Use of Plasma Therapy for Severe Fever with Thrombocytopenia Syndrome Encephalopathy

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DOI: http://dx.doi.org/10.3201/eid2207.151791

To the Editor: The central nervous system (CNS) manifestations of severe fever with thrombocytopenia syndrome (SFTS) include apathy, seizure, muscular tremor, and coma (1,2); however, the mechanism underlying CNS manifestations in SFTS is not clear. Deng et al. reported that illness of 15 (13%) of 115 patients with SFTS met the case definition for suspected encephalitis (1). However, they did not present any straightforward evidence of CNS invasion by STFS virus (SFTSV). Cui et al. similarly reported that encephalitis developed in one fifth of 538 patients with SFTS (2). They found evidence of SFTSV by isolating the virus from the cerebrospinal fluid (CSF) in 1 of 2 patients with SFTS whose CSF was obtained, but they did not mention CSF pleocytosis (2). We report a case of SFTS-associated encephalopathy, without pleocytosis and with normal CSF protein and glucose levels, that was confirmed by real-time reverse transcription PCR of the CSF. The patient was treated with experimental plasma exchange followed by convalescent plasma therapy.

During 2015, a 62-year-old woman who had a history of treated tuberculous meningitis 10 years earlier was admitted to a tertiary hospital in Seoul, South Korea (Republic of Korea), with a 5-day fever, myalgia, and headache. On hospital day (HD) 2, CSF examination revealed 1 leukocyte/mm³, protein 35 mg/dL (reference 9–58 mg/dL), glucose 74 mg/dL (reference 45–80 mg/dL), and CSF/blood glucose ratio 0.66 (reference 0.50–0.80). No bacteria or fungi were isolated from CSF. On HD 4, her headache worsened, and she displayed confused verbal responses and lacked orientation of time and place. No focal neurologic signs were observed. On HD 5, magnetic resonance imaging of the brain indicated no additional abnormalities of the parenchyma and extra-axial structures except for a focal parenchymal defect in the right midbrain that had been discovered as a

References


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sequela of tuberculous meningitis 10 years earlier. On HD 7, follow-up CSF examination revealed no leukocytes, protein 57 mg/dL, glucose 209 mg/dL, and CSF/blood glucose ratio 0.62. SFTSV was detected by real-time reverse transcription PCR (online Technical Appendix, http://wwwnc.cdc.gov/EID/article/22/7/15-1791-Techapp1.pdf) in plasma and CSF (Figure). On HD 8, the patient became comatose and had no eye, verbal, and motor responses to noxious stimuli (Glasgow coma scale 3). Bilateral exotropia was noted with spared light and corneal reflexes and oculocephalic responses. Experimental plasma exchange was performed, and her viral load declined slightly; however, consciousness and platelet count did not change. An ABO-identical nurse who had recovered from SFTS in September 2014 agreed to donate plasma; her indirect immunofluorescence antibody assay (IFA) for SFTSV IgG had been 1:1,024 in October 2014. On HD 17, the patient’s titer of SFTSV IgG was 1:64 before the plasma therapy. We obtained ≈400 mL of convalescent plasma (IFA assay for SFTSV IgG 1:256 at the time of donation) from the donor and transfused it into the patient on HD 17. The viral load in the blood decreased steeply by a factor of 10 (6 × 10^2 to 6 × 10^1 copies/mL) during the first 7 hours (4–11 PM on HD 17); it then gradually decreased from 3 × 10^1 at 7 AM on HD 18 to 6 × 10^0 copies/mL on HD 20, by which time the patient’s mental status had fully recovered (Figure).

This case is unique in that SFTS was detected in CSF in the absence of pleocytosis and with normal CSF protein and glucose levels, as in previous reports on influenza-associated acute encephalopathy (3). Although headache and encephalitis can occur in patients with SFTS (1,2), the pathophysiology of CNS manifestations in SFTS is unknown. As with influenza-associated acute encephalopathy, a possible hypothesis is direct invasion of SFTSV into the CNS; another hypothesis is that elevated cytokine levels or renal and hepatic dysfunction are associated with SFTS encephalopathy.

