PRIMARY DENGUE INFECTION: WHAT ARE THE CLINICAL DISTINCTIONS FROM SECONDARY INFECTION?

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Abstract. To determine the magnitude of the problem posed by primary dengue infection in children and the distinctive clinical clues that may differ from those with secondary infection, 996 children serologically diagnosed with dengue infection and admitted to the Department of Pediatrics, Chulalongkorn Hospital, Bangkok, Thailand between 1988 and 1995 were retrospectively reviewed. One hundred and thirty-nine cases (14.0%) were serologically proved to be primary dengue infection. Of these, 72 were males and 67 were females, with a mean age of 4.8 years. Common manifestations by order of frequency included fever (97.8%), hepatomegaly (71.9%), vomiting (59.0%), decreased appetite (55.4%), coryza (52.5%), drowsiness (39.6%), diarrhea (34.5%), rash (33.8%), abdominal pain (23.0%) and seizure (15.8%). The mean duration of fever before admission was 4.6 days. Common sites of bleeding were skin (41.7%), mucous membrane (14.4%) and the gastrointestinal tract (12.2%). Clinical diagnosis was categorized into dengue fever (22.3%), dengue hemorrhagic fever (60.4%) and dengue shock syndrome (17.3%). Three patients (2.2%) died. Compared with the children with secondary dengue infection (n=139), children with primary dengue infections tended to be younger, presented more commonly with coryza, diarrhea, rash and seizure; and less commonly with vomiting, headache and abdominal pain ($p < 0.05$). The maximal hematocrit level, the mean difference between maximal and minimal hematocrit values and the maximal percentage of neutrophils were significantly lower in the study group, whereas the maximal percentage of lymphocytes was significantly higher. Dengue fever was more common and dengue shock syndrome was less common in the study group ($p < 0.05$). This study has emphasized that primary dengue infection is not uncommon and is less severe than secondary infection. Clinical presentations and laboratory findings are somewhat different between the two conditions.

INTRODUCTION

Dengue infection is one of the major public health problems affecting children in the Southeast Asian and Western Pacific regions (Thisyakorn and Thisyakorn, 1994). Disease severity differs dependent upon several factors including serotype of the virus (Kalayanarooj and Nimmannitya, 2000) and age of the patients (Pancharoen and Thisyakorn, 2000; 2001). Patients with primary dengue infection are likely to develop less severe disease and shock syndrome, although uncommon, is possible (Scott, 1976) and may be fatal (Nogueira, 1999). At present, there are no data concerning the clinical features of primary versus secondary dengue infections. Therefore, we conducted this study in order to elucidate the magnitude of the problem and the natural history of primary dengue infection in children, as opposed to secondary infection, in terms of clinical presentation, laboratory findings, disease grading and outcome.

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PATIENTS AND METHODS

This descriptive study was conducted in the Department of Pediatrics, Chulalongkorn Hospital between January 1988 and December 1995. All hospitalized children aged 0-15

years and diagnosed with dengue infection, were reviewed from prospectively recorded dengue medical charts. Diagnosis of dengue infection included clinical diagnosis and serological diagnosis using an enzyme-linked immunosorbent assay (ELISA) or hemagglutination-inhibition (HI) test. Diagnosis of primary and secondary dengue infection was based upon the serological interpretation recommended by the World Health Organization (WHO). Comparative subjects were children, diagnosed with secondary dengue infection and sampled by the stratified sampling method for each year of the study at a ratio of one to one.

The data collected from the medical records included age, sex, clinical presentation, laboratory findings, grading of the disease and outcome. Descriptive data were analyzed using mean, range and percentage. Variables were compared by chi-square test, Student's *t*-test, Fisher's exact test, and analysis of variance (ANOVA). The level of significance was defined as a p-value < 0.05.

RESULTS

Of 996 children between 0 and 15 years of age serologically diagnosed with dengue infection, 139 were classified by serologic tests as primary infection - amounting to 14.0% of the total. There were 72 males and 67 females. The age distribution varied from 6 days to 14 years with a mean age of 4.8 ± 4.3 years and a peak age of 6-12 months. Of 139 patients in the comparative group, 72 were boys and 67 were girls. The average age was 8.6 ± 3.2 years and was significantly higher than that of the study group (p-value = 0.000).

