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

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platelet count (plt) were 41.1 percent and 81,100/mm³ 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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Received for publication. November 15, 2001.
วัตถุประสงค์ : เพื่อศึกษาปรับเปลี่ยนอาการทางคลินิกและผลตรวจทางห้องปฏิบัติการของผู้ป่วยด้วยติดเชื้อไวรัสเอดส์ กับแบบปกปุญญ และแบบทุติยภูมิ
สถานที่ที่ทำการศึกษา : ภูธรและสถานที่ส่งเสริมสุขภาพ จุดหลักภูมิ นราธิวาส
รูปแบบการวิจัย : การศึกษาเชิงพรรณนา
ผู้ป่วยที่ได้รับการศึกษา : ผู้ป่วยที่มีเริ่มต้นด้วยติดเชื้อไวรัสเอดส์ และรับยาคุมวัณโรคในท้องผ้าตกุน โรงพยาบาลจุฬาลงกรณ์
ในปี พ.ศ. 2539 จำนวน 92 คน
วิธีการศึกษา วัตถุผล : ทำการศึกษาการเปลี่ยนแปลงของผู้ป่วยในแง่กายภาพ อาการทางคลินิก ผลการตรวจทางห้องปฏิบัติการ ความรู้ของโรค และผลการรักษา
ผลการศึกษา : จากผู้ป่วยที่เป็นติดเชื้อไวรัสเอดส์ จำนวน 92 คนพบว่า 27 คน (ร้อยละ 29.3)
เป็นการติดเชื้อแบบปญญ และเพศชาย 13 คน เลสเบียน 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 ≥ 10 ปี ตามลำดับ อายุ
ทางคลินิกได้แก่ อาการไข้温度ระดับ (ร้อยละ 74.1), การทดสอบทุติยภูมิให้
ผลบวก (ร้อยละ 72.7), อาเจียน (ร้อยละ 10.4), ตับโต (ร้อยละ 44.4),
ปวดหัว (ร้อยละ 11.1) และตาแดง (ร้อยละ 7.4) ตำแหน่งของเสียงระดับ
ทบทวนได้แก่ ระบบทางเดินอาหาร (ร้อยละ 44.0), ภูมินิ่ง (ร้อยละ 40.7)
และเสียบ (ร้อยละ 11.1) ค่าเลือดของสมาคริดสูงคุณและจำนวนแอนติเลือด
ต่ำสุดเท่ากับ 41.1 เบอร์ชันด์ และ 80,000/mm3.ตามลำดับ สามารถ
จำแนกผู้ป่วยตามความรุนแรงของโรคได้เป็นภัตตา 1, 2, 3 และ 4 ติดเป็น
ร้อยละ 44.4, 44.4, 7.4 และ 3.1 ตามลำดับ ไม่มีผู้ป่วยเสียชีวิตจากการ
ศึกษา
เมื่อเริ่มต้นด้วยป่วยที่มีการติดเชื้อแบบปญญ มีจำนวน 65 คน
(ร้อยละ 70.7) ผู้ป่วยที่มีการติดเชื้อแบบปญญ มีอายุน้อยกว่าพบการติด
และป่วยเริ่มต้นน้อยกว่ายังมีป่วยสูงสุดทางคลินิก ค่าเลือดของสมาคริด
ต่ำสุดและติดเชื้อไวรัสเอดส์ ซึ่งมีการติดเชื้อแบบปญญ พบใน
ขณะที่จำแนกผู้ป่วยด้วยติดเชื้อไวรัสเอดส์

วิจารณ์และสรุป : การศึกษาไม่แสดงให้เห็นว่าผู้ป่วยที่มีการติดเชื้อไวรัสเอดส์ แบบปญญ มีได้ไม่
น้อยและมีอาการไม่ชัดเจนมาก อาการทางคลินิกและผลการตรวจทางห้อง
ปฏิบัติการมีความแตกต่างบางประการจากผู้ป่วยที่มีการติดเชื้อแบบ
ทุติยภูมิ
Dengue infection is a major public health problem affecting children in the Southeast Asia and the Western Pacific Region.\(^{(1)}\) The severity of disease depends on several factors such as the viral serotype,\(^{(2)}\) age of the patient\(^{(3-4)}\) 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.\(^{(5-6)}\) 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.**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Primary Infection</th>
<th>Secondary Infection</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>3 (11.1)</td>
<td>0 (0.0)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>1 - 4</td>
<td>8 (29.6)</td>
<td>7 (10.8)</td>
<td></td>
</tr>
<tr>
<td>5 - 9</td>
<td>7 (25.9)</td>
<td>28 (43.1)</td>
<td></td>
</tr>
<tr>
<td>10 - 14</td>
<td>9 (30.0)</td>
<td>30 (46.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>27(100.0)</td>
<td>65(100.0)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Symptoms and signs of patients with primary and secondary dengue infection.

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

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<sub>max</sub>) and minimal platelet count (plt<sub>min</sub>) 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.

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Primary infection</th>
<th>Secondary infection</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct&lt;sub&gt;max&lt;/sub&gt; (%)</td>
<td>41.1</td>
<td>44.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Hct&lt;sub&gt;min&lt;/sub&gt; (%)</td>
<td>34.9</td>
<td>36.6</td>
<td>NS</td>
</tr>
<tr>
<td>Wbc (cells/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>5,300</td>
<td>5,900</td>
<td>NS</td>
</tr>
<tr>
<td>% PMN</td>
<td>50.5</td>
<td>48.6</td>
<td>NS</td>
</tr>
<tr>
<td>% L</td>
<td>38.6</td>
<td>33.7</td>
<td>NS</td>
</tr>
<tr>
<td>% Mo</td>
<td>5.2</td>
<td>6.2</td>
<td>NS</td>
</tr>
<tr>
<td>% AL</td>
<td>7.6 ± 7.1</td>
<td>9.4 ± 9.5</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Platelet&lt;sub&gt;max&lt;/sub&gt; (/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>157,000</td>
<td>100,500</td>
<td>NS</td>
</tr>
<tr>
<td>Platelet&lt;sub&gt;min&lt;/sub&gt; (/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>81,100</td>
<td>53,400</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Na&lt;sub&gt;min&lt;/sub&gt; (mEq/L)</td>
<td>135.2</td>
<td>132.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Disease grading</th>
<th>Primary infection</th>
<th>Secondary infection</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>DHF grade 1</td>
<td>12 (44.4)</td>
<td>20 (30.8)</td>
<td>NS</td>
</tr>
<tr>
<td>grade 2</td>
<td>12 (44.4)</td>
<td>29 (44.6)</td>
<td>NS</td>
</tr>
<tr>
<td>grade 3</td>
<td>2 (7.4)</td>
<td>14 (21.5)</td>
<td>NS</td>
</tr>
<tr>
<td>grade 4</td>
<td>1 (3.7)</td>
<td>2 (3.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

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 ph_{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 %.\(^7\)\(^8\) 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,\(^3\) 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.\(^3\)-\(^4\) Our study results were similar to a previous study\(^6\) 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.\(^3\)-\(^4\)

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.\(^9\)

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.\(^10\) The results
in this study were similar to previous studies: \(^{(11-12)}\)
the percentage and absolute number of atypical lymphocytes in children with primary infection was significantly lower than secondary dengue infection. Even though the platelet count 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.

References