DIFFERENTIATING DENGUE VIRUS INFECTION FROM SCRUB TYPHUS IN THAI ADULTS WITH FEVER

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Abstract. Dengue fever and scrub typhus are common infections in Asia that often present as acute febrile illness of unclear etiology. We prospectively evaluated febrile adults presenting to the outpatient department of a hospital in northern Thailand to attempt to identify distinguishing characteristics between the two infections. Fifty-four patients were infected with scrub typhus and 35 were infected with dengue virus. Dengue virus infection was associated with hemorrhagic manifestations, particularly bleeding from the gums, which was reported by 27% of the dengue patients, but by none of the scrub typhus patients (P < 0.001, by Fisher’s exact test). A low platelet count (< 140,000/mm³) and low white blood cell count (< 5,000/mm³) were strongly associated with dengue infections: odds ratio = 26.3 (95% confidence interval [CI] = 7.4–93.2) for platelet count and 8.2 (95% CI = 2.6–25.5) for leukocyte count. Prospective evaluations of the usefulness of these simple criteria to differentiate scrub typhus from dengue infection are needed in other areas, particularly where rapid confirmatory diagnostic tests are not available.

INTRODUCTION

Dengue fever is common in Asian adults and often presents as an acute febrile illness of unclear origin.1–5 *Orientia tsutsugamushi*, the etiologic agent of scrub typhus, is also a common cause of acute febrile illness of unclear origin in Asia.6 We therefore prospectively collected data on admission clinical and laboratory findings from adult Thai patients with dengue fever or scrub typhus to identify potentially useful parameters for differentiating these two infections.

MATERIALS AND METHODS

Adult, febrile patients seronegative for human immunodeficiency virus who presented to Chiangrai Regional Hospital in northern Thailand during the rainy season of 1991 and provided informed consent were tested for scrub typhus and dengue virus. Standardized code sheets were completed and complete blood counts were made in individuals with less than two weeks of fever, no malarial parasites, no known chronic medical problems, and no history of acquired immunodeficiency syndrome–defining illnesses.

IgM and IgG antibodies to dengue virus (any of the four serotypes, not distinguished by the serologic test) and Japanese encephalitis virus were measured at the acute stage and four weeks later by an antibody-capture enzyme immunoassay.7 Recent (occurring in the previous two months) flavivirus infection was diagnosed for any individual with an IgM result > 40 units. Infection was classified as due to dengue virus or Japanese encephalitis virus depending on the relative amounts of virus-specific IgM.7 Scrub typhus was diagnosed if indirect immunoperoxidase IgG antibody titers were ≥1:1,600 or IgM titers were ≥1:400 in a single acute specimen, or if there was a four-fold or greater increase in antibody titer between acute and convalescent serum samples.8 Statistical analyses were performed using Fisher’s exact test for categorical variables and the Mann-Whitney U test for continuous variables.

RESULTS

During the four-month study period, 54 patients were diagnosed with *O. tsutsugamushi* infection, and nine died. Thirty-five dengue virus infections were confirmed, and there was one death. The patient who died was initially not suspected of having dengue, was discharged from hospital, and then returned with irreversible shock secondary to upper gastrointestinal bleeding. The admission characteristics of patients with scrub typhus were similar to those with dengue fever (Table 1). However, dengue patients had a shorter fever history (median = 4 days, range = 2–11 days) than individuals with scrub typhus (median = 9 days, range = 2–14 days; P < 0.001, by Mann-Whitney U test). Hemorrhagic manifestations were more common in dengue patients (53% versus 13%; P < 0.001, by Fisher’s exact test).

