Risk factors and clinical features associated with severe dengue infection in adults and children during the 2001 epidemic in Chonburi, Thailand

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Summary

OBJECTIVES Dengue haemorrhagic fever (DHF) is an important cause of morbidity in South-east Asia and used to occur almost exclusively in young children. In recent years, there has been a progressive shift in age-distribution towards older children and adults. We investigated an outbreak in 2001 in both children and adults, in an endemic area of Thailand.

METHODS Retrospective study of 347 patients with serologically confirmed dengue infection admitted to Chonburi Hospital during an epidemic in 2001.

RESULTS A total of 128 (37%) patients had dengue fever (DF) and 219 (63%) had DHF. Patients with DHF were significantly older than patients with DF (11 years vs. 8 years). Clinical bleeding was noted in 124 individuals, both with DF (n = 24) and DHF (n = 100), and significantly more frequently in adults. Twenty-nine (13.2%) of all DHF cases were caused by primary infection. Secondary dengue infection was associated significantly with the development of DHF in children, OR (95% CI) = 3.63 (1.94–6.82), P < 0.0001, but not in adults, OR (95% CI) = 0.6 (0.02–6.04), P = 1. Unusual clinical manifestations were observed in 23 patients: three presented with encephalopathy and 20 with highly elevated liver-enzymes. In the latter group, four patients were icteric and nine had gastrointestinal bleeding.

CONCLUSION These results indicate that DHF in South-east Asia is common in both children and adults. In dengue-endemic countries, dengue should be considered as a differential diagnosis in patients with clinical gastrointestinal bleeding in association with increased liver enzymes.

Keywords dengue fever, dengue haemorrhagic fever, Thailand, risk factors, adults

Introduction

Dengue is a mosquito-borne infection found in tropical and subtropical regions of more than 100 countries. Two-fifths of the world’s population or 2.5 billion people are now at risk for dengue, and every year approximately 50 million new cases occur worldwide (WHO 2002). The global prevalence of dengue infection has increased dramatically in recent decades, particularly in the Americas, Western Pacific, and South-east Asia (Halstead 1998). There are four serologically distinct, but closely related viruses that cause dengue. Recovery from one infection provides lifelong immunity against that serotype but confers only transient and partial protection against heterologous infections (Gibbons & Vaughn 2002) and sequential infections may increase the risk of more serious disease (Nimmannitya 1993). The role of immunity as a contributing factor to severe dengue infection is considered to be specific for some dengue virus strains as the association is not found with the American genotypes (Rico-Hesse et al. 1997; Leitmeyer et al. 1999; Watts et al. 1999; White 1999; Messer et al. 2003).

Dengue haemorrhagic fever (DHF), a potentially lethal manifestation of dengue infection, was first recognized in the 1950s during dengue epidemics in the Philippines and Thailand. Today, DHF in South-east Asia causes a significant number of deaths predominantly in children (WHO 2002) with a marked increase in the number of adult cases (Nimmannitya 1987; Hadinegoro & Nathin 1990; Capeding et al. 1997; Pinheiro & Nelson 1997; Kantachuvesiri 2002) and a higher rate of unusual clinical manifestations (Nimmannitya et al. 1987; Solomon et al. 1987).
2000; Cam et al. 2001; Sirivichayakul et al. 2002) in recent years. The changing patterns of affected age groups and clinical severity of dengue infection are not well understood. This could be due to more reports with a greater interest in adult patients, the differences of serological coverage in various endemic areas, or variations in the virulence of dengue virus strains. Our retrospective study was conducted to describe dengue infection during an outbreak in an endemic area of Thailand. The data were confined to a 2001 epidemic year, including both, adults and children, with confirmed serology of dengue infection.

Materials and methods

Study area and population
This study took place at Chonburi Regional Hospital, 80 km south-east of Bangkok. The hospital has 823 beds, of which 100 are for paediatric patients. The data were retrieved from medical charts and outpatient cards of patients who were admitted with dengue infection between January and June 2001. The evaluation was conducted in all age groups, both in children (age <15 years) and adults. Only patients with serologically confirmed dengue infection were included for further analysis.

