Cluster of Cases of Hantavirus Pulmonary Syndrome in Alberta, Canada


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Abstract. In May 2005, a cluster of four hantavirus pulmonary syndrome (HPS) cases was confirmed in Alberta, Canada. The cluster is unusual given that three cases were from a single family and involved a 7-year-old child. This is the first family cluster reported in Canada and includes one of the youngest cases of HPS reported in North America.

INTRODUCTION

The first outbreak of the highly fatal Hantavirus Pulmonary Syndrome (HPS) was observed in 1993 in the Four Corners region of the southwestern United States encompassing the borders of New Mexico, Arizona, Colorado, and Utah.1,2 The etiologic agent was subsequently identified as Sin Nombre virus (SNV), an enveloped RNA virus of the family Bunyaviridae and genus Hantavirus. The deer mouse, Peromyscus maniculatus, serves as the major viral reservoir, and humans become infected through inhalation of the virus emitted in rodent excreta.3

The Centers for Disease Control (CDC) clinical case definition requires a febrile illness in a previously healthy person with the development of bilateral interstitial pulmonary edema or infiltrates with hypoxemia requiring supplemental oxygen within 72 hours of hospitalization.4 The case definition also includes an unexplained respiratory illness resulting in death, with an autopsy examination showing noncardiogenic pulmonary edema without an identifiable cause. Clinically compatible cases are laboratory confirmed by detection of hantavirus IgM or rising titers of hantavirus IgG, detection of hantavirus RNA by polymerase chain reaction (PCR), or detection of hantavirus antigen by immunohistochemistry.4,5

SNV infection has rarely been found in family clusters, and young children seem to be less commonly affected. Few pediatric cases were observed in the original outbreaks, leading some to hypothesize that children may be better protected from pulmonary involvement.6 In North America, hantavirus infections have been rarely recognized in children < 10 years of age.7 Ramos and others8 described the clinical outcomes of North American pediatric cases from 1993 to 2000. Among 13 patients, 10–16 years of age, there was a 31% mortality rate. Although pediatric hantavirus infections are frequently mild, the mortality rate reported by Ramos and others is only marginally below that of the cumulative US mortality rate of 36%.5

Interesting differences between hantaviruses have been noted comparing the South American Andes virus (ANDV) and the North American SNV in the pediatric setting.10 The ANDV cases have involved children as young as 1.4 years of age. In comparison, the youngest case reported up to this time of SNV infection meeting the CDC clinical case definition of HPS involved a 10-year-old child. Furthermore, one half of the ANDV pediatric HPS cases have involved case clusters, whereas this phenomenon is rare in the setting of pediatric SNV infections.

As of November 1, 2006, there had been 64 laboratory-confirmed cases of HPS in Canada. In total, 34 of 64 (53%) of these cases have been reported from the western province of Alberta (unpublished data). The first pediatric case of HPS in Canada involved a 16-year-old boy in Alberta in 1997,11 although a cluster of HPS cases has not been previously reported in Canada. In May 2005, a cluster of four cases of HPS was confirmed in Alberta. Three of these cases involved three generations of a single family: a 7-year-old boy, his 26-year-old mother, and his 51-year-old grandmother. A fourth case involving a related man from the same community was later identified. In this paper, we report the first family cluster of HPS in Canada and one of the youngest identified cases of HPS in North America.

CASE REPORT

In late April 2005, an excessive number of deer mice and mouse excreta were noted in and around the central Alberta home of an aboriginal woman, mother of a 7-year-old boy. In early May, this 26-year-old mother and the boy’s 51-year-old grandmother developed fever and myalgia, followed by the onset of dry cough and progressive dyspnea. On May 6, the grandmother (Case 1) was admitted to an intensive care unit, requiring intubation and mechanical ventilation, in a tertiary care hospital in Edmonton, Alberta. She was started on empirical piperacillin-tazobactam and azithromycin. Her admitting bloodwork revealed hemoconcentration with a hemoglobin of 159 g/L and hematocrit of 0.47, as well as thrombocytopenia with a platelet count of 30 × 10^9/L. Her leukocyte count was 49.6 × 10^9/L with 33% bands. Chest x-ray revealed diffuse pulmonary edema, and despite 100% FiO2, her arterial PO2 measured only 38 mm of Hg. She died within hours.

