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Case Report

Steroid pulse therapy in patients with encephalopathy associated with severe fever with thrombocytopenia syndrome

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ABSTRACT

Severe fever with thrombocytopenia syndrome (SFTS) is a tick-borne infectious disease caused by the SFTS virus (SFTSV). Clinical symptoms of SFTS often involve encephalopathy and other central neurological symptoms, particularly in seriously ill patients; however, pathogenesis of encephalopathy by SFTSV is largely unknown. Herein, we present case reports of three patients with SFTS, complicated by encephalopathy, admitted to Tokushima University hospital: one patient was a 63-year-old man, while the other two were 83- and 86-year-old women. All of them developed disturbance of consciousness around the 7th day post onset of fever. After methylprednisolone pulse therapy of 500 mg/day, all of them recovered without any neurological sequelae. SFTSV genome was not detected in the cerebrospinal fluid of 2 out of the 3 patients that were available for examination. In these patients, disturbance of consciousness seemed to be an indirect effect of the cytokine storm triggered by SFTSV infection. We propose that short-term glucocorticoid therapy might be beneficial in the treatment of encephalopathy during early phase of SFTSV infection.

1. Introduction

Severe fever with thrombocytopenia syndrome virus (SFTSV), a tick-borne RNA virus and a novel member of the genus *Phlebovirus* belonging to the *Bunyaviridae* family, was initially identified in Central and North-Eastern China in 2009 [1]. In Japan, SFTS was first reported in 2013, mainly from the western side of Japan. Two hundred and fifty patients with SFTSV infections were diagnosed and a mortality rate of 22.4% was reported until May 2017, in Japan [2]. SFTSV sometimes triggers central nervous system symptoms in infected patients, and is thought to be associated with disease severity [3]. Pathophysiology and optimal treatment are yet to be established for SFTSV infection-associated central nervous system symptoms. Herein, we present case reports of 3 SFTSV-infected patients with disturbance of consciousness that was treated by steroid pulse therapy.

2. Case report

Case 1 was that of an 86-year-old woman, who had the habit of hiking daily, consulted her family doctor in August 2014 upon developing consistent fever for 3 days. She had past history of hypertension and osteoporosis. Further, she had Ixodes bites on her left elbow and right abdomen. Laboratory examination by a nearby doctor indicated thrombocytopenia and leukopenia; therefore, she was referred to Tokushima University hospital on the 4th day of fever from the fever onset. On examination, the patient's axillary

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temperature was 37.6 °C; heart rate: 51 beats per minute; blood pressure: 134/55 mm Hg; and oxygen saturation: 98% on room air. Laboratory examinations revealed thrombocytopenia, leukopenia with the appearance of a few atypical lymphocytes, and high serum creatinine kinase (CK) levels (Table 1). SFTSV genome was detected in her serum by reverse transcriptase-polymerase chain reaction (RT-PCR) assay. The patient developed disturbance of consciousness (Glasgow Coma Scale [GCS] of E3V4M3) and respiratory failure from the 6th day in parallel with elevated levels of serum transaminase, lactate dehydrogenase (LDH), CK, and ferritin. We assisted her respiration by noninvasive positive pulmonary pressure ventilation and administered with methylprednisolone (mPSL), 500 mg/day, for 3 days, followed by 10 mg/day of prednisolone (PSL) for another 3 days. The patient developed transient gastrointestinal hemorrhage from duodenal papilla as observed by upper gastroduodenal endoscopy on the 12th day. Anti-SFTSV IgM antibody was detected on 7th day from the fever onset, and IgG antibody was detected 16th day. She quickly recovered from consciousness disturbance after steroid pulse therapy without any neurological sequela. On the 25th day post onset of fever, she was transferred for additional rehabilitation (Fig. 1).

Case 2 was that of a 63-year-old man with a history of diabetes. In June 2014, he developed high fever, after several days of hiking; he had also engaged in harvesting oranges. When he visited the family doctor, tick bite was detected on his right thigh. He was transferred to the hospital due to prolonged high fever and development of consciousness disturbance, along with thrombocytopenia, on the 11th day post onset of fever after administration of mPSL 250 mg/day for 2 days. We evaluated his consciousness disturbance as E3V4M5 (GSC) and he was restless. On physical examination, his blood pressure was 102/78 mmHg; pulse, 68 beats per minute; body temperature, 36.6 °C; and oxygen saturation, 97% on room air. Laboratory examination revealed leukopenia with atypical lymphocytes, thrombocytopenia, and elevated serum CK, transaminase, and LDH levels (Table 1). SFTSV genome was detected by RT-PCR in his serum. The results of computed tomography of the patient's brain were normal. Examination of the patient's cerebrospinal fluid (CSF) collected by lumbar puncture indicated cell count was 1/μl; protein, 80 mg/dL; and glucose, 134 mg/dL. Realtime RT-PCR analysis of CSF showed a negative reaction for SFTS genome. Anti-SFTSV IgM and IgG antibody were detected on 17th day from the fever onset. We administered with mPSL, 500 mg/day, for additional 2 days, followed by tapering and quick withdrawal of PSL (Fig. 2). Hyperglycemia due to steroid treatment was controlled with transient continuous insulin injection. The patient recovered immediately from consciousness disturbance without any neurological sequela after mPSL pulse therapy; on the 25th day post onset of fever, he was transferred for additional rehabilitation (Fig. 2).