Serological diagnosis
The enzyme-linked immunosorbent assay (ELISA) and the haemagglutination-inhibition tests (HI) were performed at the Armed Forces Research Institute of Medical Science, Bangkok, or at the Department of Medical Science, Ministry of Public Health, Bangkok. A more than fourfold increase of HI titres in paired serum samples was considered positive for acute dengue infection. Immune response was considered primary when HI titres after ≥1 week of illness (in the convalescence serum) were less than 1:2560. In cases of inconclusive HI results, additional ELISA testing was performed. A dengue IgM-to-IgG ratio ≥1.8 defined a primary, and a ratio <1.8 defined a secondary dengue infection (Clarke & Casals 1958; Innis et al. 1989).

Definition of disease severity
The DHF was defined as the presence of plasma leakage and thrombocytopenia with platelet count <100 000/μl (WHO 1999b). The evidence of plasma leakage was defined as a rise of haematocrit ≥20% from baseline, or from average haematocrit for age and sex of the Thai population, or a drop of haematocrit ≥20% after sufficient fluid therapy. Other criteria for plasma leakage were hypoproteinemia, pleural effusion, and ascites. Haemorrhagic tendencies included a positive tourniquet test, skin bleeding (petechiae, ecchymosis, or purpura), bleeding from mucosa (epistaxis, gum bleeding, or other sites), haematemesis or melena. Clinical bleeding was defined as spontaneous bleeding including all haemorrhagic tendencies except a positive tourniquet test.

The severity of DHF was graded on discharge and classified according to WHO guidelines (WHO 1999b). Grade I and grade II were infections without signs of shock, grade III with impending and grade IV with profound shock. Severe liver involvement was defined as a more than fivetwo of serum glutamate oxaloacetate transaminase (sGOT) above normal.

Data analysis
Data were recorded and analysed using statistical software (SPSS version 11.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to describe the distribution of the demographic data, signs and symptoms of dengue infections and laboratory investigations. The categorical variables (clinical manifestations, grading of disease severity) were compared by chi-square and Fisher’s exact test. Normally distributed data (haematocrit level, duration of fever) were compared by unpaired t-tests, and data not conforming to normal distribution (other laboratory results) were compared using the Mann–Whitney U-test.

Results

Patient characteristics
In 2001, a total of 906 patients (582 children and 324 adults) were admitted to Chonburi Hospital with suspected DHF. In the following analysis 347 patients with serologically confirmed diagnosis were included, recruited of the total of 471 patients who presented during the study period (January to June 2001). The remaining 124 patients were excluded from the analysis because the serological tests were not available (n = 8 children, 60 adults), or results were uninterpretable (n = 45) and negative (n = 11). The positive predictive value of the clinical assignment to dengue infection by the hospital staff was 97% for children and 100% for adults.

The majority of the recruited patients were children, and the child to adult ratio was 4.8 to 1.0 (Table 1). The median age of the patients was 10 years; range: 4 months to 66 years. The most frequent age groups were 10–14 years (37%), 4–9 years (36%) and 15–24 years (15%).
There were 176 males and 171 females, and the sex distributions of children and adult patients were not significantly different (male:female = 0.96:1.0 in children vs. 1.4:1.0 in adults, \( P = 0.20 \)). Most (63%) patients had severe disease, DHF or dengue shock syndrome (DSS), and only 37% had classical dengue fever (DF) (Table 1). Severe infection was significantly more common in adult patients (82% vs. 59% in children, \( P < 0.001 \)).

Based on serological tests, most patients had secondary infection (79.5%), accounting for 78% of children and 87% of adults. The overall ratio of secondary to primary infection was 3.8 to 1.0. There was no significant difference in the immunological status between adults and children (secondary to primary \( = 6.5:1.0 \) vs. \( 3.6:1.0 \), respectively, \( P = 0.13 \)).

