Acute Infection With Sin Nombre Hantavirus without Pulmonary Edema

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Acute infection with Sin Nombre virus has been associated with development of hantavirus cardiopulmonary syndrome (HCPS), a severe cardiopulmonary illness with respiratory failure and shock. We present two cases of Sin Nombre hantavirus infections that did not lead to marked pulmonary complications in two otherwise healthy young adults from Utah and California. Sin Nombre virus causes a wider spectrum of disease severity than has been previously reported.

When new diseases are identified, the most severe cases are often selectively ascertained, and the full spectrum of disease does not become apparent until later. This appears to be true for hantavirus cardiopulmonary syndrome (HCPS), a rodent-borne infection due to Sin Nombre hantavirus (SNV) [1, 2]. HCPS was first identified in 1993 in the Four Corners region of the United States (New Mexico, Utah, Arizona, and Colorado) as an acute capillary-leak syndrome with cardiogenic shock, associated with a case-fatality ratio of ~80%. Even though no specific or highly effective therapy has been available, the case-fatality ratio has declined to 45% [3–5].

The decline in mortality is likely due to the recognition of milder cases. In support of this hypothesis, examination of the HCPS case registry at the University of New Mexico reveals that 43 of the 140 cases (31%) for which data are available did not require intubation at any time in the course of the illness; one patient was treated on an outpatient basis. However, subclinical infection appears to be very uncommon, as judged by the few serological surveys that have been conducted in the United States [6–8].

We describe the first North American adult patients with acute SNV infection who did not develop severe pulmonary or cardiac complications. It is hoped that the increased awareness of mild or clinically atypical cases will improve our understanding of the full spectrum of the illness.

Case Reports

Case 1

On 8 June 1998, a 32-year-old man residing in Juab County, Utah, sought care at the local emergency department for fevers, shaking chills, headaches, and profound myalgias of 3 days’ duration. He had a very mild occasional dry cough but no other respiratory symptoms. Initial examination revealed a temperature of 39.3°C, blood pressure of 138/84 mm Hg, and respiratory rate of 24/min, with oxygen saturation of 98% on room air. He appeared uncomfortable because of rigors but did not exhibit any respiratory distress. He was tachycardic, and his lungs were clear to auscultation. The remainder of the physical examination was unremarkable. A complete blood cell count (CBC) demonstrated the following values: WBCs, 5,800/mm³, with 80.7% granulocytes, 12.6% lymphocytes, and 6.7% monocytes; hematocrit, 44.3%; and platelets, 199,000/μL. Electrolyte levels and renal function were normal; the concentration of lactate dehydrogenase (LDH) was 240 U/L (normal, 105–230 U/L). Chest roentgenography demonstrated no abnormalities. Analysis of the CSF showed no abnormalities.

The patient was hospitalized for 3–4 days and was persistently febrile. The diagnosis was possible sepsis syndrome or an arthropod-born illness. Hantavirus infection was also suspected. He was treated with broad-spectrum antibiotics and gentle maintenance hydration. His headaches and myalgias were difficult to control with medications. He developed mild epigastric pain associated with nausea. No decompensation of cardiorespiratory status ensued, and the cough did not recur.

Chest roentgenography was not repeated. Follow-up CBCs were normal, and the CSF and blood cultures remained negative. The patient had a very slow recovery with prolonged myalgias, headache, and fatigue. Serological evaluation performed by the Utah State Health Laboratory was marked by a faintly positive titer of IgG to hantavirus (SNV) and a negative IgM fraction in a serum specimen obtained on 10 June 1998. The same serum sample was examined by the Centers for Disease Control and Prevention (CDC), who demonstrated an IgG titer of 400 (positivity, ≥400) and an IgM titer of 50 (positivity, ≥400) to SNV.