The median platelet count (Figure 1) in the patients with dengue (72,000/mm³, interquartile range (IQR) = 40,000–90,000/mm³) was significantly lower than that for the scrub typhus group (median = 206,000/mm³, IQR = 142,000–240,000/mm³; P < 0.001, by Mann-Whitney U test). The median white blood cell count in dengue patients (4,950/mm³, IQR = 3,500–6,200/mm³) was also lower than that of the individuals infected with *O. tsutsugamushi* (9,600/mm³, IQR = 5,900–12,200/mm³; P < 0.001, by Mann-Whitney U test). Median hematocrit was higher in the dengue group (43.0%, IQR = 40.0–49.0%) than in the scrub typhus group (38.5%, IQR = 34.0–42.0%; P < 0.001, by Mann-Whitney U test). The age-adjusted odds ratios (ORs) were 26.3 (95% confidence interval [CI] = 7.4–93.2) for the association of a platelet

<table>
<thead>
<tr>
<th>Characteristics on admission of the patients studied</th>
<th>Dengue (n = 54)</th>
<th>Scrub typhus (n = 54)</th>
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</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>31 (16–56)</td>
<td>35 (16–73)</td>
</tr>
<tr>
<td>Median days of fever (range)</td>
<td>4 (2–11)</td>
<td>9 (2–14)*</td>
</tr>
<tr>
<td>Males</td>
<td>21 (60%)</td>
<td>32 (59%)</td>
</tr>
<tr>
<td>Indoor occupation (student, housewife, office work)</td>
<td>18 (51%)</td>
<td>8 (15%)*</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>23 (66%)</td>
<td>40 (74%)</td>
</tr>
<tr>
<td>Hemorrhagic manifestations</td>
<td>19 (54%)</td>
<td>7 (13%)*</td>
</tr>
<tr>
<td>Bleeding gums</td>
<td>9 (26%)</td>
<td>0*</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>3 (9%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Hematemesis and/or melena</td>
<td>2 (6%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Erythematous rash</td>
<td>5 (14%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Pettechie and/or ecchymoses</td>
<td>3 (9%)</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

*P < 0.001.
count less than 140,000/mm³ and dengue and 8.2 (95% CI = 2.6–25.5) for the association of a leukocyte count less than 5,000/mm³ and dengue.

**DISCUSSION**

The results of this investigation are consistent with anecdotal reports that both scrub typhus and dengue virus infections are common causes of acute febrile illness of unclear origin in Chiangrai in northern Thailand, and affirm the importance of dengue as an infection of Asian adults. Diagnostic test results, even when available, rarely arrive in time to affect treatment decisions in areas endemic for dengue and scrub typhus. However, our study results indicate potentially useful distinguishing features between the two infections. Hemorrhagic manifestations were more common with dengue (Table 1), and bleeding from the gums was reported only by dengue patients (27% versus 0%; \( P < 0.001 \), by Fisher’s exact test). Median platelet counts were significantly lower in dengue patients: the OR for a count less than 140,000/mm³ was 26.3 (95% CI = 7.4–93.2). The OR for the association of a leukocyte count less than 5,000/mm³ and dengue was 8.2 (95% CI = 2.6–25.5).

Our study findings are useful for clinicians working in areas where dengue and scrub typhus are common. At Chiangrai hospital, scrub typhus and dengue infection are the two most frequently listed presumptive diagnoses in patients who present with fever of unclear etiology. Early management of acute nonspecific febrile illnesses at this hospital is based on an estimation of which of these two diagnoses is more likely. The objective markers we report could therefore help patient management. There is currently no specific antiviral therapy for dengue virus infection, but the introduction of intensive intravenous fluid replacement in dengue shock syndrome led to a marked reduction in the mortality rate in pediatric centers in Southeast Asia from approximately 20% to 2%.⁹ Patients suspected of dengue fever can be monitored closely in the hospital for upper gastrointestinal bleeding,¹ the cause of death in the dengue-infected patient in our series. Suspicion of scrub typhus permits early antibiotic treatment, which reduces the mortality of infection with *O. tsutsugamushi*.⁶ Delayed diagnosis is likely to have contributed to the high case fatality rate for scrub typhus in this series, although antibiotic resistance may also have played a role.¹⁰,¹¹

Our findings suggest ways for clinicians to distinguish between these two infections, but they must be confirmed by
prospective studies in other regions of Asia. Simple objective measures could increase the clinical suspicion of these two infections and thereby lower their morbidity and mortality in areas where rapid diagnostic tests are not available. However, potentially life-saving antibiotics should not be withheld unless scrub typhus is certain to be absent.

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