Epidemiological characteristics of severe fever with thrombocytopenia syndrome in Zhejiang Province, China

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\section*{SUMMARY}

\textbf{Objectives:} To summarize the epidemiological characteristics of severe fever with thrombocytopenia syndrome (SFTS) in Zhejiang Province, China.

\textbf{Methods:} A standardized questionnaire was used to collect information on demographic features, exposure history, clinical symptoms, and timelines of medical visits. Descriptive statistics were used to analyze the characteristics of SFTS.

\textbf{Results:} A total of 65 cases of SFTS were identified in Zhejiang Province from 2011 to 2013, of whom 34 were male and 31 were female. The median age was 66 years and 60 cases occurred in persons aged ≥50 years. The majority (91%) of SFTS cases occurred between May and August. With regard to exposure history, patients had pursued outdoor activities (63%), had a history of exposure to a tick (68%) or tick bite (29%), bred domestic animals (31%), or had a history of exposure to a mouse (57%), and some patients had a multi-exposure history. Approximately 98.46% of patients were hospitalized, and symptoms of the illness included fever (98%), fatigue (71%), chills (51%), etc. Two family clusters occurred, although there was no person-to-person transmission.

\textbf{Conclusions:} In Zhejiang Province, SFTS is prevalent between May and August among elderly persons who live in hilly areas, and clinical features are not specific. More emphasis should be given to this disease and further training of medical personnel should be carried out to prevent misdiagnosis.

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\section*{1. Introduction}

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease discovered in China and is caused by a novel bunyavirus, SFTS virus (SFTSV). SFTSV is classified in the family \textit{Bunyaviridae}, genus \textit{Phlebovirus}, and is believed to be transmitted by ticks because the virus has been detected in \textit{Haemaphysalis longicornis} ticks.\textsuperscript{7} The major clinical symptoms and laboratory abnormalities of SFTS are fever, thrombocytopenia, leukopenia, and elevated serum hepatic enzymes, and death in SFTS patients is usually the result of multiple organ failure.\textsuperscript{3} The clinical symptoms, however, are less specific and need to be differentiated from those of various other infectious diseases, in particular from hemorrhagic fever with renal syndrome (HFRS) caused by hantavirus and human anaplasmosis.\textsuperscript{2,3}

In 2011–2012, 2047 cases of SFTS and 129 deaths were reported in over 206 counties of eastern and central China.\textsuperscript{4} Cases of SFTS were also identified in Zhejiang Province, and a total of 65 cases were reported in recent years according to the information system for disease control and prevention.\textsuperscript{5–7} Here, we analyze the epidemiological and clinical characteristics of SFTS in Zhejiang Province to provide scientific information for the control and prevention of SFTS.

\section*{2. Methods}

\subsection*{2.1. Case definition}

In accordance with the document entitled “The diagnosis and treatment programs of severe fever with thrombocytopenia syndrome” issued by the Chinese Ministry of Health,\textsuperscript{8} an acutely ill person with acute onset of fever (≥38.0°C) and other symptoms (e.g., gastrointestinal symptoms, bleeding), epidemiological risk factors (being a farmer or being exposed to ticks 2 weeks before...
illness onset), and laboratory data showing thrombocytopenia and leukocytopenia, was defined as a suspected case of SFTSV. Confirmed cases of SFTSV infection were defined as those who met the criteria for a suspected case of SFTSV and who also met one or more of the following criteria: (1) detection of SFTSV RNA by a molecular method, (2) seroconversion or ≥4-fold increase in antibody titers between two serum samples collected at least 2 weeks apart, and (3) isolation of SFTSV in cell culture.

2.2. Laboratory test assays

Serum samples obtained from the patients with suspected SFTS were sent to the laboratory of the Zhejiang Provincial Center for Disease Control and Prevention (CDC). Laboratory measurements of SFTSV RNA by real-time reverse-transcription PCR (RT-PCR), of SFTSV-specific immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies, and isolation of SFTSV were performed as described previously.

2.3. Data collection

The aims of our study were explained to all patients and their consent was obtained prior to inclusion in this study. A standardized questionnaire was used to collect information on demographic features (age, gender, occupation, and residential address), exposure history, clinical signs and symptoms, date of onset, date of first medical visit, and date of confirmation. Exposure history collected included habitats of their place of residence, outdoor activities within 2 weeks before illness onset, exposure to a tick within a month before illness onset, history of tick bite within 2 weeks before illness onset, skin breakdown within 2 weeks before illness onset, breeding domestic animals, contact with wildlife, and history of exposure to a mouse within a month before illness onset.