Testing of the patient’s serum from 24 June 1998 at the University of New Mexico demonstrated positive titers of IgM and IgG to SNV, with the following reactivity pattern on immunoblot assay for SNV and Seoul hantavirus (SEOV): SNV G1 peptide = 4+; SNV N peptide = 4+; SNV N
recombinant = 4+; SEOV N recombinant = 1+. The same serum specimen was analyzed by the CDC and had an IgM titer of 6,400 and an IgG titer of 6,400 to SNV.

The patient resided on a farm in rural Utah, where rodents had been routinely seen. None of the family members developed any similar symptoms. About 2 weeks prior to becoming ill, the patient had been hunting in the surrounding wooded area and recalled an episode of inhalation of a large amount of dust in an area with visible rodent feces.

Case 2

On 23 July 1998, a 36-year-old female nurse from Inyo County, California, presented to her primary care provider. She had a 2-day history of fever, headache, malaise, and chest tightness, without any cough or shortness of breath. Initial evaluation revealed a temperature of 37.6°C, blood pressure of 90/60 mm Hg, and pulse of 130/min, without tachypnea or other respiratory distress. The WBC count was 3,500/mm³ (no differential available). The patient was treated with aspirin for presumed viral syndrome.

Further evaluation on 24 July demonstrated a temperature of 38.8°C and no respiratory problems. The WBC count was 4,800/mm³, with 83% neutrophils, 8% lymphocytes, 7% monocytes, and 4% eosinophils; the hematocrit was 42.3% and the platelet count was 169,000/µL. The aspartate aminotransferase (AST) level was 36 U/L (normal, 5–35 U/L), with otherwise normal liver function test values, electrolyte values, and renal function. Chest roentgenographic findings were normal. Azithromycin was added to the therapeutic regimen, and hantavirus serology was performed.

On 26 July the patient was evaluated in the local emergency department secondary to worsening fevers, chills, myalgias, headache with photophobia, mild and infrequent dry coughing without shortness of breath, and one episode of emesis. Upon examination, she had a temperature of 37.6°C, blood pressure of 116/61 mm Hg with pulse of 97/min while sitting, and blood pressure of 92/47 mm Hg with pulse of 130/min while standing. The respiratory rate was 18, with oxygen saturation of 94% on room air by pulse oximetry.

She appeared fatigued but nontoxic. Her chest was clear to auscultation, and the remainder of the physical examination was unremarkable. The WBC count was 8,000/mm³, with 30% bands, 40% neutrophils, 14% lymphocytes, and 11% monocytes; the hematocrit, 44.7%; platelet count, 134,000/µL; and AST level, 46 U/L. Chest roentgenographic findings were normal. The patient received intravenous hydration without any deterioration of respiratory status and was discharged home following diagnosis of a viral syndrome.

In the course of the following week, the patient defervesced but developed a transient mild rash on her back, and fatigue persisted. Follow-up laboratory tests showed an AST level of 81 U/L and an LDH level of 337 U/L (normal, 100–190 U/L) on 30 July, and on 31 July a WBC count of 6,000/mm³, with 53% neutrophils, 29% lymphocytes, 11% monocytes, and 6% eosinophils. Cultures of blood specimens obtained on 24 and 26 July were negative. PCR for cytomegalovirus and a monoclonal serum screening were negative. Serum samples collected on 24 July were positive for IgM and IgG to SNV, consistent with acute hantavirus infection, with the following reactivity pattern: SNV GI peptide = 4+; SNO V N peptide = +trace; SNV N recombinant = 2+; SEOV N recombinant = nonreactive. The same serum specimen was tested by the CDC and revealed titers of IgM of 6,400 and IgG of 400 to SNV.

The blood smear was reviewed at the University of New Mexico and demonstrated a low platelet level and the presence of plasmacytoid immunoblasts (>10% of total lymphocytes) but did not show myelocytes. About 3 weeks prior to becoming ill, the patient cleaned a trailer that was infested with mice.

Discussion

SNV has caused the vast majority of known hantavirus infections in the United States [9]. Deer mice (Peromyscus maniculatus), which inhabit virtually all areas of the United States except for eastern and southeastern coastal regions, are the primary rodent reservoirs of North American SNV [9, 10]. Since the Four Corners outbreak [11–13], sporadic cases of hantavirus infection have been identified throughout the country. There has been a suspicion that an increased rodent population following heavier winter rainfalls contributes to an increased number of hantavirus infections among humans [14].

