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Severe fever with thrombocytopenia syndrome bunyavirus-related human encephalitis

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KEYWORDS
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Summary *Background:* Severe Fever with Thrombocytopenia Syndrome (SFTS) is an emerging infectious disease caused by a novel bunyavirus. Until recently, SFTSV-associated encephalitis remained largely uninvestigated.
Methods: We made clinical investigation on SFTS patients who experienced encephalitis in one reference hospital in Henan Province from 2011 to 2013 to identify the risk factors for encephalitis occurrence and their fatal outcome development.
Results: Altogether 538 SFTS patients were included and 19.1% of them developed encephalitis. Fatal outcome occurred in 44.7% of the encephalitis patients. The risk factors associated with encephalitis occurrence and death included older age, longer delay between disease onset and hospital admission, pre-existing diabetes and myalgias, as well as the laboratory evaluations of higher virus load on admission, decreased WBC, PLT count, lymphocyte percentage and ALB, elevated neutrophils percentage, AST, ALT, LDH, CK, ALP, GGT, BUN and CREA. These parameters could be used as potential predictors referring to severe SFTS cases. One

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SFTSV strain was isolated from cerebrospinal fluid sample. Cytokine/chemokine assay revealed that blood EOTAXIN, IFN-γ, IL-15, IL-6, IP-10, TNF-α were remarkably elevated before clinical deterioration in the confirmed encephalitis patient.
Conclusions: SFTSV is capable of infecting the central nervous system and screening for SFTSV in encephalitis of unknown reason should be performed in SFTS endemic regions. The encephalitis occurrence and fatal outcome could be potentially predicted by clinical and laboratory evaluations.

Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging hemorrhagic fever reported in the rural areas of China since 2009, causing high mortality rate in hospitalized patients. The mysterious causative agent was identified to be a novel *Phlebovirus* in the *Bunyaviridae* family, named as severe fever with thrombocytopenia syndrome virus (SFTSV) in 2010.[1] The clinical manifestations of mild SFTS included fever, thrombocytopenia, leukopenia, vomiting, and diarrhea, while severe patients might develop multiple organs dysfunction and even death.[1,2] According to surveillance data released by China CDC, the geographic locations with SFTS cases reported have expanded from the initial 6 provinces in 2010 to at least 15 provinces/municipalities in mainland China in 2012.[1–5] The reported case number has increased remarkably from 571 in 2011 to 1476 in 2012.[3,6] Totally 61 deaths out of 600 confirmed SFTSV infection were reported in 2012, leading to a mortality rate of 10.30%. Its broad distribution, high incidence, and high case fatality, made this newly emerged infectious disease as one of the most important zoonosis in China. In 2012, SFTS cases were reported from Japan and South Korea, SFTS like cases caused by a novel *Phlebovirus* were also identified from USA.[7–11] This situation has raised enhanced concern of its wider spread outside China.

For an emerging infectious disease with high case-fatality rate,[12] the clinical and laboratory parameters that might predict adverse disease outcome have been investigated with high interest. Among all the identified factors, the early development of central nervous syndromes (CNS) was frequently seen and consistently found to be associated with fatal outcome.[3,13–16] However, the diagnosis of viral encephalitis was rarely made in the SFTS patients manifesting with CNS syndromes, mostly due to the low sampling rate of cerebrospinal fluid (CSF). Therefore, until recently, SFTSV associated encephalitis remained largely uninvestigated.

From 2011 to 2012, we performed a hospital-based study on SFTS patients in Xinyang administrative district of Henan Province. A cohort of confirmed SFTS cases was established, from whom clinical characteristics and predictors of fatal outcome were demonstrated.[15] Here, we increased the patient number to 634 by continuously recruiting patients till the end of 2013. Based on this large cohort, the SFTS patients with clinical encephalitis were defined and investigated to acquire their clinical and laboratory characteristics. The isolation of SFTSV from cerebrospinal fluid sample was presented as well.

Methods

Study sites and subjects

The study was performed in a SFTS reference hospital (The PLA 154 Hospital) in Henan Province, which was the most severe SFTS endemic area in China. All the confirmed SFTSV-infected patients that were hospitalized from 2011 to 2013 were recruited according to the national guideline.[4] A laboratory confirmation of SFTSV infection was made by the criteria as previously described.[13,15] Clinically-diagnosed encephalitis was defined as meeting the following criteria (1) + (2) + (3) or (1) + (2) + (4): (1) sudden onset, (2) symptoms as fever, headache, vomiting, and etc., (3) disorders of consciousness, and (4) meningeal irritation sign.[17] Laboratory confirmed SFTSV-infected patients without encephalitis-related evidences were defined as non-encephalitis SFTS.

Laboratory tests

Serum samples were collected from all patients on their admission and at regular intervals during their hospitalization for hematological and biochemical examination, to closely monitor the clinical progression. SFTSV RNA was detected by real-time reverse transcription polymerase chain reaction (RT-PCR) and was quantified by quantitative RT-PCR with specific primers and probes as previously described (supplemental material). The SFTSV-specific immunoglobulin M (IgM) and immunoglobulin G (IgG) in sera were detected by enzyme-linked immunosorbent assay (ELISA) using the recombinant nucleoprotein of SFTSV as previously described.[1] The laboratory parameters of white blood cells (WBC), neutrophil, lymphocyte, platelet (PLT), albumin (ALB), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), amylase (AMY), blood urea nitrogen (BUN), creatine kinase (CK), creatinine (CREA), gamma-glutamyltranspeptidase (GGT), hemoglobin (HGB) and lactate dehydrogenase (LDH), were included for analysis.

Viral isolation and immunological test for CSF samples

For two patients, the CSF samples were collected for SFTSV isolation and characterization. Briefly, CSF samples were inoculated on DH82 cells, cultured at 37 °C in a 5% carbon dioxide atmosphere with twice-weekly media changes. The whole genome sequences of the isolates were generated by