Clinical presentation

All patients presented with fever (100%), and more than half had gastrointestinal symptoms such as nausea (57%) and/or vomiting (59%) (Table 1). The mean (SD) duration of fever prior to admission was 4.2 days (1.3) (range: 1–8). There were no significant differences in the duration of fever between adults and children or between the disease severity groups (\( P \geq 0.06 \)). In comparing adults and children, headache, myalgia/arthritis, petechiae and severe liver involvement were significantly more common in adults (\( P \leq 0.001 \)), while cough and hepatomegaly were significantly more frequent in children (\( P \leq 0.033 \)).

Patients with DSS (\( n = 40 \)) in comparison with the remaining patients without shock (\( n = 307 \)) presented more commonly with hepatomegaly (70% with DSS vs. 43% with non-DSS), severe liver involvement (22% with DSS vs. 3.6% with non-DSS), and right-upper quarter abdominal tenderness (65% with DSS vs. 45% with non-DSS). These differences were statistically significant (\( P \leq 0.017 \)).

Factors related to disease severity

Compared with DF patients, those with severe infection (DHF and DSS) were significantly older (median \( = 11 \) vs. 8 years), and severe infection was significantly more commonly associated with secondary infection (69% vs. 41%, \( P < 0.001 \)) (Figure 1). The higher proportion of DHF-patients with secondary immune response compared with DF-patients remained significant in children (87% vs. 59%, \( P = 0.001 \)), but not in adults (81% vs. 87.5%, \( P = 1.0 \)). Therefore, secondary dengue infection was associated significantly with the development of DHF with an age-stratified OR (95% CI) = 3.12 (1.72–5.49), \( P = 0.00003 \). This significant difference was attributable to children, with an OR (95% CI) = 3.63 (1.94–6.82), \( P = 0.00002 \), but not to adults, with OR (95% CI) = 0.6 (0.02–6.04), \( P = 1.0 \).

Overall, 29 (13.2%) of all DHF-cases were caused by primary infection. Of these, four were infants, 18 were children, and seven were adults (Figure 1). The overall ratios of secondary to primary infection classified according to the disease severity were 2.0:1.0 for DF, 6.9:1.0 for...
DHF I, 6.0:1.0 for DHF II and 7.0:1.0 for DSS. Comparing the three subgroups of severe disease, there were no significant differences in the distribution of the immunological status of the patients (the ratio of secondary to primary infection) and the age distribution ($P \geq 0.27$) (Figure 1).

**Clinical outcome**

Over the course of hospitalization, all patients except one recovered fully and became afebrile. The mean (SD) duration of fever was 5.4 days (1.4). Fever clearance time was not significantly different between adults and children groups (mean ± SD: 5.7 ± 1.8 days vs. 5.3 ± 1.4 days, respectively, $P = 0.09$) or between the disease severity groups ($P = 0.30$) (Table 2). Of all studied patients, only one child with DSS died on the day of referral from a district hospital. The case fatality rate within the DHF population was 0.46%.

**Haematological findings**

The mean (SD) haematocrit level on admission of all patients was 38.9% (5.5) (Table 2) and patients with severe infection had significantly higher haematocrit levels than those with DF (40.5% vs. 36.3%, respectively, $P < 0.001$). Between the subgroups of severe infection, there were no significant differences in the baseline haematocrit levels ($P = 0.32$). During hospitalization, there were significant rises of haematocrit levels in both the DF and the DHF group ($P < 0.001$), and patients with shock (DSS) had significantly higher peaks of haematocrit.

