DHF IN INFANTS, LATE INFANTS AND OLDER CHILDREN: A COMPARATIVE STUDY

Prasonk Witayathawornwong

Department of Pediatrics, Phetchabun Hospital, Phetchabun, Thailand

Abstract. A comparative study of dengue hemorrhagic fever in infants and children was conducted at the Department of Pediatrics, Phetchabun Hospital between May,1999 and December, 2002. There were 1,924 DHF patients (aged 0-14 years). There were 40 (2.1%) infants (age 0-1years) and 27 (1.4%) young children (age 1-2 years). Sixty-seven cases (3.5%) of the older children (>2-14 years) were selected to be compared. The clinical and epidemiological data for each of the three groups were not statistically different from each other, except for age, splenomegaly, shock state and mode of dengue infection. Older children were more likely to have a second dengue infection and a shock state than younger patients. Laboratory investigation results and fluid management for each of the three groups were not significantly different from each other except for the total WBC (min), neutrophils (max), lymphocytes (max) and platelets (min). The platelets (min) in the infants were significantly lower than in the younger children and the older children. Associated symptoms, diseases, complications, and hematologic manifestations in each of the three groups were not significantly different from each other except for the presence of coryza, seizures, nausea/vomiting, rash, and petichiae. Coryza, seizures, nausea/vomiting, rash, and petichiae in the infants and younger children were significantly different from the older children.

INTRODUCTION

Dengue hemorrhagic fever (DHF) is an important health problem in Southeast Asia and can be found worldwide (Hayes and Gubler, 1992). The severity of the disease depends upon several factors, such as the serotype of the virus (Kalayanarooj and Nimmannitya, 2000), age of the patient (Nimmannitya, 1987; Kalayanarooj *et al*, 1989; Pancharoen and Thisyakorn, 2000, 2001) and management of the disease. Most cases were about 5-15 years of age, adults and very young patients were less common. The severity of the disease in each age group was evaluated by comparing the clinical manifestations, laboratory findings, complications and outcomes of treatment. This study was conducted to compare these factors in infants (0-1 years), younger children (>1-2 years) and older children (>2-14 years).

Correspondence: Prasonk Witayathawornwong ,Department of Pediatrics, Phetchabun Hospital, Phetchabun 67000, Thailand.
Tel : 056 -721751, 01 - 8867521; Fax : 056-722091
E-mail : prasonkw@thaimail.com

MATERIALS AND METHODS

This descriptive study was conducted at the Department of Pediatrics, Phetchabun Hospital between May, 1999 and December, 2002. The charts of all hospitalized children (1,924 cases) age 0-14 years with a diagnosis of dengue hemorrhagic fever were reviewed. A diagnosis of dengue hemorrhagic fever included a clinical diagnosis (WHO, 1997) and a serological diagnosis by an enzyme-linked immunosorbent assay (ELISA) or hemagglutination inhibition (HI) test. A diagnosis of primary and secondary dengue infection was based upon serology per the recommendation by the World Health Organization (WHO). Three groups of patients: infants (0-1 years), younger children (>1-2 years) and older children (>2-14 years) were compared. Older children were selected from patients admitted the same day as the other two groups at a ratio of one to one.

Data were collected from the medical records, including age, sex, clinical presentation, laboratory findings, fluid volume replacement, grading of the disease and outcome. Descriptive data were analyzed using mean, median,

range and percentage. Variables were compared by the chi-square test and analysis of variance (ANOVA). The level of significance was defined as a p-value <0.05.

RESULTS

Between May, 1999 and December, 2002, there were 1,924 DHF patients (age 0-14 years) at the Pediatric Department, Phetchabun Hospital. The numbers of infants and young children diagnosed with DHF 40 (2.1%) and 27 (1.4%) cases, respectively. Older children who were admitted on the same days as the other two groups were selected for comparison. The clinical and epidemiological data are compared in Table 1. The sex ratio, positive tourniquet test, total duration of fever (about 5 days), hepatomegaly and normal nutritional status were not significantly different. Splenomegaly was found only in infants, 3 of the 4 cases were less than 6 months old. Older children had shock more frequently than younger patients. Both infants and young children had mainly primary dengue infection. A 2-day-old infant had dengue by vertical transmission (serotype I). Older children had mainly secondary dengue infection.