We are aware of 1 report of a favorable outcome of plasma exchange and ribavirin in 2 patients with SFTS and multiorgan failure in South Korea (4). However, the patients’ clinical condition did not substantially improve despite the 5-day plasma exchange therapy and viral load only slightly decreased. Use of convalescent plasma therapy in severe acute respiratory syndrome, influenza A(H1N1) and A(H5N1), and Ebola virus disease has been reported (5–7), but little evidence exists to support its use. However, given the lack of conclusive data, these potential experimental treatments for emerging infectious diseases warrant further study in a clinical trial. Response was favorable in a mouse model of SFTS treated postexposure with antiserum from a patient who had recovered from SFTS (8).

We do not know whether the convalescent plasma therapy given to the patient described here actually had a positive effect because her IFA titer was already increasing around the time she received the plasma therapy. At the time of this writing, 2 patients with SFTS who were treated with intravenous immunoglobulin and corticosteroid had been reported (9). Cautious interpretation of these experimental therapies is necessary because these therapies may not have had anything to do with the patients’ recovery.

Acknowledgments

We thank Kye-Hyung Kim and Jongyoun Yi for performing initial work to demonstrate the evidence of CNS invasion with keen comments on the study.

This study was supported by grants from the Korea Health Technology Research & Development Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare, Republic of Korea (grant no. HI15C2774) and the Korea Centers for Disease Control and Prevention (grant no. 4800-4837-301).

References

Hepatitis A (HAV; family Picornaviridae; genus Hepatovirus) is an ≈7.5-kb single-stranded positive-sense RNA virus that causes acute inflammation of the liver in humans and nonhuman primates. Although HAV is most commonly transmitted by food and water contaminated with feces, humans have acquired HAV from handling infected nonhuman primates in captivity (1).

HAV has been detected in recently imported captive primates after spontaneous outbreaks of acute hepatitis in animal facilities, but the definitive hosts of this virus have remained obscure (2,3). We identified by next-generation sequencing HAV in the blood of a free-living olive baboon (Papio anubis) from Kibale National Park, Uganda, sampled in September 2010. Subsequent testing of a separate Kibale olive baboon troop in 2014 indicated the virus was prevalent and shed in feces.

As part of a long-term study of nonhuman primate health and ecology, 23 animals were immobilized and sampled in 2010 as previously described (4). All animal protocols received prior approval from the Uganda National Council for Science and Technology (Kampala, Uganda), the Uganda Wildlife Authority (Kampala, Uganda), and the University of Wisconsin–Madison Animal Care and Use Committee (Madison, WI, USA). All samples were shipped in accordance with international laws under Convention on International Trade in Endangered Species of Wild Fauna and Flora Ugandan permit no. 002290.

During May 2012, we subjected total RNA from 1 mL of blood plasma of each animal to next-generation sequencing as previously described (4); results showed HAV-like sequences in 1 of 23 baboons. De novo assembly of these reads yielded a nearly complete HAV genome, which we term KibOB-1. KibOB-1 is most similar (94.2% nt identity; Figure) to AGM-27, an HAV originally detected in an African green monkey (Chlorocebus aethiops) imported to a Russian primate facility from Kenya (3).

For 11 baboons, we also collected a paired fecal sample, which we analyzed for evidence of viral shedding. Samples were preserved in RNAlater (Ambion Inc., Austin, TX, USA) at −20°C, and viral RNA was isolated by using the ZR Soil/Fecal RNA MicroPrep kit (Zymo Research, Irvine, CA, USA) following manufacturer’s protocols. Reverse transcription PCR (RT-PCR) of RNA was primed with random hexamers by using the RNA to cDNA Ecodry E Comey Premix (Random Hexamers) (Clontech Laboratories, Inc., Mountain View, CA, USA), and diagnostic PCR was conducted with primers flanking the C-terminal extension of the HAV viral protein (VP) 1 gene (pX) by using the High Fidelity PCR Master Mix-Ecodry Premix (Clontech Laboratories, Inc.). Five of 11 paired samples tested positive for HAV by RT-PCR, indicating a higher prevalence of the virus in feces than in blood.

We then surveyed a second troop of habituated olive baboons at the same field site during February–April 2014 (5). From these baboons, 7 of 19 fecal samples tested positive by RT-PCR. Confirmatory Sanger sequencing of RT-PCR amplicons was successful for 3 of these 7 animals (GenBank accession nos. KT819576–KT819578). Phylogenetic analyses of these sequences demonstrate monophyly and a low degree of interhost variability (≥94% nt identity).