**Table 2** Haematological findings and results of clinical evaluations in patients with dengue infection

<table>
<thead>
<tr>
<th></th>
<th>DF</th>
<th>DHF I</th>
<th>DHF II</th>
<th>DSS</th>
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<tbody>
<tr>
<td><strong>N</strong></td>
<td>128</td>
<td>102</td>
<td>77</td>
<td>40</td>
</tr>
<tr>
<td><strong>FCT, mean (SD) (days)</strong></td>
<td>5.4 ± 1.3</td>
<td>5.7 ± 1.3</td>
<td>5.3 ± 1.3</td>
<td>5.9 ± 2.2</td>
</tr>
<tr>
<td><strong>Hct, mean (SD) (%)</strong></td>
<td>36.3 ± 3.7</td>
<td>40.3 ± 4.6</td>
<td>44.8 ± 4.7</td>
<td>451 ± 4.6</td>
</tr>
<tr>
<td><strong>Maximum hct, mean (SD) (%)</strong></td>
<td>385 ± 2.9</td>
<td>49 ± 1.2</td>
<td>6.9 ± 1.2</td>
<td>4.9 ± 1.2</td>
</tr>
<tr>
<td><strong>Day of maximum hct, mean (SD) (days)</strong></td>
<td>4.6 ± 1.4</td>
<td>113 ± 2300-20000</td>
<td>83 ± 11100-372000</td>
<td>64 ± 10900-147000</td>
</tr>
<tr>
<td><strong>Platelet count, median (range)/µl</strong></td>
<td>150,000 (20,000-290,000)</td>
<td>105,000 (11,100-200,000)</td>
<td>64,500 (6000-109,000)</td>
<td>46,500 (38,000-90,000-269,000)</td>
</tr>
<tr>
<td><strong>Minimum platelet count, mean (SD)/µl</strong></td>
<td>110,000 (9,000-269,000)</td>
<td>100,000 (9,000-269,000)</td>
<td>70,000 (7,000-147,000)</td>
<td>52,000 (9,000-269,000)</td>
</tr>
<tr>
<td><strong>Day of minimum platelet count, mean (SD) (days)</strong></td>
<td>4.6 ± 1.4</td>
<td>6.9 ± 1.2</td>
<td>5.0 ± 1.2</td>
<td>4.9 ± 1.2</td>
</tr>
<tr>
<td><strong>Tourniquet test, n (%) positive</strong></td>
<td>64/44 (59)</td>
<td>67/21 (76)</td>
<td>42/12 (78)</td>
<td>24/102 (23)</td>
</tr>
<tr>
<td><strong>Clinical bleeding, n (%) positive</strong></td>
<td>24/104 (19)</td>
<td>0/102 (0)</td>
<td>77/0 (100)</td>
<td>23/102 (23)</td>
</tr>
</tbody>
</table>

$*_{D} =$ numbers of fever days prior to the measurements.

DF, dengue fever; DHF, dengue haemorrhagic fever; DSS, dengue shock syndrome; FCT, fever clearance time after onset of fever; hct, haematocrit.

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**Figure 1** Age distribution of patients with primary (○) and secondary (●) dengue infection classified according to disease severity. DHF = dengue haemorrhagic fever. The average was calculated as median (■).
levels than the other non-shock groups \( (P = 0.038) \). The overall mean (SD) time to reach the maximum haematocrit level was 4.9 days (1.3) after onset of fever and ranged from 4 to 6 days. The mean increase of the haematocrit level was 2.2\% in DF and 3\% in the DHF group.

The median (range) platelet count of all patients on admission was 85 000 (7000–372 000/µl, and patients with DHF had a significantly lower median platelet count compared with those with DF (69 500/µl vs. 113 000/µl, \( P < 0.001 \)) (Table 2). During hospitalization, platelet counts decreased significantly in all groups of disease severity (\( P \leq 0.001 \)). The mean time (SD) for platelets to reach the lowest level in all patients was 4.8 days (1.3) after onset of fever.

### Tourniquet test

The results of the tourniquet test were recorded in 278 patients (21 adults and 257 children). The rates of positive tourniquet test were similar between adults and children (71\% vs. 69\%, \( P = 0.84 \)) but were significantly higher for DHF than DF patients (76\% vs. 58\%, \( P = 0.003 \)). At the time the tourniquet test was performed, patients who tested positive had significantly higher platelet counts (median; range = 93 000; 11 000–372 000/µl) than those with negative results (76 000; 14 000–258 000/µl), \( P = 0.021 \).

