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BRIEF REPORT

Acute Hantavirus Infection Presenting With Fever and Altered Mentation in the Absence of Pulmonary or Renal Manifestations

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Illness caused by hantaviruses is often severe and is typically characterized by diffuse pulmonary disease or renal insufficiency depending on the type of hantavirus. Here we report 2 cases of hantavirus infection that resulted in severe cognitive impairment but did not have any pulmonary or renal manifestations. These 2 cases may be indicative of previously underreported symptoms of hantavirus infection and might represent examples of hantavirus-related encephalopathy.

Keywords. hantavirus pulmonary syndrome; orthohantavirus.

Introduction

Orthohantaviruses (hantaviruses) represent a group of viruses that are spread zoonotically from rodents to humans and typically cause hemorrhagic fever with renal syndrome (HFRS) or hantavirus pulmonary syndrome (HPS) [1, 2]. The "Old World" hantaviruses are responsible for HFRS and are more common in Asia and Europe, whereas the "New World" hantaviruses are found in the Americas and are known to cause HPS. HFRS (caused by Hantaan, Dobrava, Saaremaa, Seoul, and Puumala viruses) can have a mortality rate of up to 15% [3], whereas HPS, caused by Sin Nombre virus (SNV) and Andes virus, has a mortality rate of up to 40% [4]. SNV is typically found in North America and is transmitted through exposure to the urine, feces, or saliva of *Peromyscus maniculatus* (deer mouse) [5]. Other rodents are responsible for transmission of other hantaviruses, and rare human-to-human transmission has only been reported with Andes virus. Hantaviruses generally have an incubation period of 1–5 weeks and infect endothelial cells, altering vascular permeability. Treatment consists of supportive care, and severe cases may require the use of mechanical ventilation or extracorporeal membrane oxygenation.

Case 1

In July 2020, a 70-year-old White man was admitted to a hospital in Oregon for confusion, headache, and fever. The patient's wife recalled that they had recently encountered rodents and rodent excrement around their property. His admission laboratory tests were notable for thrombocytopenia of 57,000 platelets/μL; the remainder of the tests were unremarkable. His admission imaging studies included a noncontrast brain computed tomography (CT) and a noncontrast chest CT, both of which showed no acute abnormalities (Figure 1). A lumbar puncture was performed on hospital day 1 and revealed the following cerebrospinal fluid (CSF) results: white blood cell (WBC) count, 1 cell/nL; red blood cell count, 134 cells/nL; protein, 94 mg/dL; and glucose, 93 mg/dL. Three days after admission, brain magnetic resonance imaging (MRI) with contrast revealed changes consistent with a mild subacute intraventricular hemorrhage. A thorough microbiologic evaluation was unrevealing, including negative CSF and blood cultures. However, serologic testing for hantavirus was positive for immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies (Figure 2). The patient was treated with supportive care; he ultimately defervesced, with normalization of his platelet count and mental status. He was discharged on hospital day 14 in improved condition. After discharge, additional testing performed at the receiving state health department identified the pathogen as SNV using a SNV-specific enzyme-linked immunosorbent assay (ELISA).

Case 2

In February 2021, a 66-year-old White man with type 2 diabetes mellitus, hypertension, and chronic lower back pain was transferred from an outside facility to a regional hospital in Oregon for acute onset of severe confusion, agitation, headache, nausea/vomiting, and fever (Figure 1). The patient had complained of some worsened chronic lower back pain for which he had been recently prescribed a methylprednisolone taper. He had no other symptoms, including no respiratory complaints. Prolonged exposure to mice was reported due to an infestation of the patient's home.

Records from the outside hospital showed admission blood tests notable for a WBC count of 16 cells/nL and a blood glucose of 211 mg/dL. A brain MRI and a head CT did not reveal any acute abnormalities. The CSF collected at that outside