Laboratory investigations and fluid management (in afebrile or shock stage) are compared in Table 2. Rising hematocrit, maximal atypical lymphocytes, liver enzymes (AST, ALT), PT ratio, pleural effusion index (only infants and young children), duration of fluid therapy and percent of fluid volume replacement in the first 24 hours after fever defervescence not significantly different. The minimal WBC, maximal neutrophils and lymphocytes in the infants and young children were significantly different from the older children. The minimal platelet counts in the infants was significantly lower than in the young and older children.

Associated diseases, complications and hematologic manifestations of all three groups of patients are compared in Table 3. Diarrhea, thalassemia, acute renal failure, aseptic meningitis, hepatic encephalopathy, poor appetite, hematologic manifestations and mortality in all three groups of patients were not significantly different. Coryza, seizures, nausea/vomiting, rash/convalescent rash and petichiae in the infants and younger children were significantly different from the older children. Abdominal pain, found only in older children, could not be compared.

DISCUSSION

The incidence of DHF in infants (0-1 year) in this study was 2.1%, similar to previous studies (2-3%) (Scott *et al*,1976; Sirisanthana,1988;

Table 1
Clinical and epidemiological data.

	Infants	Late infants	Older children	p-value
Cases, n (%)	40 (2.1)	27 (1.4)	67 (3.5)	
Age, mean±SD	7.8±3.3 m	1.5±0.2 y	8.7±3.3y	0.000
median (range)	8m (2d-12m)	1y8m (13-23 m)	9y (2y2m-14y)	
Sex (M:F)	21:19 (1:0.9)	12:15 (1:1.2)	38:29 (1:0.7)	NS
TT+, n (%)	40 (100)	27 (100)	67 (100)	NS
DOF, mean±SD (range)d	4.9±1.1 (2-7)	5.0±1.1 (3-7)	5.1±0.9 (3-9)	NS
Hepatomegaly, n (%)	40 (100)	27 (100)	67 (100)	NS
Splenomegaly, n (%)	4[a] (10)	0	0	0.008
Shock, n (%)	2 (5)	2 (7.4)	18 (26.8)	<0.005
Normal nut stat, n (%)	37 (92.5)	25 (92.6)	56 (83.6)	NS
Primary DI, n (%)	36[b] (90)	24 (89)	4 (6)	0.000

TT: tourniquet test, DOF: duration of fever (total), NS: no statistical significance,
DI: dengue infection, nut.stat.: nutritional status, [a]: they were 2d, 3m, 4m and 10 m old, (not thalassemic cases), [b]: another 4 cases: 3 were secondary DI and 1 was dengue vertical transmission, aged 2d (Witayathawornwong, 2003).

Witayathawornwong, 1993, 2001; Hongsiriwon, 2002). DHF in younger children (1-2 years), was 1.4%, lower than in previous studies in Thailand (Halstead *et al* ,2002). However these may not have been in the same age catagories as other infants (Pancharoen and Thisyakorn, 2001). The sex ratio was not significantly different between the 3 groups of patients, nor were the results of the tourniquet test, duration of fever, hepatomegaly or nutritional status. The male to female ratios were equal in each of the different age groups. A positive tourniquet test and hepatome-

Table 2
Laboratory investigations and fluid management (in the afebrile or shock stage).

Laboratory parameters	Infants mean±SD	Late infants mean±SD	Older children mean±SD	p-value
Hct rising, (%)	29.8±18.8	26.3±16.4	23.8±11.9	NS
WBC min, cells/mm^3	9,212.5±3,843.6	8,859.2±4,786.4	4,747.7±2,514.6	0.000
N max, (%)	22.1±16.7	28.5±19.2	42.5±22.1	0.000
L max, (%)	67.2±17.2	56.6±19.0	42.1±18.7	0.000
ATL max, (%)	7.2±8.3	9.1±6.3	11.1±13.5	NS
Plt min, x10^3/mm^3	49.7±26.4	67.4±25.6	64.0±27.0	0.01
AST (units/l)	517.7±697.9	351.4±768.3	321.0±553.4	NS
ALT (units/l)	232.7±310.7	159.6±322.4	208.9±436.9	NS
PT ratio	1.0±0.59	0.83±0.26	0.89±0.27	NS
PEI	0.14±0.09	0.09±0.07	-	NS
DOFTh (h)	43.5±8.8	42.2±6,8	44.8±12.3	NS
% of M+ 5% D	73.1±13.4	75.2±12.6	80.7±25.4	NS

Hct: hematocrit, WBC: white blood cells, N: neutrophils, L: lymphocytes, Plt: platelets, ATL: atypical lymphocytes, AST, ALT: liver enzymes, PT ratio: prothrombin time ratio, PEI: pleural effusion index, DOF Th: duration of fluid therapy, % of M+5%D: percent of fluid volume replacement in the first 24 hours after fever defervescence compared with maintenance plus 5 percent deficit.

