Epidemiology of Severe Fever with Thrombocytopenia Syndrome in Japan

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More than 17% of worldwide infectious diseases are caused by vector-borne diseases. A numerous number of living organisms can act as a vector. In Japan, tick-borne diseases are particularly important because these diseases occasionally lead to a fatal clinical outcome. Severe fever with thrombocytopenia syndrome (SFTS) is a newly identified tick-borne disease caused by phlebovirus in the Bunyaviridae family. Most SFTS patients have been observed in China, South Korea and Japan. SFTS was first identified in 2013 in Japan and reached to 310 cases by 2017 with a high case-fatality rate (7.8%). SFTS transmission cycles between ticks and wild animals have been already established throughout Japan. This review outlines the current epidemiology of SFTS in Japan, with an emphasis on ecology of vector and animals and clinical features of Japanese patients.

Key words: vector-borne diseases, severe fever with thrombocytopenia syndrome, epidemiology, Japan

Vector-borne diseases

1. Global trend of vector-borne diseases

Vector-borne diseases are the infectious diseases transmitted by living vectors, most of which are bloodsucking insects. A numerous number of living organisms can act as a vector such as mosquitoes, ticks, flies and fleas. Parasite, virus and bacteria are the causing pathogens of vector-borne diseases. Vaccinations are useful for the infection prophylaxis in some vector-borne diseases such as yellow fever and Japanese encephalitis. The most effective preventive measurement for vector-borne disease is to avoid the biting by arthropod vectors. Many people are aware of the importance of insecticides, bed nets and wearing appropriate clothing against biting arthropods. However, some vectors have unique features. Anopheles mosquitoes that transmit malaria normally bite humans in night. Tsetse fly that is a vector of African trypanosome likes flashy colored clothes and tend to jump into the moving car. In addition to ‘vector-borne’ manner, person to person transmission can also occur in some vector-borne diseases. Hence, general protective measures against vector-borne disease become more effective by increasing our knowledge of the diseases as well as biological and ecological characteristics of arthropod vectors.

World Health Organization (WHO) reported that vector-borne diseases account for more than 17% of all infectious diseases (Figure-1)1. Mosquito is the most important vectors that transmit malaria, dengue, yellow fever and so forth. Malaria is transmitted by female Anopheles mosquito and one of the three major global infectious diseases with tuberculosis and HIV/AIDS. An estimated annual number of malaria patients was 261 million with an annual death about 400,000 in 20162. Nearly 90% of malaria cases occur in sub-Saharan Africa. Dengue is transmitted by Aedes aegypti and A. albopictus. A
risk of contracting dengue fever has been estimated in over 2.5 billion people in about 100 countries. Other parasite causing vector–borne diseases such as Chagas disease, leishmaniasis and schistosomiasis affect hundreds of millions of people worldwide. Importantly, even though such a large number of individuals have contracted vector–borne diseases especially in developing countries, infection of many these diseases can be prevented with scientifically informed protective measures.

2. Vector–borne diseases in Japan

These globally important vector–borne diseases are not endemic in Japan. One exception is epidemic of dengue in the summer season in 2014\(^3\), which resulted in a total of 162 autochthonous cases \(^4\). The New Infectious Diseases Control Law in Japan includes 22 vector–transmitted infectious diseases, nine of which have not been observed in Japanese patient since 1999 (Figure–2).

The most prevalence vector–borne diseases have been scrub typhus (Tsutsugamushi disease) with 400–800 identified patients every year (Figure–3). Apart from the epidemics in 2014, all dengue cases were observed in travelers from endemic countries. In accordance with the spread of global dengue endemic area, imported dengue cases in Japan have been increasing and becomes the second most
prevalent vector-borne diseases. Japanese spotted fever is a tick-borne disease, caused by *Rickettsia japonica*. Since the first identification in 1984 in Japan\(^5\), the number of Japanese spotted fever patient has been increasing over the 15-year period, which reached to 276 recorded cases in 2016. Severe fever with thrombocytopenia syndrome (SFTS) is also an emerging tick-borne disease that was first reported in 2007 in Henan province, China\(^6\). At that time, rickettsial infection was strongly suspected because of a large outbreak of red bug (Tsutsugamushi) in the area. However, no rickettsia was identified in the patient’s blood and the causative agent, SFTS virus, was finally isolated in 2010\(^7\). Since the first SFTS case in 2013 in Japan\(^8\)\(^9\), the number of patients have been gradually raised up to 89 in 2017.

