CLINICAL FEATURES OF 62 IMPORTED CASES OF DENGUE FEVER IN JAPAN

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Abstract. To describe the clinical features of dengue cases in Japan, a retrospective study was conducted on 62 laboratory-confirmed Japanese dengue cases presented to Tokyo Metropolitan Komagome Hospital between 1985 and 2000. Age distribution was from 18 to 62 years old (mean, 31.5 years). All cases were imported from abroad and diagnosed as dengue fever. Clinical manifestations included fever (100%), headache (90%), and skin rash (82%). Laboratory examinations revealed leukocytopenia (71%), thrombocytopenia (57%), elevated levels of serum aspartate aminotransferase (78%), and lactate dehydrogenase (71%). Antibody responses were consistent with that of secondary flavivirus infection in 60% of cases. Severity of symptoms in patients with primary dengue antibody response and those with secondary flavivirus antibody responses didn’t show statistical significance. Dengue virus infection should be taken into consideration in the differential diagnosis of febrile patients who recently entered Japan from tropical or subtropical countries.

INTRODUCTION

Dengue fever (DF)/dengue hemorrhagic fever (DHF) is an acute febrile illness caused by dengue viruses. Dengue viruses, which consist of four serotypes (DEN1, 2, 3, and 4), belong to the family Flaviviridae. Dengue viruses are mosquito-borne and principally transmitted by Aedes aegypti mosquitoes that thrive close to human habitats and adapt well to urban environments. DF, a common form of febrile illness caused by dengue viruses, is a global health problem in the tropics and subtropics. DHF is the severe form of illness caused by dengue viruses. DHF is primarily a disease of children and the leading cause of hospitalization and death among children in Asian countries.

In Japan, there were large epidemics between 1942 and 1944 in Nagasaki, Kobe, and Osaka, originating in the repatriation from the tropics during the Second World War. A total of 23,338 cases were reported in Nagasaki and 1,134 were reported in Kobe. Domestic transmission has not been reported in Japan since 1946. The description of imported dengue cases has been limited to a relatively small number of cases.

Because of the increase in air travel to the tropics and subtropics, it is assumed that a larger number of overseas travelers are at risk to dengue virus infection. In 2000, 17.8 million Japanese went abroad, and > 2.6 million went to Southeast Asia. There is a possibility that a substantial number of dengue cases remain undiagnosed.

Most of the population are immune to Japanese encephalitis (JE) virus because of repeated JE vaccination and possibly occasional boost by JE virus in Japan. It has been reported that immunity caused by previous flavivirus infection or immunization modulates immune response when infected with dengue virus. The aim of this study was to precisely define the clinical features of dengue virus infections among Japanese travelers coming back from overseas countries, most of whom have immunity to the JE virus.

MATERIALS AND METHODS

The study was conducted using the data obtained from the hospital case records of Japanese patients diagnosed as DF at Tokyo Metropolitan Komagome Hospital between 1985 and 2000. This hospital is a metropolitan-based general hospital with 800 beds in Tokyo, and specializes in cancer and infectious diseases. The department of infectious diseases has 30 beds and a special outpatient unit for those including travelers and patients with HIV. The most common causes of visit are fever, diarrhea, and rash.

Dengue virus infections were confirmed by 4-fold or greater rise in hemagglutination inhibition (HI) antibody titers to DEN2 in paired serum samples or by detection of HI antibody titers ≥ 1:320 in single serum samples. Since 1992, IgM-capture enzyme-linked immunosorbent assay (ELISA) has been routinely performed on serologically positive cases. Since 1992, reverse transcriptase-polymerase chain reaction (RT-PCR) has been performed on serologically positive cases to determine the serotype. Laboratory diagnosis of dengue virus infection was performed at the National Institute of Infectious Diseases, Tokyo, Japan, as previously reported.

Data were analyzed with EpiInfo (Version 6.04d; Centers for Diseases Control and Prevention, Atlanta, GA). The χ² test was used to compare clinical features. The Wilcoxon rank sum test was used to test for non-parametric data analysis. P < 0.05 was considered significant.

RESULTS

A total of 62 Japanese cases (44 men and 18 women) were confirmed to have DF during the study period. All the cases were treated as DF based on clinical diagnosis and later confirmed by HI antibody test. No cases were treated for other diseases before establishment of DF. The number of cases increased in spring and summer when a large number of Japanese people travel abroad.

The mean age was 31.5 ± 10.5 years, with a range from 18 to 62 years. Forty-eight cases (75%) were in their 20s and 30s. Presumptive places of infection are shown in Table 1. Forty-two cases (68%) were infected in Southeast Asia. The length of stay in the presumptive countries of infection ranged from 3 to 1,201 days, the median period being 17 days. Twenty-one

470
cases (34%) developed illness during the travel. The remaining 41 cases (66%) developed illness after returning home, and the mean duration between the last day of travel (assigned as day 0) and the onset of fever was 3.2 ± 3.3 days (range: 0–18 days).

