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The differences of clinical manifestations and laboratory findings in children and adults with dengue virus infection

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Abstract

Background: Dengue haemorrhagic fever is an important public health problem and mainly occurs in children less than 15 years of age. Recently, the incidence of the disease have increased in adults but data on clinical and laboratory presentations of those affected are limited.
Objectives: To assess and compare clinical manifestations and laboratory findings of dengue virus infected children and adults in Thailand.
Study design: A 1-year study was conducted from September 2003 to August 2004 for dengue virus infected patients admitted to Phetchabun Provincial Hospital, Thailand. Physical signs, symptoms, and laboratory features were recorded. All dengue patients were confirmed using immunochromatographic test on convalescent sera.
Results: Based on serology-confirmed dengue virus infection, there was 286 dengue patients including 15 (5.3%) dengue fever and 271 (94.7%) dengue haemorrhagic fever (DHF). Among DHF cases, clinical classifications were DHF I, 40.9%; DHF II, 43%; and DHF III or dengue shock syndrome (DSS), 10.8%. Of all dengue patients, 231 cases (80.8%) were children aged less than 15 years and 55 cases (19.2%) were adults. The highest proportion of child cases was DHF I (42.9%), whereas that of adults was DHF II (51%). Some clinical manifestations were more common in adult patients, such as petechiae, melena, headache, retro-orbital pain, joint pain, myalgia, nausea and vomiting (p-value < 0.05). Signs found commonly in children were epistaxis, oliguria, and liver enlargement (p-value < 0.05). Haemoconcentration, thrombocytopenia, increased alanine aminotransferase, and longer prothrombin time were found to be significantly higher in adults than in children (p-value < 0.05).
Conclusions: Some clinical presentations of dengue disease and laboratory findings in adults are different from those in children. Therefore, adults as well as pediatric cases of DHF need appropriate and prompt case management to reduce the mortality rate of DHF.

Keywords: Dengue haemorrhagic fever; Clinical manifestations; Laboratory findings; Children; Adults

1. Introduction

Dengue fever (DF), dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS) are now considered the most important arthropod-borne viral diseases worldwide. The global prevalence of dengue cases has increased in South-East Asia, Africa, the Western Pacific and the Americas (Calisher, 2005; Guzman and Kouri, 2002). An annually estimated 500,000 DHF patients require hospitalization. DHF is a leading cause of death in children. Case-fatality rates are usually 2.5%, can exceed 20% but can be reduced to <1% with rapid diagnosis and proper treatment of the patients. DHF is a major public health problem in Thailand and continues as an endemic disease with outbreaks every rainy season and large epidemics every 2–3 years or every in consecutive years (Department of Communicable Disease, 2004). DHF occurs primarily in children less than 15 years of age with the highest attack rate in the 5–9 years age group (Nimmannitya, 1987), recently, however, the peak age of DHF patients has shifted to 10–14 years of age (Kittigul et al., 2003; Department of Communicable Disease, 2004). The shift in age predominance of DHF patients might be related to changes in places of dengue virus transmission, from households to the school

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environment, or to changes in the age structure of the population (Patumanond et al., 2003). A gradually marked increase of dengue virus infection in adults has been noted in several countries (Hammond et al., 2005; Kularatne et al., 2005; Wichmann et al., 2004). In Thailand, affected adults aged over 15 years old are reported to comprise 30–40% of dengue virus infected cases according to the Epidemiological Surveillance System. Previous studies have described the severity of clinical bleeding found in adult dengue patients (Lee et al., 2006; Malavige et al., 2006; Wichmann et al., 2004). Age-related differences in dengue severity are poorly understood and the data on clinical features in dengue adults are limited. This study was carried out to determine the differences in the clinical manifestations and laboratory findings of hospitalized children and adults with dengue virus infection.

2. Patients and methods

All patients admitted at Phetchabun Provincial Hospital, Phetchabun Province, 346 km north of Bangkok, from September 2003 to August 2004 who had the following criteria were enrolled in this study: (1) fever, (2) positive tourniquet test, (3) leukopenia or (4) thrombocytopenia or (5) haemoconcentration. Children were defined as patients with an age less than 15 years and adults with an age greater than or equal to 15 years. The total number of patients was calculated from the formula of statistics in proportion to dengue prevalence in children and adults in the study area. The minimum sample size of dengue patients in the child and adult groups, based on calculations, was 200 and 40, respectively. During the study period, all 300 patients who met the enrollment criteria and were admitted to the hospital participated in this study. After serological laboratory confirmation, the final number of study subjects (286 cases in total) was 231 children and 55 adults, which covered the sample size proposed and was taken for analysis of comparison. A record form was used to collect patient characteristics data, daily observed physical signs and symptoms. Routine laboratory investigations were performed and recorded daily blood cell count, peripheral blood film, haematocrit concentration, electrolytes, and liver function tests.

