RELATIONSHIP BETWEEN BODY SIZE AND SEVERITY OF DENGUE HEMORRHAGIC FEVER AMONG CHILDREN AGED 0-14 YEARS

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Abstract. A hospital based case-control study was conducted from October 2002 to November 2003 among children aged 0-14 years at Queen Sirikit National Institute of Child Health (Children's Hospital), Bangkok, Thailand. This study focused on body size and severity of dengue hemorrhagic fever (DHF) in children. One hundred five patients diagnosed as having DHF grade III or IV were the cases and 105 diagnosed as having DHF grade I or II were controls. They were matched at a ratio of 1:1 by their gender and age (within 5 years). Normal growth charts were used to differentiate child body size into normal, thin and obese. Data were collected using face to face interviews with caregivers, questionnaires, laboratory and physical examination reports as research tools. Multiple logistic regression analysis revealed that only two variables were related to severity of DHF: obesity (OR = 3.00, 95 % CI = 1.20-7.48) and dengue virus type II (OR = 4.94, 95 % CI = 2.57-9.47), respectively. Other variables were childhood factors: duration of breast-feeding, education, and parity; caregivers factors: age, gender, marital status, education, occupation, family income, knowledge of DHF, antipyretic type, treatment before hospitalization, and duration of fever; environmental factors: history of DHF patients in house, house pattern, time from house to hospital, and residence; and etiological factors: type of infection and history of DHF among children. These factors showed no significant association ($p>0.05$). This result can be utilized in a preventive and control program, particularly in more aggressive management of overweight children. Health personnel should continue to provide health education, particularly, signs and symptoms of shock, to the community and private sectors. Government and Non-Government Protective Projects in primary schools (5-9 years children) should be continued in the high risk groups.

INTRODUCTION

Dengue fever/dengue hemorrhagic fever (DF/DHF) is found in tropical and sub-tropical regions around the world, predominantly in urban and semi-urban areas. The viruses which cause DF and DHF belong to the family Flaviviridae, genus *Flavivirus*. There are four serotypes of dengue viruses, designated DEN-1,-2,-3 and -4; the major vector is *Aedes aegypti* (WHO, 1993, 1999a,b). In 1954, the first outbreak of DF occurred in Southeast Asia, the first place it occurred in was the Philippines in 1956; the second outbreak also occurred in the Philippines (WHO, 1993). The outbreak in 1958 was the largest epidemic, stimulating the government and people to be concerned about this problem. After that, dengue outbreaks occurred in other countries of Southeast Asia, including Thailand. Thailand had the first outbreak in Bangkok-Thonburi in 1958. In both the Thailand and Philippines outbreaks, most of the patients were children under ten years old. After the first outbreak of DF in Southeast Asia, an epidemic occurred every year in the Philippines, Thailand, Myanmar, Malaysia, Singapore, Indonesia and

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Vietnam, The number of cases in Thailand increased for 45 years. In 1960 the morbidity rate was 7 per 100,000 population. In 2001 the morbidity rate was 224 per 100,000 population. In 2002 the morbidity rate was 185 per 100,000 population. Even though this was less than in 2001, it is still high. These data indicate the dengue control program in Thailand has not succeed. The trend in dengue mortality has decreased continuously from 10 % during the first outbreak in 1958 to 0.08% in 2004 (Kalayanarooj, 2004). During the past five years (2000-2004), the 5-9 years age group had the highest morbidity, the next was the 10-14 years old group. Even though the mortality rate has decreased compared to the past (1958), the incidence is still high. The death to case ratio is high compared to the past, particularly in remote areas which lack health care centers or medical doctors. Nearly universal anecdotal clinical observations show that DHF/DSS is rarely seen in children with protein energy malnutrition (PEM). Studies of DHF (Thisayakorn and Nimmanitya, 1993; Kowsathit and Chantarojsiri, 2000) found that DHF occurred more frequently in obese children. This study investigated the factors, especially body size, involved in the severity of DHF in children (0-14 years), in an attempt to reduce the mortality due to DHF in children.