Table 3
Associated diseases, complications and hematologic manifestations.

Signs/symptoms /diseases	Infants n (%)	Late infants n (%)	Older children n (%)	p-value
Coryza	9 (22.5)	5 (18.5)	3 (4.4)	0.016
Seizure	2 (5.0)	3 (11.1)	0	0.047
Diarrhea	7 (17.5)	3 (11.1)	4 (5.9	NS
Thalassemia	7 (17.5)	3 (11.1)	4 (5.9)	NS
Aseptic meningitis	1 (2.5)	0	0	NS
ARF, hep.enceph.	2 (5.0)	0	0	NS
Poor appetite	40 (100)	27 (100)	63 (94)	NS
Nausea/vomiting	38 (95)	25 (92.6)	29 (43.3)	0.007
Abdominal pain	-	-	35 (52.2)	-
Death	1[a] (2.5)	0	0	NS
Rash/conv.rash	15 (37.5)	5 (18.5)	8 (11.9)	0.007
Petichiae	8 (20)	6 (22.2)	3 (4.4)	0.018
Melena	5 (12.5)	0	3 (4.4)	NS
Epistaxis	2 (5.0)	1 (3.7)	5 (7.4)	NS
Hematemesis	2 (5.0)	0	1 (1.5)	NS
Concealed bleeding	1 (2.5)	0	0	NS

ARF: acute renal failure, hep.enceph.: hepatic encephalopathy, conv.rash: convalescent rash,
[a]: prolonged shock and liver failure from delayed treatment, one from three cases of secondary dengue infection.

galy were detected in patients in all 3 groups. The average duration of fever in each of the age groups was equal, about 5 days, the same as in previous studies (Witayathawornwong,1993, 2001; Pancharoen and Thisyakorn, 2001; Pancharoen *et al*, 2001; Hongsiriwon, 2002). Most of the patients in the 3 groups were well-nourished (Thisyakorn and Nimmannitya,1993). Splenomegaly (non-thalassemic cases), was found only in infants, especially under 6 months, in about 10%, which is higher than some previously reported cases, 0 (Hongsiriwon, 2002), 3.2 (Witayathawornwong, 2001), 6.3 (Nimmannitya *et al*, 1969) and 9.1% (Pancharoen and Thisyakorn, 2001). Older children with mainly secondary dengue infection had dengue shock syndrome more often than in the 2 younger age groups. This finding implies that secondary dengue infection was more severe than primary dengue infection (Vaughn *et al*, 2000).

Laboratory investigations and fluid management in each of the 3 groups of patients were not significantly different regarding rising hematocrit, atypical lymphocytes (maximal), liver enzymes (AST, ALT), prothrombin time ratio, pleural effusion index (only infants and younger children), duration of fluid therapy or amount of fluid replacement. Total WBC (minimal), neutrophils (maximal) and lymphocytes (maximal) in both the infant and younger children groups were similar to each other, but sigificantly different from the older patients. These findings may be due to the difference in normal values for infants and older children (Hathirat *et al* , 1976). The normal values for WBC and lymphocytes in infants is higher than in older children, but neutrophils are lower. The platelet count (minimal) in the infants was significantly lower than in the younger children and older children, opposite of a study by Pancharoen *et al* (2002).

Associated diseases (diarrhea, thalassemia, aseptic meningitis), complications (acute renal failure, hepatic encephalopathy, poor appetite, mortality), and hematologic manifestations (melena, epistaxis, hematemesis, concealed bleeding) in each of the 3 groups of patients were not significantly different. Coryza in the two younger groups was significantly higher than the older patients, correlating with a previous study (Pancharoen *et al*, 2001). There was a study with no significant difference in coryza in any of the age groups (Pancharoen and Thisyakorn, 2001).

Seizures in both the younger age groups were significantly more frequent than in the older patients (Pancharoen *et al,* 2001; Pancharoen and Thisyakorn, 2001). Most cases with seizures (except for one with aseptic meningitis) were most likely febrile seizures (Levinton and Cowan, 1982). Nausea/vomiting and rash/convalescent rash in the 2 groups of infants were significantly more common in the older patients. The former was opposite to and the latter was similar to other studies (Pancharoen and Thisyakorn, 2001; Pancharoen *et al*, 2001). There was a study showing no significant difference in vomiting between the younger and the older patients (Pancharoen *et al*, 2002). Petichiae, the only abnormal hematologic manifestation in the 2 younger groups, was significantly more common than in the older patients. Abdominal pain in the infants could not be evaluated, so it could not be compared. One infant died because of prolonged shock and liver failure due to delayed treatment (having severe symptoms before admission). This infant was one of the three cases of secondary dengue infection.