Case 3 was that of an 83-year-old woman with a history of Alzheimer's disease. She was working as a field-laborer. One day in July 2016, she was admitted to a nearby clinic on the 3rd day post onset of fever because of loss of appetite and drowsiness, where she was administered an intravenous injection of minocycline. She was transferred to the hospital on the 7th day post onset of fever when SFTSV genome was detected in her serum. The patient presented disturbance of consciousness (quantified as E3V3M6 using GCS) characterized with apathy; her blood pressure was 161/66 mmHg; pulse, 104 beats per minute; and oxygen saturation, 94% on room air. Tick bite was found on her left upper arm. Laboratory examination indicated thrombocytopenia, and hyperferritinemia with elevation of liver enzyme (Table 1). Analysis of the patient's cerebrospinal fluid (CSF) collected by lumbar puncture revealed cell count was 1/μL; protein, 33 mg/dL; glucose, 69 mg/dL. Realtime RT-PCR analysis of the CSF showed a negative reaction for SFTS genome. The patient was administered with mPSL, 500 mg/day for 1 day, followed by 10 mg/day of PSL for 2 days. The patient quickly recovered from somnolence after mPSL therapy without any neurological sequela. She was transferred to another hospital for additional rehabilitation (Fig. 3).

Table 1
Laboratory data on admission.

	Case 1	Case 2	Case 3	Normal range
WBC (/μl)	800	10300	4700	3300–8600
Aty-lym (%)	0.5	1.0	1.0	0.0
Hb (g/dl)	11.7	13.5	11.1	13.5–17.0 (M) 11.5–15.0 (F)
Plt (×104/μl)	11.7	4.6	8.1	15.0–35.0
AST (U/l)	24	77	134	13–30
ALT (U/l)	52	65	41	7–23
LDH (U/l)	315	465	368	124–222
CK (U/l)	13	134	142	59–248
CRP (mg/dl)	<0.05	<0.05	3.2	0.00–0.14
Ferritin (ng/ml)	195	8570	2644	3–120

3. Discussion

Herein, We describe 3 SFTS patients with disturbance of consciousness treated with the short-term steroid pulse therapy. All of them recovered without any neurological sequela.

SFTSV infection causes a wide range of clinical symptoms, manifesting as mild to severe disease. Risk factors for SFTSV infection-related mortalities are elevated serum transaminase, LDH, CK, as well as the appearance of central nervous system symptoms, hemorrhagic manifestations, disseminated intravascular coagulation, and multiorgan failure [3]. Recently, SFTSV-associated encephalopathy was reported that approximately 19.1% of patients infected with SFTSV developed encephalopathy; among the encephalopathy patients, fatal outcome occurred in 44.7% of the patients, which was significantly higher than that of the 9.4% observed in non-encephalopathy patients [4]. These observations suggest that SFTSV-associated encephalopathy could be a risk factor for fatality in SFTSV-infected patient. All of the patients manifested disturbance of consciousness, suspected to arise from viral encephalopathy; therefore, we surmised that these patients were at a high risk of death. Only 2 of the 3 patients were available for CSF analysis; SFTSV genome was not detected in the CSF from both these patients though it was detected in their serum. Likewise, SFTSV was not detected in the CSF or brain in most of the other reported cases, including autopsy cases [4–8]. These facts suggest consciousness disturbance might not be induced by direct infection of the CSF or brain neurons by SFTSV, but triggered indirectly by SFTSV infection-induced cytokines or inflammation. Using single photon emission computed tomography, a transient decrease in the blood flow to the brain was reported in a patient with SFTS; thus, it might be involved in the pathophysiology of encephalopathy in SFTSV-infected patients [6]. Nonetheless, acute viral encephalopathy such as caused by herpes simplex virus tends to give rise to serious neurological sequela. We hypothesize that neurological recovery of SFTSV-triggered encephalopathy might be good if appropriate intervention is done for alleviation of cytokine storm. Further case studies and clinical investigations of SFTSV-associated encephalopathy are warranted.

SFTSV RNA was detected in the blood, spleen, liver, and kidney in mouse experimental model with SFTS during the early stage of infection [9]. In addition, in murine models, SFTSV was reported to primarily infect reticular cells in the spleen [10]. Additionally, in autopsy cases, lymph nodes, spleen, liver were reported to be the main sites of SFTSV infection [7,8,11,12]. Therefore, it is likely that

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