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## Clinical and laboratory differences between children with primary and secondary dengue infection

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- Objective** : *To compare aspects of the clinical and laboratory findings between primary dengue infection with secondary dengue infection.*
- Setting** : *Department of Pediatrics, Faculty of Medicine, Chulalongkorn University*
- Design** : *Descriptive study*
- Patients** : *Ninety-two children admitted with dengue infection to King Chulalongkorn Memorial Hospital from January to December 1996*
- Method** : *Medical chart review of age, sex, clinical presentation, laboratory findings, grading of the disease and outcome*
- Results** : *Twenty-seven cases (29.3 %) were serologically found to have primary dengue infection. There were 13 males and 14 females. The study patients were divided into various age groups: 3 cases (11.1 %) < 1 year, 8 cases (29.6 %) 1-4 years, 7 cases (25.9 %) 5 -9 years and 9 cases (30.0 %) ≥ 10 years. The common manifestations included fever on admission (74.1%), positive tourniquet test (72.7 %), vomiting (70.4 %), hepatomegaly (44.4 %), abdominal pain (11.1%) and conjunctival injection (7.4 %). Common sites of bleeding were the gastrointestinal tract (44.4%), skin (40.7 %) and mucous membranes (11.1 %). The mean maximal hematocrit level ( $Hct_{max}$ ) and minimal*

platelet count ( $plt_{min}$ ) were 41.1 percent and  $81,100/mm^3$  respectively. The categorization into dengue hemorrhagic fever was as follows: grade 1 (44.4 %), grade 2 (44.4 %), grade 3 (7.4 %) and grade 4 (3.7 %). There were no deaths. The children with primary infection were younger, and presented less commonly with hepatomegaly and abdominal pain than cases with secondary dengue infection ( $n = 65, 70.7\%$ ) ( $p < 0.05$ ). The mean  $Hct_{max}$  and the percentage of atypical lymphocytes were significantly lower whereas the  $plt_{min}$  was significantly higher in primary dengue infection.

**Conclusion** : This study shows that primary dengue infection is not uncommon and is less severe than secondary dengue infection. There are differences in clinical presentation and laboratory findings in primary dengue infection compared with secondary dengue infection in children.

**Key words** : Dengue, Primary, Secondary, Children.

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ชินณ พันธ์เจริญ, สุธรรม อรุพงศ์พิศาล, จุล ทิษยากร, อุษา ทิษยากร. ความแตกต่างของอาการทางคลินิกและผลการตรวจทางห้องปฏิบัติการในผู้ป่วยเด็กที่ติดเชื้อไวรัสเดงกีแบบปฐมภูมิและทุติยภูมิ. จุฬาลงกรณ์เวชสาร 2545 มิ.ย; 46(6): 471 - 7

- วัตถุประสงค์** : เพื่อศึกษาเปรียบเทียบอาการทางคลินิกและผลการตรวจทางห้องปฏิบัติการของผู้ป่วยเด็กที่ติดเชื้อไวรัสเดงกีแบบปฐมภูมิและแบบทุติยภูมิ
- สถานที่ที่ทำการศึกษา** : ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
- รูปแบบการวิจัย** : การศึกษาเชิงพรรณนา
- ผู้ป่วยที่ได้ทำการศึกษา** : เด็กที่ได้รับการวินิจฉัยทางคลินิกและได้รับการยืนยันทางซีโรโลยีว่ามีการติดเชื้อไวรัสเดงกี และรับไว้รักษาในหอผู้ป่วยเด็ก โรงพยาบาลจุฬาลงกรณ์ ในปี พ.ศ. 2539 จำนวน 92 คน
- วิธีการศึกษา วัตถุประสงค์** : ทำการศึกษาเวชระเบียนของผู้ป่วยในแง่ของอายุ เพศ อาการนำทางคลินิก ผลการตรวจทางห้องปฏิบัติการ ความรุนแรงของโรค และผลการรักษา
- ผลการศึกษา** : จากผู้ป่วยเด็กที่ติดเชื้อไวรัสเดงกี จำนวน 92 คน พบว่า 27 คน (ร้อยละ 29.3) เป็นการติดเชื้อแบบปฐมภูมิ เป็นเพศชาย 13 คน เพศหญิง 14 คน ผู้ป่วย 3 คน (ร้อยละ 11.1), 8 คน (ร้อยละ 29.6), 7 คน (ร้อยละ 25.9) และ 9 คน (ร้อยละ 30.0) มีอายุ < 1 ปี, 1-4 ปี, 5-9 ปี และ  $\geq 10$  ปี ตามลำดับ อาการทางคลินิกได้แก่ อาการไข้เมื่อแรกเริ่ม (ร้อยละ 74.1), การทดสอบทูนิเกตีให้ผลบวก (ร้อยละ 72.7), อาเจียน (ร้อยละ 10.4), ตับโต (ร้อยละ 44.4), ปวดท้อง (ร้อยละ 11.1) และตาแดง (ร้อยละ 7.4) ตำแหน่งของเลือดออกที่พบบ่อยได้แก่ ระบบทางเดินอาหาร (ร้อยละ 44.0), ผิวหนัง (ร้อยละ 40.7) และเยื่อ (ร้อยละ 11.1) ค่าเฉลี่ยของฮีมาโตคริตสูงสุดและจำนวนเกร็ดเลือดต่ำสุดเท่ากับ 41.1 เปอร์เซ็นต์ และ 81,100/ลบ.มม.ตามลำดับสามารถจำแนกผู้ป่วยตามความรุนแรงของโรคได้เป็นเกรด 1, 2, 3 และ 4 คิดเป็นร้อยละ 44.4, 44.4, 7.4 และ 3.1 ตามลำดับ ไม่มีผู้ป่วยเสียชีวิตจากการศึกษานี้ เมื่อเปรียบเทียบกับผู้ป่วยที่ติดเชื้อแบบปฐมภูมิจำนวน 65 คน (ร้อยละ 70.7) ผู้ป่วยที่ติดเชื้อแบบปฐมภูมิมียุคน้อยกว่าพบอาการตับโตและปวดท้องน้อยกว่าอย่างมีนัยสำคัญทางสถิติ ค่าเฉลี่ยของฮีมาโตคริตสูงสุดและค่าร้อยละของเม็ดเลือดขาวชนิด atypical lymphocyte ต่ำกว่าขณะที่จำนวนเกร็ดเลือดต่ำสุดมีค่าสูงกว่า
- วิจารณ์และสรุป** : การศึกษานี้แสดงให้เห็นว่าผู้ป่วยที่ติดเชื้อไวรัสเดงกีแบบปฐมภูมิพบได้น้อยและมีอาการไม่รุนแรงนัก อาการทางคลินิกและผลการตรวจทางห้องปฏิบัติการมีความแตกต่างบางประการจากผู้ป่วยที่ติดเชื้อเดงกีแบบทุติยภูมิ

