Can Doctors Make an Accurate Diagnosis of Dengue Infections at an Early Stage?

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Abstract

As part of a multi-centre, prospective study of dengue pathophysiology between 1994 -1997, clinical findings and simple laboratory tests were evaluated to find early indicators for the diagnosis of dengue infections so that control actions could be taken as early as possible to prevent the spread of dengue in the community. Six hundred and forty-nine febrile children with a flushed face and without signs of localized infection were followed as in-patients. Three hundred and eighteen children were confirmed to have dengue: 176 dengue fever (DF), and 142 dengue haemorrhagic fever (DHF); another 331 children had other, self-limiting febrile illness (OFI).

Tourniquet test (TT) positive and leukopenia (WBC ≤ 5,000 cells/cu.mm.) were the two screening tests that helped in the early clinical diagnosis of dengue infections.

Studies revealed that TT positive or leukopenia were the two tests that had a high sensitivity of about 90% for the diagnosis of dengue patients, but their specificity and positive predictive value (PPV) were only 50-60% and 60-70% respectively. If the two tests are combined, the sensitivity gets reduced to 74% while the specificity and PPV are increased to 85% and 83% respectively. For early, effective and rapid control of dengue outbreak, TT or leukopenia is a good indicator for initiating immediate control measures. TT positive with leukopenia is also a good indicator for immediate control measures, 83% of this immediate control measures will be necessary but about 26% of dengue cases that have no TT positive with leukopenia will be missed.

Key words: Dengue haemorrhagic fever, Tourniquet test, Leukopenia, Thailand
Introduction

Dengue infections have been one of the major diseases affecting children in Thailand for more than 40 years. First dengue epidemic was recorded with 2,158 cases in 1958 and reached a peak in 1987 when there were 174,285 cases reported. The last two epidemics occurred in two consecutive years, 1997 and 1998, when 101,689 cases and 127,189 cases, respectively, were reported. Although the case-fatality rate has been reduced from 14% (1958) to 0.34% (1998), the number of deaths was higher, from 300 deaths in 1958 to 464 deaths in 1998. Adults were affected more than expected, and their share of deaths was to about 20% in 1998.

During the last two epidemics, one of the major reasons for not taking control measures was the delay in case reporting. This delay in reporting was due to clinicians being reluctant to report dengue haemorrhagic fever (DHF) cases without serological confirmation. The disease control authorities were doubtful about the clinical diagnosis as most of the criteria used was non-specific. They preferred to wait for confirmed cases before taking control actions.

This study is a part of the collaborative dengue pathophysiology studies and was planned to find simple clinical and/or laboratory indicators for the early diagnosis of dengue infections that would help speed up the reporting system so that control actions would start early and be effective to arrest the spread of the outbreak.

Materials and methods

Twelve febrile patients were enrolled each week between 1994 and 1997 from the outpatient department of two hospitals, Children’s Hospital in Bangkok and Kampangpet Provincial Hospital. The patients met the following criteria: age 6 months to 15 years, had temperature ≥ 38.5° Celsius for < 72 hours, had facial flushing and no obvious source of infection. Parents or guardians of all patients had to sign an informed consent before participating in this project. Patients who had signs of shock or had underlying diseases were excluded from the study.

All the patients were admitted to hospital for close observation. Study physicians did the history-taking and physical examination, including tourniquet test (TT), everyday. Daily phlebotomy was done every morning for CBC, dengue serological (ELISA and Haemagglutination Inhibition test), virological (mosquito inoculation technique) and immunological study for five days or until one day after defervescence (whichever came first). Right lateral decubitus chest films to detect pleural effusion were done one day after defervescence. Blood studies were repeated on study day 9 when the patients came for a follow up. Liver function test and coagulogram were studied on the first study day, on the day of defervescence or one day after and at the time of follow-up.