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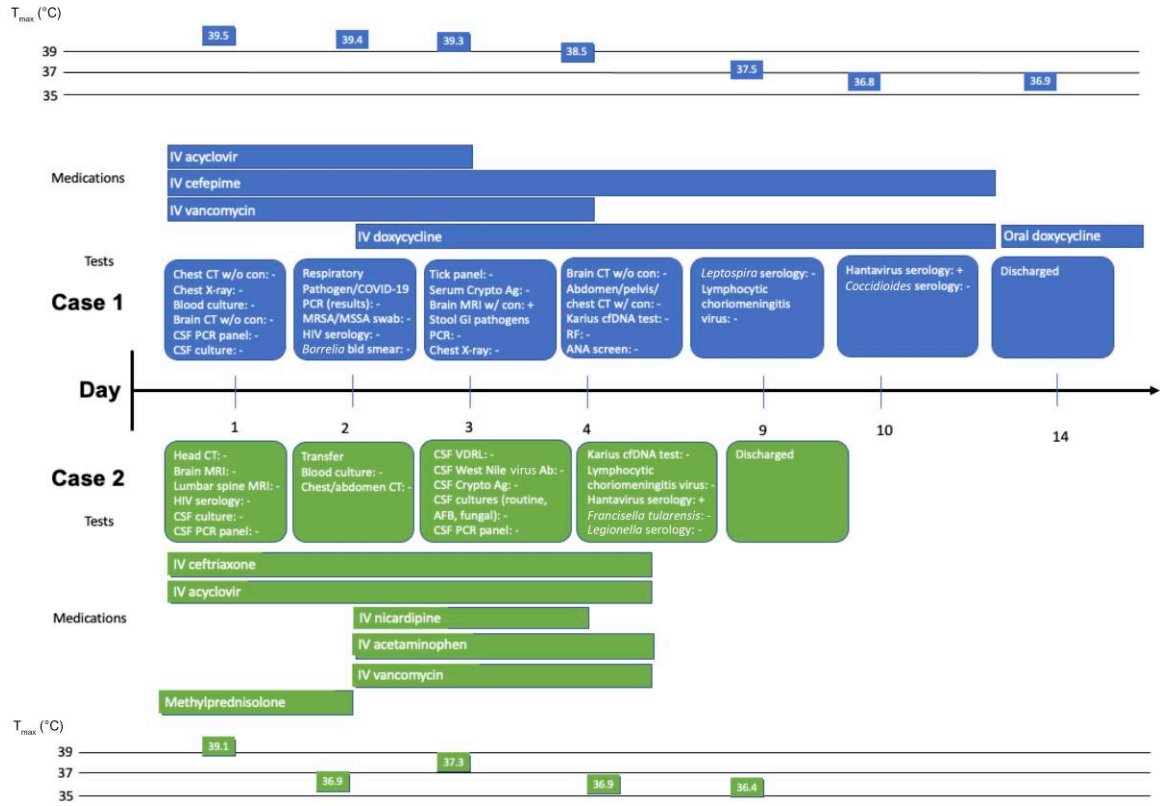

Figure 1. Timeline of patient care. Abbreviations: +, abnormal; -, normal; Ab, antibody; AFB, acid-fast bacilli; Ag, antigen; ANA, anti-nuclear antibodies; bld, blood; cfDNA, cell-free DNA; con, contrast; COVID-19, coronavirus disease 2019; CSF, cerebrospinal fluid; CT, computed tomography; GI, gastrointestinal; HIV, human immunodeficiency virus; IV, intravenous; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; PCR, polymerase chain reaction; RF, R-heumatoid Factor; T_{max}, Maximum body temperature in a 24 hour period; VDRL, Venereal Disease Research Laboratory.

hospital was normal, with a WBC of 0 cells/nL. As his symptoms did not improve, the patient was transferred to the regional hospital for further diagnostic evaluation and management. A CT scan of the chest was performed and was normal.

It was noted that the patient was persistently hypertensive, which ultimately required treatment with nicardipine. Within 24 hours after his transfer, his fevers and leukocytosis resolved without specific treatment. However, his altered mental status improved more slowly. He was discharged after 9 total hospital days. All blood culture sets remained negative. Hantavirus serologies returned positive for IgM and negative for IgG. Additional information from the laboratory that ran the serologic tests indicated that the positive IgM was for an Old World strain (Figure 2). Moreover, a SNV-specific ELISA performed at the receiving state health department revealed that the SNV IgM was negative. Specific testing for other hantaviruses was not performed. Two months later, hantavirus serologies were repeated and returned positive for IgM and negative for IgG. These test results again indicated that the positive IgM was for an Old World hantavirus (Figure 2).