2.4. Data analysis

Descriptive statistics were used to analyze the epidemiological characteristics and clinical characteristics of SFTS in Zhejiang Province, China. We used the Wilcoxon Rank Sum W test to compare the age distribution of patients with SFTSV who survived and those who died. The Chi-square test or Fisher’s exact test were used to compare symptoms between survivors and those who died. The difference was considered statistically significant when \( p < 0.05 \). The statistical analysis was performed using SPSS software (SPSS 17.0; SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Epidemiological characteristics

A total of 65 laboratory confirmed cases of SFTS were identified in Zhejiang Province from 2011 to 2013, of whom 34 were male and 31 were female. All patients lived in wooded, hilly areas and the majority of them were farmers (92%). The median age of confirmed patients was 66 years (range 31–84 years), and 60 cases (92%) occurred in persons aged ≥50 years (Figure 1). Moreover, nine deaths occurred (case fatality rate, 14%) and the age distribution of patients who died was significantly different to that of survivors \( (Z = 2.034, p = 0.042 (<0.05)) \). The majority (91%) of SFTS cases during 2011–2013 in Zhejiang Province occurred yearly between May and August (Figure 2). However, two cases were reported in March and two cases were reported in October in 2013. All cases occurred in 13 counties that were members of five cities, and the number of counties in which SFTS was identified increased from 2011 to 2013 (Figure 3). The cities with the highest numbers of reported cases were Zhoushan (69%) and Ningbo (18%). Of note, 63% (41/65) of cases were identified in Daishan County, which is a part of Zhoushan located in eastern Zhejiang Province. Daishan County is comprised of seven towns, and SFTS was indenitified in five of them (Figure 4). Gaoting town and Dongsha town accounted for 68% (28/41) of patients in Daishan County. All cases lived in hilly areas within a month before illness onset and 63% (41/65) of cases had performed outdoor activities within 2 weeks before illness onset. Of these, 36 cases farmed, 10 cases mowed, and three cases grazed (Table 1). Six cases had a history of farming and mowing, and one case had a history of farming, mowing, and grazing. Among the 65 cases, 27 of 40 with data available had a history of exposure to a tick in the month before illness onset, but only 12 of 41 cases with data available had a history of a tick bite before illness onset. In addition, 14% (9/65) of cases had skin breakdown within 2 weeks before illness onset, 31% (20/65) of cases bred domestic animals, and 57% (30/53) of cases had a history of exposure to a mouse within a month before illness onset. However, no case had a history of contact with wildlife. Of note, nine cases had a multi-exposure history to domestic animals and mice; four cases had a multi-exposure history of tick bite and mouse contact; two cases had a multi-exposure history of tick bite and contact with domestic animals; two cases had a multi-exposure history of tick bite and contact with domestic animals and mice. The estimated median incubation period for 12 confirmed cases with a history of tick bite was 12 days (range 2–47 days).

3.2. Clinical characteristics

Approximately 99% of patients were hospitalized, and symptoms of the illness included fever (98%), fatigue (71%), chills (51%),
Table 1

<table>
<thead>
<tr>
<th>Exposure history of 65 SFTS cases in Zhejiang Province</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living in a hilly area a month before illness onset (%)</td>
<td>65/65 (100)</td>
</tr>
<tr>
<td>Outdoor activities within 2 weeks before illness onset (%)</td>
<td>41/65 (63)</td>
</tr>
<tr>
<td>Farming (%)</td>
<td>36/65 (55)</td>
</tr>
<tr>
<td>Mowing (%)</td>
<td>10/65 (15)</td>
</tr>
<tr>
<td>Grazing (%)</td>
<td>3/65 (5)</td>
</tr>
<tr>
<td>History of exposure to a tick within a month before illness onset (%)</td>
<td>27/40 (68)</td>
</tr>
<tr>
<td>History of tick bite within 2 weeks before illness onset (%)</td>
<td>12/41 (29)</td>
</tr>
<tr>
<td>Skin breakdown within 2 weeks before illness onset (%)</td>
<td>9/65 (14)</td>
</tr>
<tr>
<td>Breeding domestic animals (%)</td>
<td>20/65 (31)</td>
</tr>
<tr>
<td>Contact with wildlife (%)</td>
<td>0/65 (0)</td>
</tr>
<tr>
<td>History of exposure to a mouse within a month before illness onset (%)</td>
<td>30/53 (57)</td>
</tr>
</tbody>
</table>