### Haemorrhagic manifestations

Clinical bleeding was noted in 124 patients (Table 2 and 3) with both DF \( (n = 24) \) and DHF \( (n = 100) \). Among these, results of the tourniquet test were recorded in 85 patients and were positive in 65 patients (76\%). There were no significant differences in the positive rates of the tourniquet test between adults and children (\( * P = 0.59 \)). Petechiae and gum bleeding were significantly more common in adults \( (P \leq 0.011) \), while children more frequently

<table>
<thead>
<tr>
<th>Table 3 Patients with clinical bleeding; number of cases (%)</th>
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<tbody>
<tr>
<td>Bleeding disorder</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Tourniquet test, +/-</td>
</tr>
<tr>
<td>Petechiae</td>
</tr>
<tr>
<td>Epistaxis</td>
</tr>
<tr>
<td>GI-bleeding</td>
</tr>
<tr>
<td>Haematemesis</td>
</tr>
<tr>
<td>Gum bleeding</td>
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<tr>
<td>Polymenorrhea</td>
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</tbody>
</table>

* The proportion is significantly higher than the other group; \( P < 0.05 \).

Unusual clinical manifestations

Unusual clinical manifestations were noted in 23 patients from all groups of severe infection \( (n = 3 \) DFH I, 9 \) DHF II, and 11 DSS \). Of these, three had signs of encephalopathy, and 20 patients had severe liver involvement \( (sGOT \rangle 210–5630 U/l, in all cases characteristically \( sGOT \rangle \) serum glutamate pyruvate transaminas). All patients with encephalopathy were children with secondary dengue infection who presented with drowsiness \( (n = 3) \) and convulsions during the afebrile stage \( (n = 2) \). Of 20 patients with liver involvement \( (11 \) adults vs. nine children, respectively, \( P = 0.001 \)), four presented with jaundice at the time of admission, and their baseline total bilirubin ranged from 2.7 to 6.3 mg/dl. All patients with severe liver involvement had one or more signs of bleeding disorder, including nine with clinically evident GI bleeding.

### Discussion

The DHF in South-east Asia is primarily described as a disease that almost exclusively (>95\%) affects children under the age of 15 (WHO 2002). However, in the past two decades a significant shift in the age distribution has been noted. Data from Bangkok have revealed a progressive shift of the median age of children with DHF from 3.8 years in the 1960s to 5.6 years in the 1970s and to 7.4 years in the 1980s (Nimmannitya 1987). In Jakarta, Indonesia, the proportion of DHF-cases in the age-group of patients older than 10 years increased from 11\% to 28\% between 1975 and 1989 (Hadinogoro & Nathin 1990). During the 2001 outbreak in Chonburi Province, which we investigated in this study, 906 patients were admitted at Chonburi Regional Hospital with the clinical diagnosis of suspected DHF. The child to adult ratio among these suspected cases was 1.8 to 1.0 and among serologically confirmed cases in our study population 3.5 to 1.0. Despite coverage bias in the serological testing (serology was performed in 98\% of admitted children but only 53\% of the admitted adults), the median age of DHF patients \( (n = 219) \) in our study population was 10 years. One
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Explanation for this phenomenon might be differences or changes in the serological coverage of populations in endemic areas. Variations in dengue genotypes might serve as another explanation, as several studies have already suggested that variations in dengue virus strains might play an important role in disease severity (Barnes & Rosen 1974; Watts et al. 1999), and structural differences of dengue viruses have been shown to correlate with pathogenesis (Leitmeyer et al. 1999).

Sequential dengue infection is believed to increase the risk of more serious disease (Halstead 1988). In endemic areas, adults and older children are likely to have past exposure to dengue infection and also an increasing risk for secondary infection and thus severe infection (Sangkawibha et al. 1984; Burke et al. 1988). To differentiate primary and secondary dengue infection, both HI titres and the ratio of dengue IgM to IgG antibodies were combined in this present study. The general applicability of using the HI titres alone in areas where two or more flaviviruses are co-circulating is doubted by several investigators as the IgG antibodies are broadly flavivirus reactive (Shu et al. 2003).

In our study, even with combined ELISA and HI titres, 45 patients needed to be excluded from analysis because the results were not conclusive. Recently developed tests, such as the non-structural protein NS1 serotype-specific IgG ELISA, might offer new opportunities to classify primary vs. secondary infections reliably (Shu et al. 2002).