DISCUSSION

The cases presented here demonstrate limited resemblance to typical hantavirus infections. In both cases, no acute pulmonary or renal impairment was detected, but both patients were hospitalized for altered mental status and fever. Symptoms improved with supportive care, and both tested positive for hantavirus IgM antibodies, whereas all other microbiologic tests, including cultures, polymerase chain reaction tests, and serologies, returned negative. No other cause for these patients' presenting symptoms was identified. Persisting cognitive changes associated with hantavirus infections have been reported before, with some survivors of HPS demonstrating cognitive impairment similar to patients recovering from anoxia [6]. One study that monitored hantavirus infection in human astrocytic cells and in mice suggested that neurological manifestations may be due to brain injury caused by the innate immune response [7]. However, it is unlikely that the 2 patients presented in this report were experiencing similar postinfection symptoms, considering the acute encephalopathy onset simultaneously with fever. There have also been previous reports of acute mental status alteration caused by hantaviruses [8–11], but previous cases are usually accompanied by typical

Case 1 hantavirus ELISA results

	American*	Eurasian*
IgG	4.5	2.8
IgM	6.2	1.4

Case 2 hantavirus ELISA results

	American*	Eurasian*
IgG (first test)	0.7	0.06
IgM (first test)	1.45	1.95
IgG (second test)	0.19	0.24
IgM (second test)	1.58	3.05

Figure 2. Hantavirus enzyme-linked immunosorbent assay (ELISA) testing results. Hantavirus serology was a semi-quantitative ELISA test. A value of ≥1.75 indicates a positive result for immunoglobulin M (IgM) antibodies and ≥1.1 indicates a positive result for immunoglobulin G (IgG) antibodies. Values of <0.9 and <0.8 indicate a negative result for IgM and IgG antibodies, respectively. All ELISA values are calculated by dividing the sample optical density by the cutoff value derived from positive and negative controls. *Hantavirus serology tested for 2 classes of hantavirus: Eurasian (Old World) and American (New World). Eurasian tests detected the antigen for the nucleocapsid protein of Hantaan virus, Puumala virus, and Dobrava virus; American tests detected the antigen for the nucleocapsid protein of Sin Nombre virus and Andes virus.

symptoms and signs of HPS or HFRS, including pulmonary infiltrates or renal impairment, respectively [10, 12].

In case 2, the lack of IgG seroconversion over a 2-month period was unexpected [13]. However, the detection of an IgG response may be delayed by many factors, such as the highly variable incubation periods of hantaviruses [11], underlying health conditions such as hyperglycemia (as seen in diabetic patients) [14], and immunosuppressant medications (eg, methylprednisolone and other corticosteroids). In case 2, it is also unusual that the strain of hantavirus was not identified as SNV. Instead, serologic testing indicated that the pathogen was an Old World hantavirus. The ELISA performed for case 2 was designed to detect New World as well as Old World hantaviruses, specifically Puumala virus, Dobrava virus, and Hantaan virus. Although Seoul virus is not included in this assay, it may also have been detected, as previous studies have shown that there may be significant cross-reactivity between different Old World strains during ELISA testing [15, 16]. Seoul virus has also been reported to cause symptoms of encephalopathy in the absence of renal manifestations [17]. Furthermore, it is the most likely Old World hantavirus to cause illness in the western United States, as it is has been reported to cause disease worldwide, including within the United States.

The cases presented in this report bring to light neurocognitive symptoms that are underrecognized in hantavirus infections. Although both patients presented with significant acute alterations in mental status, it is important to note that neither case was found to have confirmed encephalitis on the basis of CSF results and brain imaging studies. Our findings suggest that hantaviruses can trigger an acute encephalopathy without pulmonary or renal manifestations. This may serve to broaden the differential diagnosis in patients with rodent exposure who present with acute cognitive impairment of uncertain cause. Additionally, the identification of hantavirus cases presenting with atypical symptoms may lead to a more complete understanding of the geographic distribution of hantaviruses [18].

CONCLUSIONS

Hantavirus infections are important and potentially life-threatening zoonotic diseases in the United States and around the world. Although traditional cases of hantavirus infection are often readily diagnosed, the pathogenicity of hantaviruses remains incompletely understood. In these 2 cases, the patients presented with acute encephalopathy and fever. After extensive testing, hantavirus remained the only probable cause for their

symptoms. These cases demonstrate a previously underreported clinical presentation of hantavirus infection and may serve to bolster our understanding of the diversity of symptoms associated with this infectious disease.