SFTS, severe fever with thrombocytopenia syndrome.
headache (47%), lymphadenopathy (45%), anorexia (40%), nausea (40%), myalgia (35%), diarrhea (29%), vomiting (23%), abdominal pain (23%), gingival hemorrhage (18%), conjunctival congestion (15%), and petechiae (14%). Symptoms were similar between survivors and those who died except abdominal pain (Table 2). The median temperature of patients was 38.9 °C (range 37.3–40 °C). Laboratory abnormalities included thrombocytopenia (97%), leukocytopenia (92%), neutropenia (88%), and lymphocytopenia (83%). The minimum white blood cell, platelet, neutrophil, and lymphocyte counts in the acute phase were 0.6 × 10^9/l, 3.5 × 10^9/l, 0.01 × 10^9/l, and 0.02 × 10^9/l, respectively (Table 3). The median time from illness onset to first medical visit was 1 day (range 0–16 days) and the median time from illness onset to confirmation was 9 days (range 1–52 days). Sixty percent (39/65) of patients first visited a village or town clinic and 37% (24/65) of cases first visited a county hospital.

3.3. Family clusters

A total of two family clusters were identified in Zhejiang Province. One family cluster was identified in 2012 and the other was identified in 2013. The first family cluster comprised two persons with confirmed SFTSV infection. The index case patient was male, 50 years old, and had onset of fever, headache, nausea, abdominal pain, and diarrhea on May 18, 2012. He then visited a clinic on May 19, 2012. He had a history of tick bite within 2 weeks before illness onset. The secondary patient was his mother who was 85 years old and lived with him. She had onset of fever, abdominal pain, diarrhea, and lymphadenopathy on May 20, 2012 and visited a clinic on May 21, 2012. She then visited a hospital in Daishan County on May 26, 2012 as her condition had worsened. Serum samples of these two persons were collected on May 26 and both were confirmed with SFTS on May 27, 2012 (Figure 5). The secondary patient did not have a history of tick bite and had not pursued outdoor activities within 2 weeks before illness onset.

The second family cluster also included two confirmed SFTS patients. The first case was a 75-year-old woman who had onset of fever, fatigue, and anorexia on July 20, 2013. She visited a hospital in Daishan County and was hospitalized on July 20, 2013. She did not have history of tick exposure or tick bite. The secondary patient was her husband who lived with her and did farm work in daily life. He had the onset of clinical symptoms similar to those of his wife on July 21 and visited a hospital on July 23, 2013. Serum samples were collected from these two persons on July 23 and they were confirmed on the same day. The husband’s symptoms worsened and he was transferred to a hospital in Zhubang County for better treatment on July 24, 2013 (Figure 5).

4. Discussion

Zhejiang Province is located in southeastern China, adjacent to Jiangsu and Anhui where SFTS is endemic. Although SFTSV was first isolated in 2009, SFTSV has probably been prevalent for some time in China as the virus was found in serum samples from Anhui Province collected in 2006. In this study, 65 patients including 34 males and 31 females were identified. All patients lived in wooded, hilly areas and the majority of cases were sporadic, except for two family clusters. Nine deaths occurred and the case fatality rate was very high. However, we suspect that these confirmed cases represent the tip of the iceberg and that there are many more as yet undetected mild and asymptomatic infections. The real case fatality rate might therefore be lower than shown in our data.
Most SFTS cases occurred yearly between May and August. The reasons for this might include lots of outdoor activities, a high tick density, and the fact that ticks usually absorb their subjects’ blood in order to grow and proliferate between May and August. However, two cases were reported in March and two cases were reported in October in 2013, months when the tick density is low, indicating that there might be other transmission routes apart from tick bites.

The majority of cases occurred among persons aged 50 years or older and fatality increased with age. These findings are in agreement with corresponding data from other studies.1,4,10–14 The high proportion of elderly patients may be due to physiological factors related to ageing, such as decreased immune function and the presence of comorbidities with chronic diseases. However this may also be related to demographic features of residents in wooded or hilly areas where SFTS occurs. Generally, young adults from wooded or hilly areas go to cities to earn better money and then return to their hometown for the spring festival. As a result, the majority of residents of rural areas between the months of March and November are elderly people and children.