SNV infection leads to HCPS, a severe cardiopulmonary illness associated with rapidly progressive respiratory failure, shock, and in nearly 50% of cases, death. After an incubation period of ~8–28 days, patients have a 1–11-day prodrome phase associated with fever, severe myalgias, headache, and frequently nausea, vomiting, and diarrhea [4, 9, 10, 15]. Generally the prodrome phase progresses gradually, but the cardiopulmonary phase strikes very abruptly.

The cardiopulmonary phase is heralded by cough and increasing dyspnea, and in the most severe cases it may result in death within 3–6 hours, even with hospitalization and intubation. The laboratory profile includes leukocytosis with a left shift, thrombocytopenia, hemococoncentration, increased lactate dehydrogenase level, transaminase, and acidosis. It is rare that the patients die of hypo-oxygenation, because mechanical ventilation is generally successful [16]. Most of the deaths are due to rapid decline in the cardiac index, hypotension, and/or ventricular arrhythmias.

Relatively few clinicians are aware of the critical importance of cardiac depression in determining the outcome of HCPS. For this reason, some experts favor the more descriptive term HCPS rather than hantavirus pulmonary syndrome (HPS).

Only one prior case of mild SNV infection, with only prodromal-phase symptoms that did not progress to the cardiopul-
monary phase, has been previously reported. It involved a 4-year-old child [17]. The studies in the United States among household or occupational contacts of confirmed cases of HCPS suggest that seropositivity without evidence of disease is very rare [8]. Although antibodies to SNV can persist for at least 36 years, seroprevalence studies have revealed no group with prevalence higher than 1.7%, and the largest of the studies using >10,000 samples revealed a seroprevalence of only 0.2% [4, 6, 12].

Serological surveys performed in South America documented evidence of prior exposure to Sin Nombre–like hantavirus infection among residents of different countries. Studies in Argentina, Bolivia, and Uruguay during 1985–1987 revealed that 2.7% of the general population and 13.9% of rodent-exposed laboratory workers had a positive titer of IgG to hantavirus, without any history of clinical illness [18]. Serological evidence of prior hantavirus (Laguna Negra virus) infection was found in 40% of the Paraguayan Indians [19].

Both patients in our report had a characteristic onset of illness but an atypical subsequent course of SNV infection. The mildness of the previously reported disease caused by SNV in the 4-year-old child could reasonably be explained on the basis of age. Children can exhibit lesser degrees of illness with other viral infections such as measles or chickenpox. Mild cases of SNV infection involving adults have not been reported before in North America. It is not clear whether hantavirus infections without development of HCPS simply have not been suspected and thus not recognized or whether they never occurred.

The diagnosis of an acute SNV infection was confirmed for both cases at the University of New Mexico, following the perplexing initial serologies of case 1. Both serum samples were examined with a strip immunoblot test that incorporated synthetic SNV peptide antigens from G1 and N proteins, as well as full-length recombinant-expressed N proteins from Sin Nombre, Puumala, and Seoul viruses [4]. The antigens are in the solid phase and are used to detect serum antibodies to the SNV G1 peptide. The reactivity to viral G1 peptide has been shown to be specific for infection with SNV [7].

Additional serological tests consisted of IgG- and IgM-format western blotting with use of purified recombinant SNV N antigen, and both IgG and IgM antibodies were present [20, 21]. Furthermore, an ELISA conducted at the CDC also demonstrated IgG and IgM reactivity against SNV recombinant N antigen [22]. The CDC recognizes both cases as acute hantavirus infection.

In summary, our reported cases suggest that SNV can produce a wider spectrum of clinical disease than previously thought. These cases should prompt primary care and emergency department physicians to search for a history of potential hantavirus exposure for patients with typical prodromal symptoms of SNV infection.

References