Patients were classified as DF and DHF according to the WHO criteria. DHF severity was also classified according to the WHO criteria. Patients with bacterial or other definite infections other than dengue were excluded from the study. Patients with self-limited febrile illness without definite sources of infection were classified as other febrile illness (OFI).
Comparisons between the clinical and simple laboratory indicators for the two groups of patients, DHF/DF and OFI, were done. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of each indicator(s) for the diagnosis of dengue infection were calculated using serological and/or virological tests as the standard diagnosis of dengue infections\(^5\).

### Results

#### Patients’ profile

There were 649 patients who were eligible for this study. Among the 318 dengue patients, 176 were of DF and 142 of DHF (42 DHF grade I, 78 DHF grade II, and 22 DHF grade III). There were 331 patients in the OFI group. The male/female ratios for dengue and OFI patients were 1: 1.12 and 1:1.45, respectively. The mean ages for DF, DHF grade I, DHF grade II, DHF grade III and OFI patients were 8.01 (± 2.93), 8.25 (±3.58), 8.9 (± 2.86), 7.48 (± 2.4) and 6.59 (± 3.15) years, respectively.

#### Serology

A total of 313 patients (98.43%) were confirmed serologically: 21.09% were primary while 78.91% were secondary dengue infections. Primary and secondary dengue infections were found in 30.64% and 69.36% of DF patients while 9.29% and 90.71% of the primary and secondary dengue infections were found in DHF patients (Table 1).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Primary (%)</th>
<th>Secondary (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DF</td>
<td>53 (30.64)</td>
<td>120 (69.36)</td>
<td>173 (55.27)</td>
</tr>
<tr>
<td>DHF</td>
<td>13 (9.29)</td>
<td>127 (90.71)</td>
<td>140 (44.73)</td>
</tr>
<tr>
<td>Total</td>
<td>66 (21.09)</td>
<td>247 (78.91)</td>
<td>313 (100)</td>
</tr>
</tbody>
</table>

#### Virology

A total of 302 patients (94.96%) had dengue viral isolation: 39.74% were type 1, 23.18% type 2, 28.15% type 3, and 8.61% were type 4, while 0.33% could not be identified (Table 2).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Den 1 (%)</th>
<th>Den 2 (%)</th>
<th>Den 3 (%)</th>
<th>Den 4 (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DF</td>
<td>75 (39.74)</td>
<td>29 (23.18)</td>
<td>47 (28.15)</td>
<td>15 (8.61)</td>
<td>166</td>
</tr>
<tr>
<td>DHF</td>
<td>45</td>
<td>41</td>
<td>38</td>
<td>11</td>
<td>135</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>70</td>
<td>85</td>
<td>26</td>
<td>301</td>
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#### Fever

The mean duration of fever for DF, DHF grade I, DHF grade II, DHF grade III and OFI patients was 4.08 days (± 1.19), 4.51 days (± 0.90), 4.38 days (± 0.99), 5.27 days (± 1.72) and 3.13 days (± 1.69), respectively. Among DHF patients 2.16% had fever for 2 days, 10.07% had fever for 3 days, 41.01% had fever for 4 days, 30.94% had fever for 5 days, 11.51% had fever for 6 days and 2.16% had fever for 7 days (Figure 1).
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Figure 1. Duration of Fever

Figure 2. Tourniquet test
**Tourniquet test**

The percentage of TT positive (≥ 10 petechiae/square inch) in DF, DHF grade I, DHF grade II, DHF grade III and OFI patients was 87.50%, 90.48%, 94.87%, 90.91% and 51.96%, respectively.

In dengue patients TT was positive in 45.59%, 55.56%, 67.27% and 77.82% of cases on day 4, 3, 2, 1 before defervescence and 89.92% on the day of defervescence. DHF patients had a much higher percentage of TT positive as compared to DF patients (Figure 2).

The sensitivity, specificity, PPV and NPV for TT for the diagnosis of dengue infections were 89.94%, 48.04%, 62.45% and 83.25%, respectively (Table 3).