Despite upward trend of case numbers, these tick-borne diseases are still rare infectious diseases in Japan. However, the diseases potentially result in severe clinical courses. Japanese spotted fever (0.91%) and scrub typhus (0.48%) had high mortality\(^10\). SFTS shows much higher case fatality rate (7.8%). Nevertheless, SFTS is not widely recognized as an important vector-borne disease in Japan, perhaps simply because it is a quite new emerging infectious disease. This article reviews SFTS in Japan, with an emphasis on vector and animals’ ecology and clinical epidemiology.

FTS: recently identified tick-borne disease

1. Clinical epidemiology in Japan

SFTS is caused by a newly identified phlebovirus in the *Bunyaviridae* family\(^7\)\(^6\). SFTS cases have been mostly found in China, South Korea and Japan. Molecular phylogenetic analysis revealed that SFTS virus strains were classified into Chinese and Japanese groups, which were further divided into five and three genotypes, respectively\(^11\).

In Japan, 310 laboratory-confirmed cases were detected between 2013 (when the first case of SFTS was identified) and 2017\(^12\). All patients were reported from western or southern part of Japan, mostly occurred between April and August. Ishikawa prefecture is the northernmost area with the report of SFTS\(^13\). Majority of SFTS patients were seniors with a median age of 74 years. Nearly all cases experienced a behavior for tick exposure such as trekking, hiking and gardening before the onset of the disease, as in the cases in China where 97% of SFTS patients were farmers living in wooded and hilly areas\(^6\).

Several sero-epidemiological studies have been performed to estimate the prevalence of SFTS infection in general population. There was no anti-SFTS antibodies positive case in the general blood donors from the Japanese Red Cross Kyushu Block Blood Center in Kagoshima prefecture, one of the top prefectures with the number of cumulative SFTS patients, in 2016 (n = 1,000)\(^14\) and in nine prefectures in West Japan (Chugoku-Shikoku district) in 2015-2016 (n = 3,990)\(^15\). In Kagoshima, however, one study in 646 healthy individuals demonstrated that anti-SFTS-virus antibody positive was observed in two serums (0.3%)\(^16\). This result suggests that very mild SFTS case might potentially occur.

Before the first identification of Japanese SFTS case, SFTS may have been misdiagnosed as the

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**Figure 3** Reported number of vector-borne diseases in Japan by year since 1999
other tick–borne diseases such as scrub typhus and Japanese spotted fever. To elucidate this possibility, antibodies against SFTS virus were assessed in 464 serum samples obtained from rickettsiosis suspected patients between 1999 and 2012 and one sample (1/222, 0.5%) showed SFTS antibody-positive.

2. Epidemiology of SFTS viruses in ticks and animals in Japan

*Haemaphysalis longicornis* is known as a main vector for SFTS. In Japan, SFTS virus was also detected in several other ticks which include *H. flava, H. megaspinosa* and *Amblyomma testudinatum*. Of note, despite that human SFTS cases have been limited in western and southern part of Japan, genetic epidemiology study revealed that ticks harboring SFTS virus genes were distributed in nearly all prefectures including Hokkaido, northernmost prefecture, in 2013-2015. SFTS virus is also widely distributed in wild animals. Sero-epidemiological survey conducted in 2007-2015 displayed that SFTS virus-specific antibodies were detected in Japanese deer, captured even in the regions where human SFTS cases were not identified. Average prevalence of antibody–positive Japanese deer was higher in SFTS-patient identified regions (37%) than that in SFTS-patient non-identified regions (8.4%). SFTS virus-specific antibodies were also detected in raccoon (9.8%), racoon dog (7.5%) and other wild animals such as boar, badger, civet and Japanese macaque in Wakayama prefecture. Importantly, prevalences of SFTS virus-specific antibodies positive racoon were maintained approximately 5% until 2013 but since then, rapidly increased to 24% in 2014 in Wakayama prefecture. Similar upward trend was also observed in racoon dog: 0% by 2008 to 30% in 2015. These observations strongly suggest that natural transmission cycle of SFTS virus from tick to wild animals has already established and has been spreading in the habitats for SFTS-susceptible wild animals throughout Japan. As a result, a risk for contracting SFTS would be highly expected in areas where these habitats overlap with human living spaces.