The study evaluated the effects of the following factors on the severity of DF/DHF: childhood factors: duration of breast-feeding, education, and parity; caregivers factors: age, gender, education, occupation, family income, body temperature reduction method, treatment before hospitalization, duration of fever before hospitalization and knowledge of DHF; environmental factors: history of DHF patient in the house, house pattern, time from house to hospital and residential area; and etiological factors: type of dengue virus, type of infection and history of DHF associated with the severity of DHF in children of various body sizes.

MATERIALS AND METHODS

A hospital based case-control study was conducted among children age 0-14 years old admitted to Queen Sirikit National Institute of Child Health, Bangkok between October 1, 2002 and November 30, 2003.

The cases were the DHF patients, grades III or IV diagnosed by the attending physicians from clinical and laboratory finding according to WHO classification (WHO, 1999a). They were randomly selected based on specific inclusion criteria of age, gender and willingness to enroll in the study. There were 105 cases.

The controls were DHF patients, grade I or II diagnosed using WHO classification (WHO, 1999a). They were randomly selected using the same criteria, as cases. There were 105 controls. They were matched at a ratio of 1:1 by gender and age (within 5 years).

Exclusion criteria

The patients were excluded if the final diagnosis by the physician was DF or viral infection, or there was no data for weights and heights. The sample size was calculated using the formula of Lemeshow *et al* (1990):

$$n = \frac{\left\{Z_{\alpha/2}\sqrt{2P(1-P)} + Z_{\beta}\sqrt{P_1(1-P_1) + P_0(1-P_0)}\right\}^2}{(P_1 - P_0)^2}$$

When $Z_{\alpha/2} = 1.96$ at $\alpha = 0.05$, $Z_{\beta} = 1.28$ at $\beta = 0.10$, P_1 = proportion of overweight among cases as 0.66, P_0 = proportion of overweight among controls as 0.43. An adequate sample size was at least 97 for each group. The data were collected from the medical records and questionnaires. The questionnaires were pretested among 30 caregivers. The reliability of the questionnaire on DHF knowledge was 0.66 (KR-20). Factors of interest were gathered by caregiver interview. Medical records were collected after caregivers gave informed consent. Knowledge of caregivers meant a knowledge of DHF (signs and symptoms, signs of shock), first care before hospitalization, vectors and transmission, prevention and control. Knowledge levels were classified by low level (score less than group mean) and high level (score equal or higher than group mean).

Definition of variables

Caregivers who often take care of children: father, mother, grandfather, grandmother, aunt, uncle, baby-sitter, etc.

Body size or nutritional status which is defined by a normal growth chart using weight for age and weight for height scales and categorized into three groups as follows: normal (mean ±1.5 SD); malnutrition or thin (1.5 SD below mean or lower); obese (1.5 SD above mean or greater) (Kittigul *et al*, 2003).

Type of dengue virus identified by hemagglutination inhibition (HI) test from patient blood.

Type of infection, in which primary infection is the first infection, and secondary infection means the patient has previously been infected with at least one serotype of dengue virus before this recent infection. The data were collected from laboratory.

Grading severity for dengue hemorrhagic fever

DHF is classified into four grades of severity, where grades III and IV are considered to be DSS. The presence of thrombocytopenia with concurrent hemoconcentration is difined as grades I and II DHF.

Grade I. Fever accompanied by non-specific constitutional symptoms; the only hemorrhagic manifestation is a positive tourniquet test and/or easy bruising.

Grade II. Spontaneous bleeding in addition to the manifestations of Grade I, usually in the form of skin or other hemorrhages.

Grade III. Circulatory failure manifested by a rapid, weak pulse and narrowing of pulse pressure or hypotension, with the presence of cold, clammy skin and restlessness.

Grade IV. Profound shock with undetectable blood pressure and pulse (WHO, 1999 a).