<table>
<thead>
<tr>
<th>Table 3. Comparison of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) between dengue and OFI patients in the diagnosis of dengue infections</th>
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<tr>
<td>TT positive</td>
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<tr>
<td>%</td>
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<tr>
<td>Sensitivity</td>
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<tr>
<td>Specificity</td>
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<tr>
<td>PPV</td>
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<td>NPV</td>
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</table>

**WBC**

The mean WBC in DF, DHF grade I, DHF grade II, DHF grade III and OFI patients were 4,929 (± 2,705); 5,147 (± 2,667); 4,808 (± 2,420); 5,576 (± 2,969) and 8,754 (± 4,860) cells/cu.mm, respectively.
The mean WBC in DF, DHF grade I, DHF grade II, DHF grade III and OFI patients one day before defervescence were 3,834 (± 2,216); 3,870 (± 1,553); 3,257 (± 1,583); 4,595 (± 2,415) and 9,743 (± 6,391) cells/cu.mm, respectively (Figure 3).

The percentage of leukopenia (≤ 5,000 cells/cu.mm) found in DF, DHF grade I, DHF grade II, DHF grade III and OFI patients was 89.77%, 95.24%, 92.31%, 90.91% and 40.18%, respectively.

The sensitivity, specificity, PPV and NPV for leukopenia (≤ 5,000 cells/cu.mm.) for the diagnosis of dengue infections were 91.19, 59.82, 68.56 and 87.61%, respectively (Table 3).

Tourniquet test and leukopenia (≤ 5,000 cells/cu.mm)

The percentage of TT positive and leukopenia found in DF, DHF grade I, DHF grade II, DHF grade III and OFI patients was 72.16%, 73.81%, 80.77%, 68.18% and 14.50%, respectively.

The sensitivity, specificity, PPV and NPV for TT positive and leukopenia for the diagnosis of dengue infections were 74.21%, 85.50%, 83.10% and 77.53%, respectively (Table 3).

Aspartate aminotransferase (AST)

The mean values of AST in DF, DHF grade I, DHF grade II, DHF grade III and OFI patients were 61.65 (± 56.36), 68.45 (± 52.20), 99.04 (± 112.61), 162.43 (± 222.14) and 38.05 (± 18.42) units(U), respectively. The percentage of AST > 40 U in DF, DHF and OFI patients was 90.91%, 98.59% and 57.1%, respectively (Figure 4).

The percentage of AST > 60 U in DF, DHF and OFI patients were 63.07, 92.96 and 15.1%, respectively.

The sensitivity, specificity, PPV and NPV for AST (≥ 60U) for the diagnosis of dengue infections were 76.42%, 84.89%, 82.89% and 79.93%, respectively.

Alanine aminotransferase (ALT):

The mean values of ALT in DF, DHF grade I, DHF grade II, DHF grade III and OFI patients were 33.71 (± 28.77), 32.43 (± 21.31), 53.09 (± 9.98), 69.45 (± 80.27) and 21.72 (± 14.27) units(U), respectively.

The percentage of ALT > 40 U in DF, DHF and OFI patients was 53.98%, 77.47% and 12.69%, respectively (Figure 5).

The percentage of ALT > 60 U in DF, DHF and OFI patients was 28.98%, 47.89% and 5.10%, respectively.

The sensitivity, specificity, PPV and NPV for ALT (≥ 60U) for the diagnosis of dengue infections were 37.42%, 94.86%, 87.50% and 61.21%, respectively.

Discussion

Males and females are affected equally by dengue viruses. The peak age of contracting dengue infection was between 5 and 9 years\(^4,5\). As reported earlier, 90.71% of DHF patients in this study had secondary dengue infection while 69.36% of DF patients had secondary dengue infection \(^4,5\).
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Figure 4. Percentage of patients with elevation of AST

Figure 5. Percentage of patients with elevation of ALT
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All the four dengue serotypes were found. DEN-1 was more predominant while DEN-4 was less common.