Notes

Financial support. Authors did not receive financial support in writing this report.

Patient consent. Written consent was obtained by the patient described in case 1. Permission from the patient in case 2 was provided to the patient's long-standing primary care provider, who then provided written confirmation of the patient's verbal consent (the second patient has a history of illiteracy, and had moved out of the region by the time of writing the case report). These case reports comply with all Health Insurance Portability and Accountability Act (HIPAA) guidelines for case report publication.

Potential conflicts of interest. The authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. MacNeil A, Ksiazek TG, Rollin PE. Hantavirus pulmonary syndrome, United States, 1993–2009. Emerg Infect Dis **2011**; 17:1195–201.
2. Vapalahti O, Mustonen J, Lundkvist Å, Henttonen H, Plyusnin A, Vaheri A. Hantavirus infections in Europe. Lancet Infect Dis **2003**; 3:653–61.
3. Brocato RL, Hooper JW. Progress on the prevention and treatment of hantavirus disease. Viruses **2019**; 11:610.
4. Centers for Disease Control and Prevention. Hantavirus: ecology. **2012**. Available at: https://www.cdc.gov/hantavirus/technical/hps/ecology.html. Accessed February 6, 2022.
5. Netski D, Thran BH, St. Jeor SC. SNV virus pathogenesis in *Peromyscus maniculatus*. J Virol **1999**; 73:585–91.
6. Hopkins RO, Larson-Lohr V, Weaver LK, Bigler ED. Neuropsychological impairments following hantavirus pulmonary syndrome. J Int Neuropsychol Soc **1998**; 4:190–6.
7. Shin OS, Song GS, Kumar M, Yanagihara R, Lee H-W, Song J-W. Hantaviruses induce antiviral and pro-inflammatory innate immune responses in astrocytic cells and the brain. Viral Immunol **2014**; 27:256–66.
8. Bergmann F, Krone B, Bleich S, Prange H, Paulus W. Encephalitis due to a hantavirus infection. J Infect **2002**; 45:58–9.
9. Cerar D, Avšič-Županc T, Jereb M, Strle F. Case report: severe neurological manifestation of Dobrava hantavirus infection. J Med Virol **2007**; 79:1841–3.
10. Hautala N, Partanen T, Kubin A-M, Kauma H, Hautala T. Central nervous system and ocular manifestations in Puumala hantavirus infection. Viruses **2021**; 13: 1040.
11. Mattar S, Guzmán C, Figueiredo LT. Diagnosis of hantavirus infection in humans. Expert Rev Anti Infect Ther **2015**; 13:939–46.
12. Talamonti L, Padula PJ, Canteli MS, Posner F, Marczeski FP, Weller C. Hantavirus pulmonary syndrome: encephalitis caused by virus Andes. J Neurovirol **2011**; 17: 189–92.
13. Padula PJ, Rossi CM, Valle MOD, et al. Development and evaluation of a solid-phase enzyme immunoassay based on Andes hantavirus recombinant nucleoprotein. J Med Microbiol **2000**; 49:149–55.
14. Hanley P, Sutter JA, Goodman NG, et al. Circulating B cells in type 1 diabetics exhibit fewer maturation-associated phenotypes. Clin Immunol **2017**; 183: 336–43.
15. Morii M, Yoshimatsu K, Arikawa J, Zhou G, Kariwa H, Takashima I. Antigenic characterization of Hantaan and Seoul virus nucleocapsid proteins expressed by recombinant baculovirus: application of a truncated protein, lacking an antigenic region common to the two viruses, as a serotyping antigen. J Clin Microbiol **1998**; 36:2514–21.
16. Hofmann J, Heuser E, Weiss S, et al. Autochthonous ratborne Seoul virus infection in woman with acute kidney injury. Emerg Infect Dis **2020**;26:3096–9.
17. Liu E, Lv S, Yi P, et al. Central nervous system infection with Seoul orthohantavirus in a child after hematopoietic stem cell transplantation: a case report. Virol J **2022**;19:75.
18. de St Maurice A, Ervin E, Schumacher M, et al. Exposure characteristics of hantavirus pulmonary syndrome patients, United States, 1993–2015. Emerg Infect Dis 23:733–9.