SFTS cases were identified in 13 counties from 2011 to 2013 and most cases were from Daishan County. However one case from Anji and another case from Pujiang were identified in 2013. Both cases visited a hospital in Hangzhou and were confirmed in Hangzhou. This informs us that some SFTS cases may be misdiagnosed because no county-level CDC has the capacity to identify SFTSV infection except Daishan CDC. Moreover, SFTSV seroprevalence is found in the general populations of Hubei Province, Shandong Province, and Jiangsu Province, suggesting that subclinical SFTSV infections or a relatively mild form of SFTS illness may occur in humans.15–17

Some patients performed outdoor activities within 2 weeks before illness onset or had a history of exposure to a tick within a month before illness onset. However, only 29% of patients had a history of tick bite within 2 weeks before illness onset. The reason for this may be that they did not find a tick bite or that there are other transmission routes. It is notable that 31% of cases bred domestic animals and 57% of cases had a history of exposure to a mouse within a month before illness onset. We postulate that domestic animals and rodents living in close contact with humans are reservoirs for SFTSV, whereas ticks are the vectors that transmit the virus from animal hosts to humans. Some studies on SFTSV prevalence among domestic animals confirm this hypothesis. Niu et al. detected SFTSV-specific antibodies in 69.5% of sheep, 60.5% of cattle, 37.9% of dogs, 3.1% of pigs, and 47.4% of chickens.18 Another study in Shandong Province showed 111/134 goats to be seropositive for SFTSV,19 and a serosurvey of domesticated animals conducted in Jiangsu Province found SFTSV antibody positivity rates of 57% in goats, 32% in cattle, 6% in dogs, 5% in pigs, and 1% in chickens, but no antibodies in geese or mice.17

The clinical presentation of SFTS includes fever, fatigue, chills, headache, lymphadenopathy, anorexia, nausea, myalgia, diarrhea, vomiting, and abdominal pain. These symptoms are not specific and are consistent with many infectious causes including bacteria and viruses. For example, infection with an *Ehrlichia* species transmitted through ticks has been shown to cause ehrlichiosis presenting as fever, lymphopenia, and thrombocytopenia in the USA.20 Furthermore, infection with *Anaplasma phagocytophilum* and SFTSV could occur concurrently in some patients suffering from SFTS.20

The median time from illness onset to first medical visit was 1 day, but the median time from illness onset to confirmation was 9 days. These may be related to patient low incomes and poor access to medical care because they were all from rural areas. Rural residents commonly visit small hospitals or outpatient clinics in villages or towns. These hospitals do not have the capacity to identify and cure SFTSV infection. As a result, the patients then have to attend hospitals with better facilities for further care. Also, the majority of samples are transported to the Zhejiang Provincial CDC for testing. It is possible that there are many other patients with infections in rural areas who do not have the opportunity to seek further care at better hospitals with laboratory capacity to identify SFTSV.

A few clusters of SFTS cases have been identified in the provinces of Shandong, Jiangsu, Hubei, and Anhui, and virological investigations have verified limited human-to-human transmission of SFTSV.21–23 In our study, we also identified two family clusters in Daishan County. However, given the fact that the secondary patient lived together with the index patient in two family clusters and the time intervals of illness onset between the index patient and the secondary patient were within the median incubation period of SFTS, suggests that the index patient and the secondary patient were infected from the same infectious source rather than transmission being person-to-person.

In summary, we have summarized the epidemiological and clinical characteristics of SFTS in Zhejiang Province, which will be useful for the prevention and treatment of SFTS. A total of 65 SFTS cases were identified and the majority of them occurred in elderly persons from wooded, hilly areas between May and August. Most patients pursued outdoor activities, had a history of exposure to ticks (with some patients having a history of tick bites), and bred domestic animals; some patients had a multi-exposure history. Clinical features of SFTS were not specific and were consistent with many other diseases, indicating that some cases of SFTS might be misdiagnosed. Family clusters occurred, although they were not as a result of person-to-person transmission. More emphasis should be given to this disease and further training of medical personnel should be carried out to prevent misdiagnosis. Laboratory capacity and the surveillance of ticks, domestic animals, and mice should be strengthened for the control and prevention of SFTS in Zhejiang Province.

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Ethical standards: The experimental research reported in this study was performed with the approval of the ethics committee of Zhejiang Provincial Centre for Disease Control and Prevention (Zhejiang CDC). Human research was carried out in compliance with the Declaration of Helsinki.

Conflict of interest: No conflict of interest exists in the submission of this manuscript.

References


