Four Cases of Autochthonous Dengue Infection in Japan and 46 Imported Cases: Characteristics of Japanese Dengue

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Abstract

Objective  A dengue outbreak occurred in Japan 2014. We investigated the characteristics of dengue infection among Japanese.

Methods  We investigated the medical charts retrospectively.

Patients  The study participants are patients who came to our clinic between 2008 and 2014.

Results  We investigated 4 domestic cases and 46 imported cases of Japanese with laboratory confirmation of dengue. Major symptoms were fever (100%), rash (86%), fatigue (84%), headache (81%), joint pain (66%), muscle pain (49%), and bleeding (6%). A late rash that appeared near the time of fever resolution was observed in 37 cases (74%). A total of 38/43 (88%) cases had low WBC count (<3,500/μL) during the febrile period, 42/48 (88%) cases had a low platelet (PLT) count (<130×10³/μL), and 44/50 (88%) cases had a C-reactive protein (CRP) <2.0 mg/dL.

Conclusion  Patients with a high fever, late rash, fever-associated leukopenia, low PLT count, low CRP, and elevated aminotransferases are generally suspected of having a dengue infection.

Key words: Dengue, Japan, autochthonous, diagnosis

(DOI: 10.2169/internalmedicine.54.4475)

Introduction

Dengue virus (DENV) infection occurs in most of the tropical and subtropical areas of the world and is one of the most prominent vector-borne infectious diseases. Over the past few decades, the incidence of dengue has increased drastically around the world. Over 2.5 billion people, over 40% of the world’s population, are now at risk of contracting dengue. It is estimated that 50-100 million dengue infections may occur worldwide every year (1). In 2013, dengue cases occurred in the state of Florida in the United States of America (USA) and in the Yunnan province in China. Japan experienced dengue outbreaks during the period of 1942-1945 in Nagasaki, Hiroshima, Kobe, and Osaka (2), but none thereafter. However, a dengue case without a patient history of visiting foreign countries was confirmed in Japan on August 27, 2014 (3). In addition, 160 cases were reported between that day and October 31, 2014. In our clinic, we experienced 5 domestic cases of dengue during this period. We describe and clarify the clinical features of the domestic and imported cases, all involving Japanese observed in our clinic.

Materials and Methods

We investigated the medical charts between 2008 and 2014. A confirmed dengue case was defined as being positive for anti-dengue IgM, serum non-structural protein 1 (NS1), and/or serum DENV RNA by polymerase chain reaction (PCR). In cases where patients brought medical evidence indicating that they had tested positive for one or

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Received for publication November 10, 2014; Accepted for publication March 1, 2015

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more of these tests at other clinics, we included these patients in the group of confirmed dengue cases. Foreign people were excluded in our study.

We used Dengue IgG/IgM Combo Rapid Test-Cassette® (CTK Biotech, San Diego, USA) to detect anti-dengue IgM/IgG and Dengue NS1 Ag Strip® (Bio-Rad, Marnes-la-Coquette, France) to detect NS1. We did not use laboratory data from patients who developed other diseases such as bacterial pneumonia.

This study was approved by the Yokohama Municipal Citizen’s Hospital Ethics Committee.

### Results

Initially, we found 5 domestic and 52 imported cases of dengue. One of 5 domestic cases involved an Italian patient and was therefore excluded. The 4 remaining domestic cases involved patients who had not been traveling to foreign countries or visiting the southern islands of Japan. Six of the 52 imported cases were excluded due to the lack of diagnostic test results.

Case 1. A healthy man in his twenties developed headache and nausea seven days after a mosquito bite in Yoyogi Park. He presented to our clinic with 4 days of high-grade fever (>39°C), fatigue, arthralgia, and myalgia. His vital signs and physical examinations were normal (the patient was taking acetaminophen). The hematological test results showed a white blood cell count (WBC) of 1,950/μL, a platelet count (PLT) of 60×10^3/μL, and a hematocrit (Hct) of 50.1%. His aspartate aminotransferase (AST) was 55 IU/L (8-38), alanine aminotransferase (ALT) was 15 IU/L (4-44), and C-reactive protein (CRP) was 0.44 mg/dL (0-0.5). The serum NS1 and PCR were positive (DENV serotype 1) but anti-dengue IgG and IgM were negative. The patient’s body temperature decreased to a normal range after 6 days when a diffuse erythema then appeared in the extremities. The serum aminotransferases reverted to the normal range on day 24.

Case 2. A pregnant woman in her twenties developed joint pain four days after a mosquito bite in Yoyogi Park. She developed a fever the next day, which was resolved on day 5 but reappeared on day 6. The fever resolved completely and a rash appeared in the extremities on day 7 when she came to our clinic. Physical findings on the patient included diffuse erythema on the hands and a maculopapular rash on the legs. Her hematological test results showed a WBC count of 4,540/μL, a PLT count of 14.7×10^3/μL, a Hct of 35.5%, an AST of 86 IU/L, an ALT of 61 IU/L, and a CRP of 0.3 mg/dL. Her serum anti-dengue IgG and IgM were positive. She recovered without complications for herself or her fetus.