Data analysis

Chi-square test and *t*-test were utilized to compare general characteristics between cases and controls. Odds ratio (OR) and 95% confidence intervals for OR were performed to define each associated factor's relationship with DHF. Multiple logistic regression was used to define the associated factors after adjusting for confounding factors.

RESULTS

General characteristics of children

The largest age range for both group was 5-9 years (50.0%). Most had normal body weight (59.6%). The numbers of those with grades III and II DHF were 37.6% and 34.3%, respectively. Most of those under age 5 had been breast-fed (97.1%). The average length of breast-feeding was three months (54.6%). The majority of them studied in primary school (60.5%) and were the first or second child (57.1% and 36.4%, respectively). Most did not have a previous history of DHF (88.6%). Seventy-six of them lived in Bangkok.

General characteristics of caregivers

The majority age of caregivers were 35-44 years old (45.7%). Eighty-seven percent were female, married (85.7%), mothers (74.3%), had a primary school education (52.9%), were employees/labors (49.5%), had a family income 5,000 -10,000 baht/month (36.2%), or 10,001-20,000 baht/month (32.9%).

Knowledge and practice of caregivers

The majority of caregivers 68.1% had a high knowledge level. Most used tepid sponge and paracetamol (50.0% and 46.9%) for reducing fever. When their children got sick, they first took them to a clinic before going to the hospitals (38.6%). The secondary most common choice was to take them to a government hospital. Most (63.8%) had a duration of fever of 3-4 days before hospitalization.

Comparison of the knowledge of caregivers

The majority of caregivers (53.3%) in the cases had a high knowledge level, unlike the controls, they had a low knowledge level (62.9 %) which was statistically significant ($p = 0.018$). Most caregivers had a low knowledge level of the signs of shock for both the cases and controls (77.1% and 94.3%, respectively). The majority of subjects had no history of DHF (85.7% of cases, and 91.4% of controls).There was no significant difference in having a history of DHF between the cases and controls ($p=0.193$). There was a significant difference between the type of dengue virus between the cases and controls ($p=0.001$). Most cases (54.3%) had DEN-2 virus and most controls (64.7%) had DEN-1 (Table 1).

The associated factors and severity of DHF

Univariate analysis was conducted on potential risk factors and their association with the

Table 1
Comparison of etiological factors between cases and controls.

Etiological factors	Cases		Controls		p-value[a]
	Number	Percentage	Number	Percentage	
Type of dengue virus					
DEN-1	34	32.4	68	64.7	0.001[b]
DEN-2	57	54.3	24	22.9	
DEN-3	8	7.6	6	5.7	
DEN-4	6	5.7	7	6.7	
Type of infection					
Primary	10	9.5	12	11.4	0.652
Secondary	95	90.5	93	88.6	
History of DHF					
Yes	15	14.3	9	8.6	0.193
No	90	85.7	96	91.4	

[a]Pearson's chi-square test. [b]Significant at p-value < 0.05

severity of DHF. The patients who had obesity were at increased risk for more severe DHF (OR = 2.77, 95 %CI 1.19 - 6.45) compared to those at normal weight. The caregivers of the cases had a higher level of knowledge about DHF than controls (OR = 1.93, 95 %CI 1.11 - 3.36). The patients whose (PCR) test showed DEN-2 had a higher risk for more severe DHF than those with DEN-1, -3 or -4 (OR = 4.75, 95 %CI 2.53 - 8.92).

Unconditional multiple logistic regression was provided by controlling for the effects of weight, knowledge of caregivers regarding DHF, type of dengue virus, age and gender of caregivers. After controlling for the confounding factors, there were 3 risk factors found: body size, knowledge of caregivers regarding DHF and type of dengue virus (Table 2).