In conclusion, the common clinical manifestations, except for shock, laboratory investigations, complications and outcomes of treatment, for each of the age groups were not significantly different. Some differences were due to specific characteristics of each age group, such as the mode of dengue infection, splenomegaly in the very young, hematologic laboratory parameters (CBC; WBC, N, L) and complications (febrile seizures, nausea/vomiting). And all data showed that infants (0-1 year) and young children (>1-2 years) can be placed in the same group.

ACKNOWLEDGEMENTS

The author would like to thank the officials of Regional Medical Science Center, Phitsanulok Province and the officials of the Department of Virology, Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok, Thailand for the dengue serology testing.

REFERENCES

Halstead SB, Lan NT, Myint TT, *et al*. Dengue hemorrhagic fever in infants: Research opportunities ignored. *Emerg Infect Dis* 2002; 8: 1474-9.

Hathirat P, Isarangura P, Sasanukul W, *et al*. Hematologic findings in normal Thai children. *J Med Assoc Thai* 1976; 59: 53-7.

Hayes EB, Gubler DJ. Dengue and dengue hemorrhagic fever. *Pediatr Infect Dis* 1992;11:311-7.

Hongsiriwon S. Dengue hemorrhagic fever in infants. *Southeast Asian J Trop Med Public Health* 2002; 33: 49-55.

Kalayanarooj S, Nimmannitya S, Eaksangsri P, *et al*. Fatal cases of dengue hemorrhagic fever at Children's hospital 1987. *Bull Dept Med Serv* 1989;14: 771-8.

Kalayanarooj S, Nimmannitya S. Clinical and laboratory presentations of dengue patients with different serotypes [Abstract]. Chiang Mai, Thailand: The First International Conference on Dengue/Dengue Hemorrhagic Fever. November 20-24, 2000.

Levinton A, Cowan LD. Epidemiology of seizure disorders in children. *Neuroepidemiology* 1982;1: 40-83.

Nimmannitya S, Halstead SB, Cohen SN, *et al*. Dengue and chikungunya virus infection in man in Thailand 1962-1964. *Am J Trop Med Hyg* 1969; 18: 954-71.

Nimmannitya S. Dengue hemorrhagic fever in Thailand. *Southeast Asian J Trop Med Public Health* 1987; 18: 281-4.

Pancharoen C, Thisyakorn U. Dengue infection in teenage children. *J Infect Dis Antimicrob Agents* 2000; 17: 93-6.

Pancharoen C, Mekmullica J, Thisyakorn U. Primary dengue infection: what are the clinical distinctions from secondary infection? *Southeast Asian J Trop Med Public Health* 2001; 32: 476-80.

Pancharoen C, Thisyakorn U. Dengue virus infection during infancy. *Trans R Soc Trop Med Hyg* 2001; 95: 307-8.

Pancharoen C, Thisyakorn U, Urupongpisarn S, *et al.* Clinical and laboratory differences between children with primary and secondary dengue infection. *Chula Med J* 2002; 46: 471-7.

Scott RM, Nimmannitya S, Bancroft WH, Mansuwan P. Shock syndrome in primary dengue infections. *Am J Trop Med Hyg* 1976; 25: 866-74.

Sirisanthana V. Dengue hemorrhagic fever at the Department of Pediatrics, Chiang Mai University Hospital in 1987. *J Pediatr Soc Thai* 1988; 27: 36-43.

Thisyakorn U, Nimmannitya 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.

Witayathawornwong P. Dengue hemorrhagic fever in infants under 1 year of age: A report of 5 cases. *Region 8 Med J* 1993; 3: 237-45.

Witayathawornwong P. Dengue hemorrhagic fever in infancy at Petchabun Hospital, Thailand. *Southeast Asian J Trop Med Public Health* 2001; 32: 481-7.

Witayathawornwong P. Parturient and perinatal dengue hemorrhagic fever. *Southeast Asian J Trop Med Public Health* 2003; 34: 797-9.

World Health Organization. Dengue hemorrhagic fever: diagnosis, treatment, and control. 1997.