Blood samples for serological diagnosis were collected from the patients during the convalescent phase or before the patients' discharge from the hospital. Informed consent was obtained from parents or patient's guardians of children as well as from adult patients. The study was approval by the Ethical Committee on Human Rights Related to Human Experimentation, Mahidol University. Serological diagnosis of dengue virus infection was performed using a Dengue Duo IgM and IgG Rapid Strip Test (PanBio, Brisbane, Australia) based on immunochromatographic assay. Detection of IgM and/or IgG could be interpreted as primary or secondary dengue infection (Kittigul and Suankeow, 2002).

Patients were classified as having DF or DHF according to the WHO criteria (1997). The diagnostic criteria for DHF was the presence of thrombocytopenia (platelet count: less than 100,000 mm^{-3}) and plasma leakage (haemoconcentration: an increase in haematocrit $\geq$20% above the average haematocrit for age and sex of the Thai population or the presence of pleural effusion or ascites). DHF cases were further graded as I–IV in severity, according to WHO guidelines (1997). DHF grades III and IV were considered to be DSS.

3. Statistical analysis

Descriptive statistics were used to describe the distribution of the patient characteristics data, signs and symptoms, and laboratory values of dengue virus infection. Comparisons of clinical and laboratory findings in children and adults were analysed by Chi-squared test, one way ANOVA, and *t*-test.

4. Results

A total of 300 patients who met the study criteria were admitted to Phetchabun Provincial Hospital from September 2003 to August 2004. With clinical and laboratory confirmation, 286 patients were diagnosed as having dengue virus infection. The high peak of dengue cases (60.8%) was in June–July, during the rainy season. The incidence was highest in the age group of 5–9 years old (37.8%) followed by 10–14 years old (37.2%) and 15–19 years old (11.8%). Three female cases were aged less than 1 year, accounting to 1%. Male to female ratio of dengue patients was 1.09:1. There were 15 (5.3%) DF, 117 (40.9%) DHF I, 123 (43.0%) DHF II, and 31 (10.8%) DHF III or DSS patients. The patients had fever ranging from 3 to 19 days (mean $\pm$ S.D., 7.4 $\pm$ 2.2 days). Length of stay in the hospital ranged 3–9 days (mean $\pm$ S.D., 4 $\pm$ 1.0 days).

Dengue patients included 231 (80.8%) children and 55 (19.2%) adults. The child to adult ratio was 4.2:1. The highest peak of dengue adults occurred in June while that of affected children occurred in July. The mean age was 8.8 (range 0.8–14) years old in the child group and 20.6 (range 15–50) years old in the adult group. The male to female ratios were 1.02:1 and 1.4:1 in the child and adult groups, respectively. There was no significant difference in sex between the child and adult groups (*p*-value, 0.315). Children were found in the highest percentages in DHF I group (99 cases, 42.9%) while adults were most frequently found in DHF II group (28 cases, 51%). Severe infection (DHF II and DSS) was more common in adult patients than in children (63.7% versus 51.5%). However, there was no statistical difference in disease severity in the child and adult groups (*p*-value, 0.449). The ratios of secondary to primary infection were 5.6:1.0 in children and 12.8:1 in adults, but not significantly different (*p*-value, 0.126), as shown in Table 1.