The clinical manifestations are shown in Table 2. Fever was detected in all the cases, and the mean duration of fever was 5.6 ± 2.0 days (range: 1–10 days). In some cases, fever was modulated by antipyretics given by doctors who saw the patients before us. Small macular rashes similar to those of rubella or measles were seen in 41 cases (arms and/or legs, 31 cases; trunk, arms and/or legs, 7 cases; face, arms, and legs: 3 cases). The mean time between onset of fever and appearance of skin rash was 5.7 days (range: −3–9 days). Skin itching at defervescence was present in 14 cases (arms and/or legs, 3 cases). The clinical manifestations are shown in Table 2. Fever was detected in all the cases, and the mean duration of fever was 5.6 ± 2.0 days (range: 1–10 days). In some cases, fever was modulated by antipyretics given by doctors who saw the patients before us. Small macular rashes similar to those of rubella or measles were seen in 41 cases (arms and/or legs, 31 cases; trunk, arms and/or legs, 7 cases; face, arms, and legs: 3 cases). The mean time between onset of fever and appearance of skin rash was 5.7 days (range: −3–9 days). Skin itching at defervescence was present in 14 cases (arms and/or legs, 3 cases).

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Percent (‰) positive cases (positive/numbers)</th>
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<tbody>
<tr>
<td>Fever</td>
<td>100 (62/62)</td>
</tr>
<tr>
<td>Headache</td>
<td>90 (54/60)</td>
</tr>
<tr>
<td>Skin rashes</td>
<td>82 (41/50)</td>
</tr>
<tr>
<td>Itchy of the skin</td>
<td>74 (14/19)</td>
</tr>
<tr>
<td>Profuse sweating</td>
<td>61 (19/31)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>60 (31/49)</td>
</tr>
<tr>
<td>Platelet count &lt; 100,000/mm³</td>
<td>57 (34/60)</td>
</tr>
<tr>
<td>Chills</td>
<td>56 (28/50)</td>
</tr>
<tr>
<td>Retroorbital pain</td>
<td>55 (24/44)</td>
</tr>
<tr>
<td>Diarrhea&lt;sup&gt;a&lt;/sup&gt;</td>
<td>53 (31/59)</td>
</tr>
<tr>
<td>Hemorrhagic manifestation</td>
<td>45 (9/20)</td>
</tr>
<tr>
<td>Tourniquet test</td>
<td>30 (7/23)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Diarrhea was defined as loose bowel movements equal to or more than twice a day.
cases; palms or soles, 6 cases; unknown, 5 cases). Hemor-
rhagic manifestations were observed in 9 cases (epistaxis, 2
cases; gingival hemorrhage, 2 cases; melena, 2 cases; all, 3
cases). Upper respiratory tract symptoms were not evident
except for one case with bacterial bronchitis who responded
good to antibiotics administration. Depression was not seen
during the observed period.

Leukocytopenia (leukocyte count < 3,500/mm$^3$) was de-
tected in 71% of the cases (41/58; the mean leukocyte count
on admission was 3,062/mm$^3$; range, 1,000–9,700/mm$^3$),
thrombocytopenia (platelet count < 100,000/mm$^3$) in 57%
(34/60; the mean platelet count was 101,400/mm$^3$; range,
10,000–298,000/mm$^3$), increased serum aspartate aminotrans-
ferase (AST) in 78% (45/58; mean AST = 82 IU/L; range,
13–375 IU/L; reference range, 11–32 IU/L), and increased
lactate dehydrogenase (LDH) in 71% (41/58; mean LDH =
336 IU/L; range, 120–1,195 IU/L; reference range, 120–220
IU/L) on admission.

Figure 1 shows the time-course of laboratory data obtained
from 62 cases. The mean leukocyte count and the mean plate-
let count reached the nadir on the sixth and eighth days of
illness, respectively. The mean AST level reached the peak on
the ninth day. The mean leukocyte and platelet counts re-
turned to the normal levels within 10 days, whereas the mean
AST level stayed at the normal range after > 3 weeks.

Figure 2 shows the time-course of HI antibody titers to
dengue and JE virus antigens in 61 cases. Thirty-seven cases
(60%) showed convalescent titers ≥ 1:2,560. These cases also
showed elevated HI antibody titers to JE virus. History of JE
vaccination was not asked to all the cases. Dengue virus-
specific IgM was positive in 21 of 22 tested cases, using blood
specimens drawn between the first and twentieth days of ill-
ness. RT-PCR determined dengue serotypes in 19 of 27 tested
cases (Table 1).

Primary and secondary infections were determined, accord-
ing to World Health Organization (WHO) criteria: primary
dengue antibody response, HI antibody titer ≥ 1:1,280; sec-
ondary flavivirus antibody response, convalescent HI anti-
body titer $\geq 1,2560$. Twenty-five cases (40%) were determined to be primary dengue antibody response and 37 (60%) to be secondary flavivirus antibody response. We compared these two groups for the clinical manifestations and laboratory tests showed in Table 2 but they didn’t show statistical significance. There were no differences in age distribution between these two groups (Table 3). These two groups were also compared for clinical features: duration of fever, tourniquet test, hemorrhagic manifestation, and platelet count (Table 4). There was no significance between two groups.