In the study group, almost all patients (97.8%) had fever prior to admission with an average duration of 4.6 ± 1.8 days. This was not statistically different from that of the comparatives (4.3 days). Common symptoms and signs included hepatomegaly (71.9%), vomiting (59.0%), decreased appetite (55.4%), coryza (52.5%), drowsiness (39.6%), diarrhea (34.5%), rash (33.8%), abdominal pain (23.0%), seizure (15.8%), conjunctival injection (8.6%), myalgia (6.5%) and headache (5.8%) (Table 1). Common bleeding sites included the skin (41.7%), mucous membranes (14.4%) and the gastrointestinal tract (12.2%). Unusual neurological manifestations and co-infection were found in 3.6% and 4.3% respectively. Three patients died, thus giving a mortality rate of 2.2%. The mean maximal hematocrit value (Hct max) was 40.5 volume%. The mean difference between maximal and minimal hematocrit values (ΔHct) was 6.6 volume%.

Table 1
Symptoms and signs of study patients, compared with those in patients with secondary infection.

	Study group No. (%)	Comparative group No. (%)	p-value
1. Hepatomegaly	100 (71.9)	112 (80.6)	NS
2. Vomiting	82 (59.0)	101 (72.7)	0.023
3. Decreased appetite	77 (55.4)	91 (65.5)	NS
4. Coryza	73 (52.5)	42 (30.2)	0.000
5. Drowsiness	55 (39.6)	46 (33.1)	NS
6. Diarrhea	48 (34.5)	27 (19.4)	0.007
7. Rash	47 (33.8)	17 (12.2)	0.000
8. Abdominal pain	32 (23.0)	76 (54.7)	0.000
9. Seizure	22 (15.8)	6 (4.3)	0.003
10. Conjunctivitis	12 (8.6)	7 (5.0)	NS
11. Myalgia	9 (6.5)	10 (7.2)	NS
12. Headache	8 (5.8)	27 (19.4)	0.001

Note: NS = no statistical significance

Table 2
Complete blood count and serum sodium in study patients, compared with those in patients with secondary infection.

Laboratory parameter	Study group Mean ± SD	Comparative group Mean ± SD	p-value
Hct max (%)	40.5 ± 5.4	44.8 ± 5.9	0.000
ΔHct (%)	6.6 ± 4.2	8.2 ± 5.1	0.02
Wbc min (cells/mm^3)	5,392.1 ± 4,108.7	5,503.5 ± 3,509.8	NS
% PMN max	46.5 ± 20.1	57.5 ± 16.9	0.000
% L max	55.1 ± 18.8	38.8 ± 14.4	0.000
% AL max	7.6 ± 7.1	9.4 ± 9.5	NS
Platelet min (x $10^3/mm^3$)	118.6 ± 131.6	105.5 ± 104.1	NS
Na min (mEq/l)	135.2 ± 6.9	134.7 ± 5.1	NS

NOTE : Hct = hematocrit, max = maximum, Δ = differences between maximal and minimal hematocrit, min = minimum, mm^3 = cubic millimeter, PMN = polymorphonuclear cell, L = lymphocyte, AL = atypical lymphocyte, Na = sodium, mEq/l = milliequivalent per liter, NS = no statistical significance

Table 3
Disease grading of study patients compared with that of patients with secondary infection.

Disease grading	Study group No. (%)	Comparative group No. (%)	p-value
Dengue fever	31 (22.3)	10 (8.5)	0.000
Dengue hemorrhagic fever			
Grade I	21 (15.1)	20 (16.9)	
Grade II	63 (45.3)	32 (27.1)	
Grade III	21 (15.1)	55 (49.6)	
Grade IV	3 (2.2)	1 (0.8)	

The mean minimal value of the white blood cell (wbc min) count was 5,392 cells/mm^3. The mean maximal percentage of neutrophils, lymphocytes and atypical lymphocytes was 46.5, 55.1 and 7.6%, respectively. The mean minimal value of the platelet count was 118,600/mm^3 (Table 2). A minimal value of the platelet count of ≤ 50,000/mm^3 and ≤ 20,000/mm^3 was found in 31.9 and 8.0% of the cases respectively. The mean minimal serum sodium (Na min) value was 135.2 mEq/l. A minimal serum sodium value of ≤ 135 and ≤ 130 mEq/l (hyponatremia) was found in 50.8 and 30.2 percent respectively. According to WHO classification, the patients were categorized into dengue fever (DF) (22.3%), dengue hemorrhagic fever (DHF) (grade I = 15.1%, grade II = 45.3%) and dengue shock syndrome (DSS) (grade III = 15.1%, grade IV = 2.2%) (Table 3). The mean age of patients with DSS was significantly lower than that of patients with DF and DHF.