DISCUSSION

Weight was defined by a normal growth chart using height for age and weight for height scales and categorized into three groups: normal, underweight and overweight. The study subjects who were overweight on the weight-for-height scale by more than +1.5 SD were 2.77 times more likely to develop more severe DHF (OR = 2.77, 95%CI 1.19-6.45) than those at normal weight. After adjusting for variables by multiple logistic regression analysis, this was still significant (OR = 3.00, 95%CI 1.20-7.48). These findings suggest a direct correlation between increasingly being overweight and the severity of DHF, which agrees with Halstead (1980) who found that DSS is rarely seen in clinically-malnourished children. Thisayakorn and Nimmanitya (1993) reported rare finding of DHF in undernourished children.

The major pathophysiologic hallmarks of DHF/DSS are abnormal hemostasis and increased vascular permeability, leading to plasma leakage. A critical loss of plasma leads to hypovolemic shock and death (WHO, 1999a). The synergy between malnutrition and infection is well recognized (Thisayakorn and Nimmanitya, 1993). The development of DF/DHF depends on the host immune response. Malnourished children have less severe DHF/DSS because they have a decreased cellular immune response (Halstead, 1997). Obese children are expected to have a stronger immune response than malnourished children so they are at higher risk of developing DF/DHF.

Most caregivers knew that DHF is a disease transmitted by mosquito bite and occurs in children. The most common mosquito breeding places are water containers and reservoirs. Paracetamol is the first drug of choice. Using a tepid sponge to reduce fever was also well known. There was no significant difference be-

Table 2
Associated factors and severity of DHF.

Risk factors	Crude OR	95 %CI	Adjusted OR	95 %CI	p-value[a]
Body size					
Normal	1		1		
Thin	0.77	0.40 - 1.47	0.76[b]	0.38 - 1.55	0.451
Obese	2.77	1.19 - 6.45	3.00[b]	1.20 - 7.48	0.001[e]
Knowledge					
Low	1		1		
High	1.93	1.11 - 3.36	1.66[c]	0.90 - 3.04	0.102
Type of dengue virus					
DEN-1	1		1		
DEN-2	4.75	2.53 - 8.92	4.94[d]	2.57 - 9.47	0.001[e]
DEN-3	2.67	0.86 - 8.30	2.63[d]	0.82 - 8.44	0.105
DEN-4	1.71	0.53 - 5.50	1.36[d]	0.39 - 4.74	0.628

[a] Chi-square test, [b] Adjusted for type of dengue virus, [c] Adjusted for body size and type of dengue virus, [d]Adjusted for body size, [e] Significant at p-value < 0.05

tween the knowledge of caregivers in the two groups after controlling for other variables.

Many studies have suggested that the knowledge level of caregivers is an important factor in the severity of DHF. However, this study found that the caregivers in the cases had a better knowledge than the controls. This may be because their children were admitted to the hospital. This gave them the opportunity to obtain knowledge regarding DHF and the signs and symptoms of shock (Kittigul *et al*, 2003).

Many previous studies have found that DHF is more severe when there has been a prior DHF infection (Sangkawibha *et al*, 1984; Rodriguez-Figueroa *et al*, 1995; Kalayanarooj *et al, 2*004; Wichmann *et al*, 2004). One study conducted on 3,185 children in Rayong Province in 1980 found the risk factor for DSS in Rayong Province was a secondary infection with DEN-2, and a primary infection with DEN-1, DEN-3 or DEN-4 (Sangkawibha *et al*, 1984). Most of the samples in both cases and controls (90.5% and 88.6 %, respectively) had a prior infection with dengue virus. Only DEN-2 was found to be significantly associated with the severity of DHF. Many researchers have suggested that the type of dengue virus is an important factor in the severity of DHF (Sangkawibha *et al,* 1984; Thein *et al,* 1997; Vaughn *et al,* 2000; Nisalak *et al*, 2003). Nisalak *et al* (2003) found that DEN-2 caused a more severe form due to the presence of heterotypic dengue antibody, rather than immunologic priming of cellular or T-cell immunity.