To study the differences between children and adult dengue cases in clinical manifestations and laboratory findings, signs and symptoms and hematological profile were

Table 1
Characteristics of dengue virus infected patients

	Children	Adults	Total
No. of dengue patients (%)	231 (80.8)	55 (19.2)	286 (100)
Age; mean (range), years	8.8 (0.8–14)	20.6 (15–50)	11 (0.8–50)
Sex; male: female	1.02:1.0	1.4:1.0	1.09:1.0
Duration of fever; mean (range), days	7.5 (3–19)	7.0 (4–11)	7.4 (3–19)
Duration of hospitalization; mean (range), days	4.0 (3–9)	4.1 (3–8)	4.0 (3–9)
Dengue fever[a], no. (%)	13 (5.6)	2 (3.6)	15 (5.3)
Dengue haemorrhagic fever[a]			
DHF I, no. (%)	99 (42.9)	18 (32.7)	117 (40.9)
DHF II, no. (%)	95 (41.1)	28 (51.0)	123 (43.0)
DSS, no. (%)	24 (10.4)	7 (12.7)	31 (10.8)
Type of infection[b]			
Primary infection	35 (15.2)	4 (7.3)	39 (13.6)
Secondary infection	196 (84.8)	51 (92.7)	247 (86.4)

[a] *P*-value, 0.449 in disease severity for comparison of the child and adult groups.
[b] *P*-value, 0.126 in type of infection; primary or secondary antibody response between children and adults with dengue virus infection.

investigated daily and recorded. Some clinical manifestations were more common in adults than children such as petechiae, melena, headache, retro-orbital pain, nausea/vomiting, joint pain, and myalgia (p-value < 0.05). In contrast, epistaxis, oliguria, and liver enlargement were more prevalent in children than adults (p-value < 0.05), as shown in Table 2. Other signs and symptoms were present in both groups with no significant difference, i.e., gum bleeding, hematemesis, uterine bleeding, diarrhea, anorexia, abdominal pain, coryza, flush face, and shock. Anorexia and abdominal pain were predominate symptoms in children (88.3% and 63.6%) and adults (96.4% and 65.5%, respectively).

On the day of admission, platelet count and haematocrit level were performed in all confirmed cases and analysed by disease severity (DF, DHFI, II, and DSS). In children, the higher the degree of thrombocytopenia or haemoconcentration, the more severe the dengue disease observed (p-value < 0.001). In adults, only haemocencentration was significantly associated with severity (p-value < 0.006). The adult patients with DHF I and DHF II showed thrombocytopenia and haemoconcentration significantly different from children (p-value < 0.001), as shown in Table 3. Comparing adults and children with different dengue severity, there was no statistically significant difference in primary antibody response (p-value 0.469) or secondary antibody response (p-value < 0.735).

At day of defervescence, the thrombocytopenia in adults was found to be of statistically significant marked difference to that found in children (p-value, 0.001). Atypical lymphocytes, aspartate aminotransferase (AST), and partial thromboplastin time (PTT) were higher than normal levels in children and adults but there was no significant difference between these two groups. Alanine aminotransferase (ALT) level was higher in adults than children (p-value, 0.002). Although prothrombin time (PT) in both groups was in the normal range, time required for blood clotting was longer in the adult group (p-value, 0.047), as shown in Table 4.

Table 2
Signs and symptoms of the patients with dengue virus infection

Signs and symptoms	Children (n = 231) no. (%)	Adults (n = 55) no. (%)	p-value[a]
Adults > children			
Petechiae	90 (39.0)	30 (54.5)	0.035
Melena	30 (13.0)	19 (34.5)	<0.001
Headache	117 (50.6)	46 (83.6)	<0.001
Retro-orbital pain	20 (8.7)	16 (29.1)	<0.001
Nausea/vomiting	116 (50.2)	42 (76.4)	<0.001
Joint pain	47 (20.3)	20 (36.4)	0.012
Myalgia	91 (39.4)	37 (67.3)	<0.001
Children > adults			
Epistaxis	64 (27.7)	8 (14.5)	0.043
Oliguria	83 (35.9)	9 (16.4)	0.005
Liver enlargement	212 (91.6)	42 (72.4)	0.010

[a] Statistical significance: p-value < 0.05 by χ^2-test.

5. Discussion

DHF has been recognized as a leading cause of childhood hospitalization. However, an increased number of DHF in adults has been reported (Hammond et al., 2005; Kularatne et al., 2005; Wichmann et al., 2004). The mean age of the present study subjects was 11 years, range was from 8 months to 50 years old, and a high incidence among the 10–14 years (37.2%) age group indicated a progressive shift in age distribution of DHF from a pediatric age to teenage groups. This finding is similar to previous studies from the region located in the east of Thailand (Wichmann et al., 2004) and other countries (Agarwal et al., 1999; Hammond et al., 2005). At present, the morbidity rate of DHF in Thailand is declining while the average age of dengue patients is increasing. The evidence of rising age of DHF cases has been explained by association with demographic transition, modern housing, and commercial development (Halstead, 1994).