OFI patients tended to have a shorter duration of fever (3 days) than dengue patients (4-5 days). The shortest duration of fever for DHF patients was 2 days (2.16%). Most of the DHF patients (72%) had fever for 4-5 days. This is very important and needs to be emphasized to the clinician that the earliest day of shock in DHF patient could be on day 3 of the illness, i.e. one day after defervescence, and the critical day for most DHF patients would be the fifth or sixth day of their dengue illness.

TT positive alone has the sensitivity of 89.94% for the diagnosis of dengue infections as compared to the previous finding of 97.1%. PPV of TT positive is 62.45%. Specificity is 48.04% as compared to the previous report of 97.2% because 51.96% of other viral infections in this study had positive TT while only a few cases of viral infection were included in the previous study. Experienced clinicians however can differentiate dengue clinically from other viral infections on the basis of TT positive as most of dengue patients have bigger petechiae size as compared to the very fine petechiae in other viral infections. About half of the dengue patients had positive TT on the first day of illness. The percentage of TT positive in dengue patients increased everyday and 78% had positive TT one day prior to defervescence, which could help clinicians to make presumptive clinical diagnosis before they entered into critical periods. (About 90% of DHF patients had TT positive before they had defervescence.)

The mean WBC in dengue patients was lower than in the OFI group. A mean WBC of ≤ 5,000 cells/cu.mm was found in all DHF patients one day prior to defervescence as reported previously, so this is a good indicator to warn clinicians that the patient is near to the critical stage of the disease. Also, leukopenia of ≤ 5,000 cells/cu.mm had the sensitivity for the diagnosis of dengue infection = 91.19%, specificity = 59.82%, and PPV = 68.56%. Although leukopenia had a little bit better sensitivity, specificity and PPV than TT, but it occurred much later in the course of the illness as compared to the occurrence of positive TT.

When we combined the findings of TT positive and leukopenia, the sensitivity for the diagnosis of dengue infection was reduced to 74.21%, but the specificity and PPV increased to 85.50% and 83.19%, respectively.

Since 63.07% and 92.96% of DF and DHF patients had AST > 60 U while only 15.1% of OFI patients had it, AST is also a good indicator for differentiating dengue from other viral illnesses. AST elevation occurred as early as in the first few days of the illness. AST > 60 U had the sensitivity, specificity and PPV of 76.42%, 84.89% and 82.89%. AST cannot be done in all small hospitals, so it may not be as useful as TT or leukopenia for early diagnosis of dengue infection. When DHF patients present with encephalopathy, AST/ALT should be done. If the values exceed 200 U, they suggest that the patient may have hepatic dysfunction/ hepatic encephalopathy.
In this study, very few dengue patients had petechiae so it did not help in early clinical diagnosis. Platelet counts \( \leq 100,000 \text{ cells/cu.mm} \) occurred late in the course of dengue illness, which did not help in early diagnosis.

**Conclusion**

From this study it is evident that TT positive is the earliest test that occurs in dengue illness to make clinicians think of dengue infection. If they report dengue infection as soon as they find TT positive, and control activities are initiated within 24 hours, it is most likely that the spread of dengue outbreak can be checked and controlled without much damage. Clinicians should also report dengue infection when they see leukopenia in febrile patients (leukopenia usually occurs later than TT positive). If control actions are taken as soon as TT positive or leukopenia are observed, DHF outbreaks can be substantially controlled up to 90% (sensitivity), but the control activities may be unnecessary in the presence of 31% for leukopenia and 38% for TT (100-PPV).

When outbreak control activities are undertaken with the finding of TT positive and leukopenia together, which occur later than TT positive or leukopenia alone, the control actions will provide only 74.21% (sensitivity) of coverage for dengue infection, but the actions are unnecessary at 14% level (100-PPV).

To control dengue outbreaks more effectively, we suggest that clinicians should report dengue cases as soon as they find TT positive because it is most rapid and has the highest sensitivity. Nevertheless, control strategies for dengue outbreak should be thoroughly examined by the authorities in order to get the maximum benefit for the manpower and the budget available in that time frame.

**References**