Compared with the comparatives, children with primary dengue infection presented more commonly with coryza, diarrhea, rash and seizure; and less commonly with vomiting, abdominal pain and headache (Table 1). Bleeding from skin, mucous membrane and the gastrointestinal tract was not significantly different between the two groups. Co-infection was found significantly more frequently in the study group. As to laboratory findings, the Hct max, ΔHct and maximal percentage of

neutrophils were found to be significantly lower, whereas the maximal percentage of lymphocytes was significantly higher in the study group ($p < 0.05$) (Table 2). Clinical categorization was significantly different, indicating that dengue fever was more common and dengue shock syndrome was less common in the study group ($p < 0.05$) (Table 3). The mortality rates of both groups were not significantly different.

DISCUSSION

Our study shows that the incidence of primary dengue infection was not low (14.0%). The incidence reported in previous studies has varied from 5.8% (Hayes *et al,* 1988) to 52.0% (Reed *et al,* 1977). This variation in incidence depends upon the method of patient enrollment. Patients with primary dengue infection are likely to develop mild symptoms and may not require hospitalization.

Small children with dengue infection have mostly primary infections (Pancharoen, Thisyakorn, 2001) and vice versa our study showed that the children with primary dengue infection tended to be very young.

Several clinical presentations of the children with primary dengue infection were somewhat different from those with secondary infection *ie* coryza, diarrhea, rash and seizure were more common whereas vomiting, headache and abdominal pain were less common. These distinctions probably arise because children with primary infection are younger and the clinical manifestations of young children with dengue infection differ from those of older children (Pancharoen and Thisyakorn, 2000; 2001). Moreover, our study showed that co-infections in our patients with primary infection were more common. This may possibly be explained by the fact that dual infections were more common in younger children with dengue infection as indicated by a previous study showing that 6 out of 14 reported cases of co-infections in dengue patients were ≤ 1 year of age (Pancharoen and Thisyakorn, 1998). Our study and a previous study (Reed *et al,* 1977) demonstrated that bleeding in patients with primary and secondary dengue infections was not significantly different, and the skin was the most common site of bleeding in our study and previous dengue studies (Pancharoen and Thisyakorn, 2000; 2001).

The severity of disease in these patients was relatively less severe *ie* more cases with DF and fewer cases of DSS. The clinical presentation of children with primary dengue infection is known to be less severe (Pancharoen *et al,* 2001). However, DSS may be present in patients aged 6-12 months when the passive antibody obtained from the mother is below the protective level. Similarly to secondary infection, the antibody response is enhanced after the first dengue virus infection.

The level of Hct in our patients was significantly lower than those with secondary infection. This is probably due to the lesser severity of disease and the lower normal value of Hct in younger children. The mean levels of platelet min of the study patients and the comparatives were not significantly different, and the sites and severity of bleeding were similar.

In conclusion, primary dengue infection is not uncommon and is relatively less severe than secondary disease. Clinical presentation and laboratory findings are different in some aspects from those in children with secondary infection.

REFERENCES

Hayes CG, Manaloto CR, Gonzales A, Ranoa CP. Dengue infection in the Philippines: clinical and virological findings in 517 hospitalized patients *Am J Trop Med Hyg* 1988; 39: 110-6.

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

Nogueira RMR, Miagostovich MP, Cunha RV, *et al*. Fatal primary dengue infections in Brazil. *Trans R Soc Trop Med Hyg* 1999; 93: 419.

Pancharoen C, Thisyakorn U. Coinfection in dengue patients. *Pediatr Infect Dis J* 1998; 17: 81-2.

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

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

Pancharoen C, Urupongpisarn S, Thisyakorn C, Thisyakorn U. Clinical and laboratory differences between children with primary and secondary dengue infection, 2001 (submitted).

Reed D, Maguire T, Mataika J. Type 1 dengue with hemorrhagic disease in Fiji: epidemiologic findings. *Am J Trop Med Hyg* 1977; 26: 784-91.

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

Thisyakorn U, Nimmannitya S, Ningsanond V, Soogarun S. Atypical lymphocyte in dengue hemorrhagic fever: its value in diagnosis. *Southeast Asian J Trop Med Public Health* 1984; 15: 32-6.

Thisyakorn U, Thisyakorn C. Diseases caused by arboviruses-dengue haemorrhagic fever and Japanese B encephalitis. *Med J Aus* 1994; 160: 22-6.

Wongsawat J, Pancharoen C, Ningsanond V, Thisyakorn U. Kinetics of peripheral blood leukocyte alterations in Thai children with dengue infection [Abstract]. The First International Conference on Dengue/Dengue Haemorrhagic Fever. Chiang Mai, Thailand. November 20-24, 2000.