test, hepatomegaly/abdominal tenderness and convalescent rash were more common among children. These findings are similar to other studies (Wichmann *et al*, 2004; Hammond *et al*, 2005; Kittigul *et al*. 2007; Hanafusa *et al*, 2008). However, we did not

find a difference in headaches, arthralgia, nausea/vomiting between adults and children. This is different from a study from Taiwan (Wang *et al*, 2009) which reported arthralgia, headaches and gastrointestinal bleeding were more common among adults. However, it is worth noting that these studies included all dengue infected cases (*ie*, DF and DHF/DSS); therefore, the results from our study are not comparable to those studies.

The finding that children had a lower hematocrit and serum creatinine than adults may be due to differences in normal physiology between children and adults. The finding that children with DHF had lower serum albumin and sodium levels and a higher prevalence of pleural effusions and ascites, suggested children with DHF have more prominent plasma leakage leading to shock and metabolic acidosis. These findings are consistent with a study by Hammond *et al* (2005) and can be explained by higher microvascular permeability in children (Gamble *et al*, 2000).

In this study there was a non-significantly higher association between children and the prevalence of bleeding compared to adults. However, more adults needed blood transfusions in our study. These findings suggested adults may have more severe bleeding compared to children. These results are similar to those of other studies (Chan *et al*, 1995; Wichmann *et al*, 2004; Malavige *et al*, 2006). The more severe bleeding in adults may be explained by the significantly lower platelet count in adults. This study did not find a link between coagulopathy and bleeding in DHF since no patient had a severely prolonged coagulation time.

This study had several limitations because of its retrospective nature. The most important issue is that the diagnostic criteria were only clinical-based, as already discussed. Another issue is incomplete clinical and laboratory data. There might be other data that could explain the findings in this study. For example, we do not have data regarding the use of non-steroidal anti-inflammatory drugs use which could explain the more severe bleeding in adults. However, this study does provide additional insight into DHF/DSS among adults and children and may be beneficial for clinicians caring for adults and children.

In summary, this retrospective study suggests the incidence of DHF in adults is not low. There were some differences in clinical features between children and adults. Children had higher risk of developing DSS while adults had a higher risk of developing severe bleeding.

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REFERENCES

Binh PT, Matheus S, Huong VT, Deparis X, Marechal V. Early clinical and biological features of severe clinical manifestations of dengue in Vietnamese adults. *J Clin Virol* 2009; 45: 276-80.

Chan KP, Lau GK, Doraisingham S, Chan YC. Adult dengue deaths in Singapore. *Clin Diagn Virol* 1995; 4: 213-22.

Gamble J, Bethell D, Day NP, *et al*. Age-related

changes in microvascular permeability: a significant factor in the susceptibility of children to shock? *Clin Sci (Lond)* 2000; 98: 211-6.

Gupta E, Dar L, Kapoor G, Broor S. The changing epidemiology of dengue in Delhi, India. *Virol J* 2006; 3: 92.

Guzmán MG, Kouri GP, Bravo J, Soler M, Vazquez S, Morier L. Dengue hemorrhagic fever in Cuba, 1981: a retrospective seroepidemiologic study. *Am J Trop Med Hyg* 1990; 42: 179-84.

Hammond SN, Balmaseda A, Pérez L, *et al*. Differences in dengue severity in infants, children, and adults in a 3-year hospital-based study in Nicaragua. *Am J Trop Med Hyg* 2005; 73: 1063-70.

Hanafusa S, Chanyasanha C, Sujirarat D, Khuankhunsathid I, Yaguchi A, Suzuki T. Clinical features and differences between child and adult dengue infections in Rayong Province, southeast Thailand. *Southeast Asian J Trop Med Public Health* 2008; 39: 252-9.

Kittigul L, Pitakarnjanakul P, Sujirarat D, Siripanichgon K. The differences of clinical manifestations and laboratory findings in children and adults with dengue virus infection. *J Clin Virol* 2007; 39: 76-81.

Kularatne SA, Gawarammana IB, Kumarasiri PR. Epidemiology, clinical features, laboratory investigations and early diagnosis of dengue fever in adults: a descriptive study in Sri Lanka. *Southeast Asian J Trop Med Public Health* 2005; 36: 686-92.

Malavige GN, Velathanthiri VG, Wijewickrama ES, *et al*. Patterns of disease among adults hospitalized with dengue infections. *QJM* 2006; 99: 299-305.

Nimmannitya S. Dengue haemorrhagic fever in Thailand. *Southeast Asian J Trop Med Public Health* 1987; 18: 291-4.

Phuong CX, Nhan NT, Kneen R, *et al*. Clinical diagnosis and assessment of severity of confirmed dengue infections in Vietnamese children: is the World Health Organization classification system helpful? *Am J Trop Med Hyg* 2004; 70: 172-9.

Rigau-Pérez JG, Vorndam AV, Clark GG. The dengue and dengue hemorrhagic fever epidemic in Puerto Rico, 1994-1995. *Am J Trop Med Hyg* 2001; 64: 67-74.

Srikiatkhachorn A, Gibbons RV, Green S, *et al*. Dengue hemorrhagic fever: the sensitivity and specificity of the world health organization definition for identification of severe cases of dengue in Thailand, 1994-2005. *Clin Infect Dis* 2010; 50: 1135-43.

Wang CC, Lee IK, Su MC, *et al*. Differences in clinical and laboratory characteristics and disease severity between children and adults with dengue virus infection in Taiwan, 2002. *Trans R Soc Trop Med Hyg* 2009; 103: 871-7.

World Health Organization. Dengue and dengue hemorrhagic fever. Geneva: WHO, 2009. Fact sheet No. 117. Revised March 2009. [Cited 2011 Sep 27]. Available from: URL: www.who.int/mediacentre/factsheets/fs117/en/

World Health Organization (WHO). Dengue hemorrhagic fever: diagnosis, treatment, prevention and control. Geneva: WHO, 1997.

Wichmann O, Hongsiriwon S, Bowonwatanuwong C, Chotivanich K, Sukthana Y, Pukrittayakamee S. Risk factors and clinical features associated with severe dengue infection in adults and children during the 2001 epidemic in Chonburi, Thailand. *Trop Med Int Health* 2004; 9: 1022-9.