In contrast to wild animals, little is available on SFTS epidemiology in domestic animals and livestock in Japan. One study described that 2% of cattle in Shimane prefecture had SFTS virus–specific antibodies, with significantly higher seropositivity in breeding cattle (15.4%) and milk cows (4.8%) than in fattening cattle (0.5%). Ministry of Health, Labour and Welfare, Japan has announced SFTS confirmed cases in dog and cat and one fatal human SFTS case with a history of cat bite. These indicate a potential risk of SFTS transmission from domestic animals and livestock to human. Indeed, in China, much higher positive prevalences were reported in regions with large number of SFTS patients; 69.5% in sheep, 60.4% in cattle, 3.1% in pigs, 37.9% in dogs, and 47.4% in chickens. Further epidemiological studies are strongly required to estimate the risk of SFTS virus transmission from domestic animals and livestock.

3. Clinical epidemiology in Japanese patients

SFTS is transmitted by tick–bite, typically within two weeks from the onset of symptoms. However, SFTS infection would not be excluded solely based upon the absence of site of tick bite, since tick bite was not observed in approximately half of SFTS cases in Japan. Incubation period is 5–14 days with an abrupt onset of fever, then typical laboratory abnormalities, decline in platelets and white blood. Occurrence of other influenza-like symptoms and signs were also reported, including malaise (66%), anorexia (65%), diarrhea (59%), lymphadenopathy (35%), abdominal pain (19%), myalgia (17%), and headache (18%). Neurological findings are observed in 35% of cases, most of which are disorientation. Fever reaches to ≥38°C in majority cases and lasts 5–11 days. Laboratory abnormalities include leucopenia (88%) and thrombocytopenia (95%). Viral loads of SFTS virus peak on 7–10 days after the onset of initial symptom.

Multiple organ failure occasionally develops in some patients, progression of which leads to fatal clinical outcome. SFTS mortality reached to 35% in 2013, the year in which the first Japanese case was identified, and thereafter it has gradually dropped to 7.8% in 2017 (Figure-4). This mortality was same as the overall SFTS mortality in China (7.3%). Average number of days from the onset of initial symptoms to the fatal outcome was eight-day. Several symptoms and signs were associated with fatal cases, which include neurological abnormalities (59% in fatal vs 27% in survived), purpura (28% vs 9%), and gastrointestinal bleeding (24% vs...
6%)\(^{16}\). High level of concentrations of lactate dehydrogenase and aspartate aminotransferase were also associated with fatal clinical outcome\(^{21}\). Meta-analysis across all endemic countries (China, South Korea and Japan) further described laboratory abnormalities that were significant in the fatal cases, which included high viral load, low serum albumin and platelet count, high alanine aminotransferase and creatinine phosphokinase, and prolonged activated partial thromboplastin time\(^{23}\).

Some patients may present a mild clinical course of SFTS\(^{24,25}\). A 78-year SFTS patient with thrombocytopenia and leukocytopenia experienced high fever (39–40°C) alone, despite that fever continued longer than 2 weeks\(^{25}\). The other previously healthy 71-year woman experienced only diarrhea, anorexia, and lymphadenopathy without fever\(^{24}\). As mentioned above, anti-SFTS-virus antibody positive have been observed in the serum from general population\(^{14}\). Again, SFTS patients presenting mild symptoms has potentially been underdiagnosed and underreported.

4. Treatment

There is no available antiviral drug that has promising clinical efficacy for the treatment of SFTS virus. Supportive care is routinely applied for the management of SFTS patients. Ribavirin is a synthetic nucleoside analogue and widely used for treating SFTS, since it has potential antiviral efficacy against bunyavirus infections. However, in vitro activity of ribavirin against SFTS virus is controversial. One study described an inhibitory effect of SFTS virus replication\(^{26}\). The other group reported that the in vitro inhibitory effect of ribavirin substantially decreased when Vero cells were pre-infected with SFTS virus\(^{27}\). Meta-analysis has shown that ribavirin has a very limited clinical advantage for the treatment of SFTS\(^{23}\). Beneficial effect of short-term methylprednisolone pulse therapy has been reported in the treatment of encephalopathy during early phase of SFTS virus infection in two Japanese patients\(^{28}\). Effective measures for case management are still inadequate and thus, development of vaccines, novel antiviral agents, and new therapy against fatal cases is strongly required.

Concluding remarks

SFTS is zoonosis and transmission cycles have been established between ticks and wild animals in Japan. Therefore, it would be extremely difficult to control SFTS in a complicated environment where reservoir hosts of SFTS viruses are widely distributed. Available epidemiological studies strongly suggest that SFTS virus is rapidly spreading in ecosystem where SFTS transmission cycles are circulating. As such, educational outreach activities for general population as well as health care workers are essential to prevent an infection of SFTS and for prompt diagnosis.

References

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