Patients with secondary infection were significantly older than those with primary infection (median = 10 vs. 7 years, respectively, P = 0.001). As a consequence, severe infection (DHF or DSS) was significantly more common among adult patients (82% vs. 59%, respectively). However, although the total number of serologically confirmed cases in adults is small (n = 60) and the analysis was not statistically significant, it is surprising that secondary infection in this age group did not tend to cause more severe disease than primary infection with an OR (95% CI) of 0.6 (0.02–6.04). About 13% of all cases with DHF (n = 29) were caused by primary infection. Of these, four were infants, in whom transplacentally transmitted maternal dengue antibodies are hypothesized to be linked to more severe disease (Hung et al. 2004). Continued catabolism results in the loss of enhancing antibodies at around 1 year of age (Kliks et al. 1988). Therefore, it might be considered that 25 patients with DHF in this present study did not have any actively or passively acquired pre-existing dengue antibodies.

Several studies have compared the clinical signs and symptoms of dengue virus infection in infants with those in older children. Pancharoen and Thisyakorn (2001) showed that infants tended to present more often with convulsions, rash, diarrhoea and splenomegaly but less often with abdominal pain and a positive tourniquet test. In our study, we observed that adults with dengue suffered from headache and myalgia significantly more often than children. The incidence of petechiae (50% vs. 15%, respectively) was also higher in adults.

Liver involvement is a common finding during dengue infection, particularly in DHF patients (Kuo et al. 1992; Wahid et al. 2000). However, involvement is usually mild or moderate with levels of sGOT not increased more than fivefold. At Chonburi Hospital investigations for liver function are not routinely performed unless clinically indicated. In this study, liver function tests were only available in 38 patients, but 20 revealed a significant liver involvement with more than fivefold increased sGOT. Of these, 11 were adults and nine were children, but the incidence or severity of liver involvement between the two groups cannot be compared because of the limited numbers. Liver involvement in dengue infection is usually associated with other severe complications as found in our study, where 45% of the patients had gastrointestinal bleeding. Our results correspond well with other studies which suggest that highly increased liver enzymes are an early warning sign for severe disease and severe clinical bleeding (Nguyen et al. 1997; Murgue et al. 1999).

The tourniquet test is a simple clinical procedure reflecting capillary fragility and is recommended as a screening test for dengue infection. The test is incorporated in the WHO case definition for DHF, where it is the only but required bleeding disorder in grade I DHF (WHO 1999a). However, the specificity of the tourniquet test seems to be low (Kalayanarooj et al. 1997), and it poorly differentiates between DF and DHF (Cao et al. 2002).

In our study, tourniquet tests were positive in 59% of the DF cases and 76% of the DHF cases, slightly higher than the figures recently reported by Cao et al. (2002) from Vietnam: 38% in DF and 45% in DHF. As most children had already presented with some kind of bleeding disorder, the tourniquet test in the latter study provided additional diagnostic information in only 5% of cases. The sensitivity of the tourniquet test in dengue infection also depends on how often the test is performed over the course of the disease. In our population, tourniquet tests were not repeated in all cases, especially when the patient already presented with other evidence of bleeding disorder. There were no significant differences in the incidences of positive tourniquet tests between adults and children (71% and 69%, respectively). Overall, these findings support the additional diagnostic role of the tourniquet test in dengue infection, both in adults and children, but demonstrate also its poor ability to differentiate between DF and DHF.

Our study has several limitations because of its retrospective nature and hospital-based design.
Nevertheless it revealed a significant shift in the age distribution of DHF towards older children and adults. Severity of the infection was associated with secondary immune response only in children. For adults, however, the sample size was not large enough to demonstrate a significant role of the immune status. Surprisingly, 13% of all DHF cases in our study population were caused by primary infection. Further studies are recommended to elucidate the phenomenon of primary infections to cause DHF in the absence of pre-existing (actively or passively acquired) dengue antibodies. During this 2001 outbreak in Chonburi Province, clinical bleeding and unusual clinical presentations were not uncommon and were associated with significant liver involvement. In dengue endemic countries, dengue infection should be considered as a differential diagnosis in patients with clinical gastrointestinal bleeding in association with increased liver enzymes.

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