Dengue infection is a major public health problem affecting children in the Southeast Asia and the Western Pacific Region.<sup>(1)</sup> The severity of disease depends on several factors such as the viral serotype,<sup>(2)</sup> age of the patient<sup>(3-4)</sup> and whether it is primary or secondary infection. Patients with primary dengue infection develop less severe disease and are not likely to develop the shock syndrome which is uncommon.<sup>(5-6)</sup> We conducted this study to find out the incidence of primary dengue infection in hospital admissions and to review its natural history as compared to secondary infection in children.

### Patients and methods

This descriptive study was conducted in the Department of Pediatrics at King Chulalongkorn Memorial Hospital from January to December 1996. All medical charts of hospitalized children aged 0-15 years and diagnosed with dengue infection, were studied. The diagnosis of dengue infection included clinical diagnosis and serological diagnosis using an enzyme-linked immunosorbent assay (ELISA) test. Diagnosis of primary and secondary dengue infection followed the serological interpretation recommended by the World Health Organization (WHO). Data collected included age, sex, clinical presentation, laboratory findings, grading of the disease (WHO criteria) and outcome. The data was analyzed using mean, range and percentage. Variables were compared by Chi-square test, Student t-test, Fisher's Exact test and analysis of variance (ANOVA). The level of significance was defined as a p-value < 0.05.

### Results

There were 92 children in the study. Both

clinical and serological diagnosis of dengue infection were reviewed. Twenty-seven children were classified serologically with primary infection – making up to 29.3 percent of the total number and comprising 13 males and 14 females. There were 65 children were classified with secondary infection comprising 34 males and 31 females. The age distribution of the subjects is summarized in Table 1. Children with primary infection were significantly younger than those with secondary infection. All children below one year of age were found to have primary dengue infection. Three-quarters of children older than one year were found to have secondary infection.

Common clinical manifestations of primary infection included fever on admission (74.1 %), positive tourniquet test (72.7 %), vomiting (70.4 %), hepatomegaly (44.4 %), abdominal pain (11.1 %) and conjunctival injection (7.4 %). Common bleeding sites included the gastrointestinal tract (44.4 %), skin (40.7 %) and mucous membranes (11.1 %) (Table 2). Overall, two patients developed abnormal neurological manifestations namely encephalopathy (one child with secondary dengue infection) and signs of meningeal irritation (one child with primary dengue infection).

**Table 1.** Age of patients with primary and secondary dengue infection.

Age (years)	Primary infection No. (%)	Secondary infection No. (%)	p-value
< 1	3 (11.1)	0 (0.0)	< 0.05
1 - 4	8 (29.6)	7 (10.8)	
5 - 9	7 (25.9)	28 (43.1)	
10 - 14	9 (30.0)	30 (46.2)	
<b>Total</b>	<b>27(100.0)</b>	<b>65(100.0)</b>	

**Table 2.** Symptoms and signs of patients with primary and secondary dengue infection.

Symptoms and signs	Primary Infection No. (%)	Secondary Infection No. (%)	p-value
Fever on admission	20 (74.1)	50 (76.9)	NS
Vomiting	19 (70.4)	51 (78.5)	NS
Hepatomegaly	12 (44.4)	47 (72.3)	< 0.05
Abdominal pain	3 (11.1)	25 (38.5)	< 0.05
Conjunctival injection	2 (7.4)	10 (15.4)	NS
Bleeding			
- skin	11 (40.7)	36 (55.4)	NS
- mucous membrane	3 (11.1)	12 (18.5)	NS
- GI system	12 (44.4)	47 (72.3)	NS