Within our 1-year study in Phetchabun Province, located in the north of Thailand, of 300 suspected dengue cases

Table 3
Haematological profile of dengue virus infected children and adults classified by disease severity on hospital admission

	Platelet count (cells/mm^3)			Haematocrit (%)		
	Children	Adults	p-value[b]	Children	Adults	p-value[b]
DF ($n=15$)	163,230 (±43,209)[a]	157,500 (±20,506)	0.860	37.3 (±4.1)[a]	42.5 (±0.7)	0.109
DHF I ($n=117$)	93,949 (±36,088)	60,722 (±48,350)	<0.001	40 (±4.3)	45 (±4.8)	0.001
DHF II ($n=123$)	87,127 (±41,810)	47,642 (±33,299)	<0.001	40.8 (±4.3)	44.7 (±6.3)	<0.001
DSS ($n=31$)	52,583 (±50,039)	57,285 (±45,492)	0.825	44.4 (±6.8)	47.8 (±5.3)	0.227
Total ($n=286$)	90,745 (±45,562)	57,145 (±44,184)	<0.001	40.8 (±4.8)	45.1 (±5.7)	<0.001
p-value[c]	<0.001	0.006		<0.001	0.534	

[a] Mean ± S.D.
[b] Statistically significant difference between children and adults: p-value <0.05 by t-test.
[c] Statistically significant difference in disease severity of children or adults: p-value < 0.05 by one way ANOVA.

Table 4
Laboratory findings of dengue virus infection in 286 confirmed dengue patients at day of defervescence

Laboratory findings[a]	Mean (±S.D.)		p-value[b]
	Children ($n=231$)	Adults ($n=55$)	
Platelet count (cells/mm^3)	72,512 (±30,932)	45,642 (±33,331)	0.001
Haematocrit (%)	42.2 (±4.7)	45.8 (±5.3)	0.001
White blood cells (cells/mm^3)	5,770 (±14,182)	4,697 (±2,911)	0.578
Neutrophils (%)	45.9 (±18.9)	48 (±21.4)	0.471
Lymphocytes (%)	44.2 (±15.9)	37.6 (±17.5)	0.472
Atypical lymphocytes (%)	8.8 (±8.5)[c]	13.8 (±12.7)[c]	0.092
AST (U/L)	200.4 (±313.5)	299.8 (±459.7)	0.057
ALT (U/L)	90.4 (±129.5)	165.9 (±241.3)	0.002
PT (sec)	14.8 (±11.2)	18.7 (±17.9)	0.047
PTT (sec)	45.8 (±31.7)	47.1 (±31.5)	0.782

[a] Normal range levels in blood circulation: platelet count: 100,000–440,000 cells/mm^3; haematocrit: 37–54%; white blood cells: 5000–10,000 cells/mm^3; neutrophils: 40–75%; lymphocytes: 20–50%; atypical lymphocytes: 0–3%; AST and ALT: 0–40 U/L; PT 12–18 s; PTT: 25–38 s. AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time; PTT, partial thromboplastin time.
[b] Statistical significance: p-value < 0.05 by t-test.
[c] Atypical lymphocyte counts were performed in 229 children and 54 adults.

diagnosed by screening clinical criteria; fever with positive tourniquet test and leukopenia or thrombocytopenia or haemoconcentration, 286 cases (95.3%) were serologically confirmed as having dengue virus infection. Using the immunochromatographic (IC) test as the confirmation of dengue diagnosis, this positive predictive value (PPV; 95.3%) is higher than previous reports in Thailand. Sawasdivorn et al. (2001) used fever with positive tourniquet test and leukopenia for clinical diagnosis and found a PPV of 72.7%. The study was only amongst DF patients, however; in DF whereas, the study of Kalayanarooj et al. (1997), using the same clinical criteria, showed a PPV of 83.2% in dengue virus infected patients. In our study, the higher PPV might be due to the use of additional laboratory criteria (thrombocytopenia or haemoconcentration) which narrowed down a more accurate diagnosis.