### DISCUSSION

The number of imported dengue fever cases has been increasing in our hospital in recent years. Classic DFs are characterized by fever, headaches, bone or joint and muscular pains, skin rashes, and leukopenia. Historically, DF has been called “break-bone fever” because of its intractable pain. Clinical manifestation included flu-like illness associated with fever in most of the patients. The skin rash appeared around the day of defervescence in most of the rash-positive cases. Leukopenia, thrombocytopenia, and elevation of AST or LDH, which are well-recognized features of DF, were observed in a high percentage of the cases. The changes in these laboratory markers were transient, and patients recovered accordingly.

In Japan, a national JE vaccination program has been successfully implemented, and children < 15 years old have been repeatedly vaccinated since 1954. Of all the DF cases in this study, 50 cases (81%) were born after 1954. It is reported that > 80% of the Japanese population had positive neutralizing antibody to JE virus during national surveillance. Although the history of JE vaccination or JE virus was not confirmed for all the cases, it is likely that most of the cases were immune to JE virus. Indeed, HI antibody titers were consistent with the secondary flavivirus antibody response in 60% of the cases. Our data showed that severity of symptoms in the primary dengue antibody group and secondary flavivirus antibody group didn’t show statistical significance. Previous studies reported that JE vaccination might decrease severity of subsequent DHF or protect from developing dengue illness. A larger-scaled, case control study should be performed to clarify whether immunity to JE virus has a beneficial effect on dengue virus infection.

Two cases (30- and 33-year-old women) were considered as DHF, according to the WHO case definition. Both cases showed mild hemorrhagic manifestations, platelet counts < 100,000/mm$^3$, and drop in hematocrit after fluid administration > 20%. Both cases were clinically mild and improved shortly after administration of fluid and thus were diagnosed as DF clinically. Both cases had no history to travel to endemic areas but showed secondary flavivirus antibody response.

There is no domestic dengue virus transmission today in Japan, and all DF/DHF cases were imported ones. Dengue viruses are endemic in many neighboring countries in Asia and Oceania to which many Japanese people visit for sightseeing or business. Individuals previously infected by one serotype of dengue virus may be at higher risk of developing DHF or dengue shock syndrome after secondary infection with other serotypes. Such risks should be taken into consideration for diagnosis.

DF/DHF is also a disease to be considered for differential diagnosis of other severe febrile illnesses, including malaria, typhoid and paratyphoid fever, and rickettsiosis. The symptoms in DF cases in Japan seem to be less severe than those described in the textbook. When dengue virus infection is suspected, one could avoid treatment that may cause bleeding such as aspirin administration and avoid excess treatment such as steroid administration or platelet transfusion so that the duration of hospitalization can be shortened. Skin rashes are highly suggestive that the clinical diagnosis is dengue. Laboratory tests for confirmation are recommended, especially in the cases that resemble other communicable diseases (e.g., measles or rubella). In some patients, small macular rashes resembling to those of measles or rubella with or without itchy sensation on extremities, in particular, in palms and/or soles, were the only skin manifestations.

In conclusion, DF/DHF is important not only as an infectious disease in tropical and subtropical countries but also as an imported infectious disease in countries in the temperate zone including Japan. DF/DHF should be considered in the differential diagnosis of febrile patients returning or coming from dengue-endemic countries, even when they lack typical signs and symptoms. It is possible that a substantial number of DF/DHF patients are unrecognized and under-reported at present. Under careful observation, with the appearance of skin rashes, one can suspect dengue and send blood specimens for confirmation early to avoid excess and inappropriate treatment.

### Table 3
Age distribution of patients with primary dengue antibody response and with secondary flavivirus antibody response

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Primary dengue antibody response</th>
<th>Secondary flavivirus antibody response</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–19</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>20–29</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>30–39</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>40–49</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>50–59</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>60–69</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>mean age (range)</td>
<td>29.5 (18–62)</td>
<td>32.8 (19–56)</td>
</tr>
</tbody>
</table>

### Table 4
Clinical features of patients with primary dengue antibody response and with secondary flavivirus antibody response

<table>
<thead>
<tr>
<th></th>
<th>Patients with primary dengue antibody response</th>
<th>Patients with secondary flavivirus antibody response</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean duration of fever (range)</td>
<td>5.1 days (2–9)</td>
<td>6.0 days (1–10)</td>
<td>1.55</td>
</tr>
<tr>
<td>Percent positive tourniquet test (positive/case numbers)</td>
<td>11% (1/9)</td>
<td>43% (6/14)</td>
<td>0.23</td>
</tr>
<tr>
<td>Percent positive hemorrhagic manifestation (positive/case numbers)</td>
<td>25% (2/8)</td>
<td>58% (7/12)</td>
<td>0.31</td>
</tr>
<tr>
<td>Percent cases with platelet count &lt; 100,000/mm$^3$ (positive/case numbers)</td>
<td>50% (12/24)</td>
<td>61% (22/36)</td>
<td>0.65</td>
</tr>
</tbody>
</table>
REFERENCES