Note: NS = no statistical significance, GI = gastrointestinal

A review of the 27 cases with primary dengue infection found that the mean maximal hematocrit level ( $Hct_{max}$ ) and minimal platelet count ( $plt_{min}$ ) were 41.1 percent and 81,100/mm<sup>3</sup> respectively (Table 3). The clinical diagnosis was categorized into dengue hemorrhagic fever grade 1 (44.4 %), grade 2 (44.4 %),

grade 3 (7.4 %) and grade 4 (3.7 %) (Table 4). Fluid replacement required (crystalloid and colloid) and the number of days of hospital admission were not statistically different between the two groups. There were no fatalities.

**Table 3.** Complete blood count and serum sodium in patients with primary versus secondary infection.

Laboratory parameter	Primary infection	Secondary infection	p-value
$Hct_{max}$ (%)	41.1	44.8	< 0.05
$Hct_{min}$ (%)	34.9	36.6	NS
Wbc (cells/mm <sup>3</sup> )	5,300	5,900	NS
% PMN	50.5	48.6	NS
% L	38.6	33.7	NS
% Mo	5.2	6.2	NS
% AL	7.6 ± 7.1	9.4 ± 9.5	< 0.05
Platelet <sub>max</sub> (/mm <sup>3</sup> )	157,000	100,500	NS
Platelet <sub>min</sub> (/mm <sup>3</sup> )	81,100	53,400	< 0.05
Na <sub>min</sub> (mEq/L)	135.2	132.2	NS

Note : Hct = hematocrit, max = maximum, min = minimum, mm<sup>3</sup> = cubic millimeter, PMN = polymorphonuclear cell, L = lymphocyte, Mo = monocyte, AL = atypical lymphocyte, Na = sodium, mEq/L = milliequivalent per liter, NS = no statistical significance

**Table 4.** Disease grading of patients with primary versus secondary infection.

Disease grading	Primary infection	Secondary infection	p-value
	No. (%)	No. (%)	
DHF grade 1	12 (44.4)	20 (30.8)	NS
grade 2	12 (44.4)	29 (44.6)	NS
grade 3	2 (7.4)	14 (21.5)	NS
grade 4	1 (3.7)	2 (3.1)	NS

Note: DHF = dengue hemorrhagic fever, NS = no statistical significance

Hepatomegaly and abdominal pain were less common in primary infection ( $p < 0.05$ ) (Table 2). The mean age of children with primary infection (3.7 years) who developed shock (DHF grade 3 and 4) was significantly lower than that of children with secondary infection (8.6 years). The mean  $Hct_{max}$  and the percentage of atypical lymphocytes in children with primary infection were significantly lower whereas the  $plt_{min}$  was significantly higher. The percentage of children with shock was not significantly different between primary (11.1 %) and secondary (24.6 %) infection.

## Discussion

Our study shows that the incidence of primary dengue infection admissions was not uncommon (29.3 % incidence among total dengue hospital admissions). The incidence of dengue admissions reported in previous studies has varied from 5.8 % to 52.0 %.<sup>(7-8)</sup> This variation in incidence of admissions depends upon the method of patient enrollment because patients with primary infection usually have mild symptoms and do not require hospitalization.

Small children with dengue infection have mainly primary infections,<sup>(3)</sup> and this was shown in our study that children with primary dengue infection tended to be very young.

The clinical presentation of children with primary dengue infection was different from those with secondary infection in that hepatomegaly and abdominal pain were less common in primary infection. These differences 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.<sup>(3-4)</sup> Our study results were similar to a previous study<sup>(8)</sup> that demonstrated that bleeding in patients with primary and secondary dengue infections was not significantly different. The gastrointestinal tract was the most common site of bleeding in this study whereas skin bleeding was more commonly found in previous studies.<sup>(3-4)</sup>

The severity of primary and secondary infection in these patients was not different. Shock (classified as DHF grade 3 and 4) can occur in children aged 6-12 months with primary dengue infection when passive antibody levels from the mother are below the protective level. Similar to secondary infection, antibody response is enhanced after the first dengue virus infection.<sup>(9)</sup>

The level of  $Hct_{max}$  in patients with primary infection was significantly lower than those with secondary infection. This is probably due to the lower normal value of Hct in small children.<sup>(10)</sup> The results

in this study were similar to previous studies: <sup>(11-12)</sup> the percentage and absolute number of atypical lymphocytes in children with primary infection was significantly lower than secondary dengue infection. Even though the platelet<sub>mm</sub> among children with primary infection was significantly lower than that of children with secondary infection, the occurrence of bleeding was not different between primary and secondary dengue infection groups.

This study has emphasized that primary dengue infection is not uncommon and is less severe than secondary disease. Clinical presentation and laboratory findings in primary infection are different to those in children with secondary infection.

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