Using the inclusion criteria mentioned above, every case with a positive tourniquet test was enrolled in the study. It seems that only severe adult patients participated in the study because adults normally show less capillary fragility than children (Gamble et al., 2000). Unfortunately, the findings of positive tourniquet tests in similar frequency between dengue adult and child groups admitted to hospital (Hammond et al., 2005; Wichmann et al., 2004) may not support the identification of positive tourniquet tests as the only sign of severe adult infection. Therefore, a tourniquet test might be used as an additional simple diagnostic tool for both children and adults with dengue virus infection.

Fourteen patients were diagnosed negative for dengue virus infection by IC test. Serum samples from these patients were collected at the convalescent phase and after day 5 of illness. In previous studies the IC test has provided 100% sensitivity after day 5 of illness (Kittigul and Suankeow, 2002; Vaughn et al., 1998). However, use of sensitive diagnostic tests to confirm diagnosis, including reverse transcriptase-polymerase chain reaction and enzyme-linked immunosorbent assay were not done in this study.

This prospective study demonstrates the similarities and differences in clinical features between dengue children and adults. Physical signs and symptoms including anorexia, enlargement of the liver, and abdominal pain were found in greater than 60% of dengue children and adults. Abdominal tenderness of right upper quarter and liver enlargement were most frequently found in DHF and correlated with disease severity. Abdominal pain is one of the important warning signs that DSS is impending (Gibbons and Vaughn, 2002).

Interestingly, epistaxis, oliguria and liver enlargement were more prevalent in children than adults. This may be

due to the difference in anatomy and physiology of organs between children and adults. Epistaxis was significantly associated with children more than adults, similar to the findings of Wichmann et al. (2004) and Hammond et al. (2005). The adults showed significantly higher incidence than children of petechiae, melena, headache, retro-orbital pain, nausea/vomiting, joint pain and myalgia, comparable to one retrospective study in Thailand (Wichmann et al., 2004). Adults are more likely to be able to report symptoms and some physical signs were registered in adults in higher frequency than in children. Bleeding manifestations including petechiae and melena were also frequently found in adults in Sri Lanka (Malavige et al., 2006).

In this study, high severity of dengue disease (DHF II and DSS) was found in adults more often than children. In addition, observed thrombocytopenia and haemoconcentration in adults on hospital admission were significantly different from children. Although children are more likely to develop hypovolaemic shock than adults in DHF characterized by increased microvascular permeability (Gamble et al., 2000), a high mortality rate was seen in the adults with dengue virus infection (Malavige et al., 2006).

Liver involvement during dengue virus infection was described and reviewed. Alterations in AST and ALT were seen and elevations in serum AST appear to be greater than ALT levels (Seneviratne et al., 2006). In this study, increase in liver enzymes found in both children and adults indicated liver involvement during dengue virus infections. It is likely that relatively more adult dengue patients had more liver impairment than children. Nevertheless, dengue virus infection was an important cause of acute hepatic failure in Thai children (Poovorawan et al., 2006). Regarding type of dengue virus infection, the ratio of secondary to primary dengue infection in adults was approximately two times higher than that in children, since Thailand is an endemic area of dengue virus and nearly all adult patients had experience with dengue infection. However, the children and adult dengue patients with high disease severity (DF, DHFI, DHFII, and DHFIII or DSS) were not different in either primary or secondary antibody response. Vaughn et al. (2000) found increased dengue severity in children correlated with DEN-2 serotype, and secondary infection. Balmaseda et al. (2006) reported that DEN-2 was predominate in the patients with shock and internal hemorrhage; whereas, DEN-1 was associated with increased vascular permeability. In Thailand, using national data, during 1999–2004, DEN-1 and DEN-2 infected the majority of cases. This has switched to DEN-3 and, recently, DEN-4 has infected the Thai population in a higher proportion (Department of Communicable Disease, 2004). Secondary immune status was a risk factor for severe dengue disease in children but not in adults (Hammond et al., 2005).

The limitations of the present study include the lack of serotype identification and hospital based design. Physical signs and symptoms of the patients were observed and recorded daily during hospital admission regardless of treatment provided. Future studies on the natural history of dengue disease in children and adults still need to be conducted. Nevertheless, this observational study was based on the comparison of dengue virus infected children and adults. The study design calculated the number of subjects according to a proportion formula based on statistics of dengue prevalence in both groups in the study area. Therefore, the data on clinical characteristics of child and adult dengue patients can contribute to developing guidelines for appropriate management of dengue disease in adult as well as in child cases.

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