Imported dengue fever cases in Gunma prefecture, Japan

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Dengue virus (DENV), which is classified into four serotypes designated as DENV-1 to DENV-4, is endemic in more than 100 countries in both tropical and subtropical regions, with south-east Asia and the western Pacific being the most seriously affected [1]. According to the World Health Organization (WHO), the global prevalence of dengue fever (DF) and dengue haemorrhagic fever (DHF) has dramatically increased in recent decades (http://www.who.int/mediacentre/factsheets/fs117/en/). Concern is therefore growing over DF/DHF as one of the most important mosquito-borne human infectious diseases [2]. In Japan, relatively large epidemics of DF occurred between 1942 and 1944 in Nagasaki, Kobe and Osaka, originating from persons repatriating from the tropics during World War II; these epidemics were eliminated in 1946 [11]. In recent years, between 10 to 70 cases of DF/DHF have been reported annually in Japan, all of which were imported as a traveller’s disease [3-6]. The number of the reported DF/DHF cases has shown an increasing trend since the late 1990s (http://idsc.nih.go.jp/idwr/kansen/k04/k04_50/k04_50.html [in Japanese]). In 2007, a total of 89 cases of DF/DHF were reported, the highest number recorded in Japan thus far.

Gunma prefecture, located in the northwest corner of the Kanto region on Honshu island, has a population of approximately 2 million, and 10% of its residents travel overseas. In 2007, we experienced 2 cases of DF: one patient (Case 1) diagnosed with DENV-3 was plausibly infected in Ho Chinh City, Viet Nam [7], and the other patient (Case 2) diagnosed with DENV-2 was infected in Kingston, Jamaica. In general, when hospital doctors in Japan suspect a case of DF/DHF as one of the most important mosquito-borne human infectious diseases [2], Concern is therefore growing over DF/DHF as one of the most important mosquito-borne human infectious diseases [2]. In Japan, relatively large epidemics of DF occurred between 1942 and 1944 in Nagasaki, Kobe and Osaka, originating from persons repatriating from the tropics during World War II; these epidemics were eliminated in 1946 [11]. In recent years, between 10 to 70 cases of DF/DHF have been reported annually in Japan, all of which were imported as a traveller’s disease [3-6]. The number of the reported DF/DHF cases has shown an increasing trend since the late 1990s (http://idsc.nih.go.jp/idwr/kansen/k04/k04_50/k04_50.html [in Japanese]). In 2007, a total of 89 cases of DF/DHF were reported, the highest number recorded in Japan thus far.

In the present two cases, specimens were sent to our institute (Gunma Prefectural Institute of Public Health and Environmental Sciences) and virological analysis was performed for each case. In Case 1, from a blood sample collected on hospital day 3, we detected the DENV gene by reverse transcription-
polymerase chain reaction (RT-PCR) using the DENV-3-specific primers covering E-NS1 gene (GenBank accession number: AB362210)\textsuperscript{[8]} (Figure 1), although we could not isolate the virus using various cell lines (Vero, RD, HEp-2, and HEL cells). In Case 2, from serial blood samples collected on hospital days 3 and 4, DENV was not detected by RT-PCR, but specific IgG and IgM antibodies against DENV were significantly raised. In addition, DENV was propagated and isolated from Vero cell cultures. From the isolate, we confirmed DENV-2 by RT-PCR and phylogenetic analysis for the E gene (AB470342) of the virus (Figure 2).

**Figure 1:** Phylogenetic tree based on the E-NS1 sequences of DENV-3

[Phylogenetic distance was calculated using Kimura’s two-parameter method, and the tree was plotted using the neighbor-joining method. Numbers at each branch indicate the bootstrap values of the clusters supported by that branch. Inscriptions indicate the country where the dengue virus gene was detected, GenBank accession numbers, and collection year.]
As mentioned above, DF is an important infectious disease not only in tropical and subtropical regions but even in countries in temperate zones such as Japan. There is currently no vaccine available for human use, and as in the present cases, there is the potential for relatively severe clinical manifestations such as continuous high fever, hepatic disorder, leukocytopenia and thrombocytopenia to develop. There is no evidence of domestic DENV transmission in Japan; however, Aedes albopictus, one of the main vectors, is widely distributed across the country, with the exception of Hokkaido, and an outbreak of DF/DHF is possible in Japan once the virus enters the country. This is especially important to consider in the light of the large numbers of overseas travellers who are at risk of DENV infection. Thus, attention to trends in DENVs and the incidence of DF/DHF in Japan is required.
References