In conclusion, the 2 main purposes of this study was to determine the factors associated with the severity of DHF among children aged 0-14 years, and to evaluate relationships among these risk factors. DEN-2 had a significant association with the development of DHF. Knowledge of DHF among caregivers had no significance. However, the caregivers' knowledge of the signs of shock was significant (p = 0.001). Most caregivers had a low knowledge of the signs of shock. The results revealed that overweight children as measured by weight for age and weight for height (the standard growth curve of Thai children, Department of Health, 2000), and type of dengue virus, were risk factors for DHF severity.

We recommend: 1. Children with DHF, especially overweight children, should be diagnosed and treated early, and have special monitoring of the severity of DHF; 2. Health personnel should advise caregivers regarding proper nutrition. 3. Caregivers should be educated regarding the signs and symptoms of shock.

4. Laboratory diagnosis of the type of dengue virus is important since it predicts the severity of DHF.

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REFERENCES

Halstead SB. Dengue haemorrhagic fever-a public health problem and a field for research. *Bull World Health Organ* 1980; 58: 1-21.

Halstead SB. Epidemiology of dengue and dengue hemorrhagic fever. In: Gubler DJ, Kuno G, eds. Dengue and dengue haemorrhagic fever. Wallingford, New York: CAB International, 1997: 23-4.

Kalayanarooj S, Nimmannitya S. Guidelines for dengue hemorrhagic fever case management: Bangkok: WHO Collaborating Center for Case Management of Dengue/ DHF/ DSS, Queen Sirikit National Institute of Child Health, Department of Medical Services, Ministry of Public Health, 2004.

Kittigul L, Suankeow K, Sujirarat D, Yoksan S. Dengue hemorrhagic fever: knowledge, attitude and practice in Ang Thong Province, Thailand. *Southeast Asian J Trop Med Public Health* 2003; 34: 385-92.

Kowsathit P, Chantarojsiri T. Transfusion requirements in patients with dengue hemorrhagic fever. *Southeast Asian J Trop Med Public Health* 2000; 31: 10-4.

Lemeshow S, Hosmer DW, Klar J, Lwanga S. Adequacy of sample size in health studies. West Sussex: John Wiley & Sons, 1990: 19.

Nisalak A, Endy TP, Nimmannitya S, Kalayanarooj S, Thisayakorn U, Scott RM. Serotype-specific dengue virus circulation and dengue disease in Bangkok, Thailand from 1973 to 1999. *Am J Trop Med Hyg* 2003; 68: 191-202.

Rodriguez-Figueroa L, Rigau-Perez JG, Suarez EL, Reiter P. Risk factors for dengue infection during an outbreak in Yanes, Puerto Rico in 1991. *Am J Trop Med Hyg* 1995; 52: 496-502.

Sangkawibha N, Rojanasuphot S, Ahandrik S, *et al*. Risk factors in dengue shock syndrome: a prospective epidemiologic study in Rayong, Thailand. I. The 1980 outbreak. *Am J Epidemiol* 1984; 120: 653-69.

Thein S, Aung MM, Shwe TN, *et al*. Risk factors in dengue shock syndrome. *Am J Trop Med Hyg* 1997; 56: 566-72.

Thisayakorn U, Nimmanitya S. Nutritional status of children with dengue hemorrhagic fever. *Clin Infect Dis* 1993; 16: 295-7.

Vaughn DW, Green S, Kalayanarooj S, *et al*. Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity. *J Infect Dis* 2000; 181: 2-9.

Wichmann O, Hongsiriwon S, Bowonwatanuwong C, Chotivanich K, SukthanaY, 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.

World Health Organization. Monograph on dengue/ dengue haemorrhagic fever. New Delhi: Regional Publication, SEARO, 1993; 22.

World Health Organization. Guidelines for treatment of dengue haemorrhagic fever in small hospitals. New Delhi: World Health Organization, Regional Office for South-East Asia; 1999a.

World Health Organization. Prevention and control of dengue haemorrhagic fever: Comprehensive guidelines. New Delhi: World Health Organization, Regional Office for South-East Asia, 1999b.