Case 3. A woman in her twenties with psychiatric disease developed severe joint pain, headache, systemic rash, and fever 12 days after a mosquito bite while in the area around Yoyogi Park; she came to our clinic 3 days after developing these symptoms. Her physical examination showed slight conjunctival injection, tenderness of the lower legs and knee joints, and a diffuse light erythema on her back and upper extremities. Her hematological test results included a WBC count of 1,510/μL, a PLT count of 86×10^3/μL, a Hct of 44.4%, an AST of 40 IU/L, an ALT of 25 IU/L, and a CRP of 1.2 mg/dL. Her serum NS1 was positive. The patient’s fever resolved on day 5 and her rash expanded and covered her entire body. Her AST/ALT increased to 178/113 IU/L on day 9 and reverted to the normal range on day 16.

Case 4. A healthy man in his twenties developed a high fever (40°C) 2 days after acquiring a mosquito bite while around the area of Yoyogi Park. He came to our clinic after having five days of fever (transient fever resolution on day 3), myalgia, and arthralgia. His physical examination revealed cervical lymph adenopathy. His hematological test results showed that his WBC count was 1,390/μL, PLT count was 10.2×10^3/μL, the Hct was 44.4%, AST was 53 IU/L, ALT was 36 IU/L, and CRP was 0.8 mg/dL. His serum NS1 and anti-dengue IgM were positive but IgG was negative. His fever resolved and a systemic diffuse erythema appeared on day 7.

Among the imported cases, the average patient age was 42 years (Table 1). The most frequently visited countries, by these patients, were India and Indonesia, and almost all of the patients had been exposed to the virus in South or South East Asia (Table 2). Their major purpose for traveling included tourism and business (Table 3). The patients had stayed abroad for an average of 14.5 days (median; mini-
The number of dengue infection cases with the highest temperature. All cases had a fever and 74% of cases reached 39.0 °C or more.

**Table 3. Travel Purposes.**

<table>
<thead>
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</thead>
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<tr>
<td>tourism</td>
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</tr>
<tr>
<td>business</td>
<td>18</td>
</tr>
<tr>
<td>VFR</td>
<td>4</td>
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<tr>
<td>student</td>
<td>4</td>
</tr>
<tr>
<td>volunteer</td>
<td>1</td>
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<tr>
<td>VFR: visiting friends and relatives</td>
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diseases in Japan in the cases with no travel history. Frequent symptoms of both groups in this study were fever, rash, fatigue, and headache, none of which have signs that are pathognomonic for dengue infection. Myalgia and arthralgia were less frequent than the aforementioned symptoms. As for fever, 74% of cases reached a body temperature of 39.0°C or more, which is consistent with previous reports (4). A late rash was characteristic of the so-called “white islands in red sea” type, observed in 74% of the cases. This rash is diagnostic but not useful in the early phase of the clinical course. Signs and symptoms in our study were more frequent than that observed in a different report (11). For instance, joint pain was seen in 66% of the total cases in our study, but only 5-42% in other studies (11, 12). Our study included only Japanese so the difference in signs and symptoms may be related to the race of our patients (13). The development of symptoms is also influenced by the patient’s age, sex, DENV serotype, and past history of dengue infection (14, 15).

The results of the laboratory data are in support of previous reports, although few reports have mentioned CRP titers (16, 17). Mild to moderately elevated serum aminotransferases (AST and ALT <5× normal) are common in DENV infection; however, liver dysfunction appears to be common in dengue hemorrhagic fever (severe dengue) (18). AST and ALT reached a level that was 5 times greater than the normal range in 11 (22%) and 7 (14%) cases, respectively, and usually reached the highest level a few days after fever resolution, as observed in Case 1. Hence, liver damage may be more severe than generally considered. There were no correlations observed between the laboratory data and underlying diseases or previous history of dengue infection.

The diagnosis of dengue infection is confirmed by PCR, a positive culture, anti-dengue IgM seroconversion, or IgG titer elevation in paired sera according to WHO guidelines (4). In addition to these criteria, being serum NS1 antigen positive or anti-dengue IgM positive in a single serum sample with compatible symptoms also confirms dengue infection for public notification in Japan (19). However, no commercial diagnostic tests are available in Japan. The government should therefore be encouraged to quickly approve diagnostic tests for dengue that are to be covered by medical insurance.

In conclusion, these days, dengue infection should be differentiated from other febrile illnesses in Japan. Cases of high fever, late rash, leukopenia during the febrile period, a low PLT count, low CRP, and elevation of aminotransferases should lead to a suspicion of dengue infection.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement
We are grateful to Maria Ikeda, a nurse in our clinic, who played an important role in looking after these patients.

References