Just before the grandmother’s death, the mother (Case 2) became increasingly unwell during the early morning of May 7 and left the grandmother’s bedside to receive medical attention in the emergency department. Bloodwork revealed a hemoglobin of 151 g/L with a hematocrit of 0.44 and platelets of 71 × 10^9/L. Although her leukocyte count was only 4.3 × 10^9/L, she was noted to have 49% bands. Within hours, she developed severe respiratory distress requiring intubation and intensive care unit (ICU) admission. She was treated...
supportively with vasoactive drugs, corticosteroids, and empirical cefotaxime and azithromycin.

That same day, May 7, her 7-year-old son (Case 3) was brought to the emergency department by his father with a 5-day history of fevers, dry cough, increasing dyspnea, nausea, and emesis. On history, the son had spent time at his mother’s home around April 23 and had noted deer mice at that time. Deer mice had also been observed around a storage trailer on his father’s property, and it was felt that the boy may have been exposed to deer mice and excreta in either setting. On examination, he was noted to have a fever of 39.5°C. Although he initially maintained an oxygen saturation of 97% on room air, he was noted to be tachypneic with a respiratory rate > 40 breaths/min, and his chest radiograph showed severe pulmonary edema. Initial laboratory studies included an elevated hematocrit of 0.41 with a platelet count of 125 × 10^9/L. Although his leukocyte count was within normal limits measuring 5.0 × 10^9/L, he showed 34% bands. Renal function was normal with a creatinine of 51 μmol/L. He was admitted to the pediatric ICU and treated empirically with cefaclor, cefotaxime, and azithromycin. Despite intermittent fevers and the need for 2 L/min supplemental oxygen, he remained stable with milder illness. He did not require hemodynamic support and was transferred to a pediatric ward on May 9.

The son’s hospital course was generally uncomplicated. His platelet count nadir was 75 × 10^9/L on May 8 before improving to 96 × 10^9/L on May 11. By May 12, after a 6-day admission, the son was discharged home in good health. The mother remained intubated in the ICU for a total of 5 days. However, she was eventually extubated and discharged home on May 14 after an 8-day admission.

Serologic testing and RT-PCR were performed on blood samples (serum and EDTA blood) from each patient collected between Days 3 and 10 after the onset of symptoms. Hantavirus-specific IgM serology was performed using an IgM capture-ELISA test based on antigen prepared from Black Creek Canal virus–infected Vero E6 cells according to a previously published protocol. IgG-specific antibodies were determined by a previously described ELISA using an in-house, purified Black Creek Canal IgG lysate. Antibody titration was done in 4-fold dilutions of patient serum starting with 1:100. Test results were interpreted as positive where titers ≥ 400 were obtained. RNA was isolated from whole blood (EDTA blood) using the Viral RNA Mini kit from Qiagen (Mississauga, Ontario, Canada) and was analyzed by RT-PCR using the One-Step RT-PCR kit (Qiagen) and the primers SN5F 5’-gtttattgtttattgttatgt and SN5R 5’-tagtagtatgcctgttga. The PCR targets the nucleoprotein gene (S segment) of SNV and amplifies a 427-bp fragment (unpublished data).

All three cases were PCR-positive on the initial EDTA blood sample, indicating a recently acquired hantavirus infection. All amplicons were sequence-confirmed and aligned with published hantavirus sequences deposited into GenBank. The alignment revealed SNV sequences in all three cases with identical sequences for Cases 1 and 2 and a single mutation (G to A) for Case 3. The single serum sample from Case 1 was equivocal for IgM but showed a titer of 6,400 in IgG, supporting the diagnosis of an SNV infection. Cases 2 and 3 were IgM-positive on the initial serum sample and seroconverted in regard to IgG on the follow-up samples, also confirming a SNV infection in these cases. A summary of the results of diagnostic testing is shown in Table 1.

A fourth case of HPS was subsequently confirmed shortly thereafter at a second Edmonton hospital. In this case, a previously healthy 28-year-old male relative of the previous three cases presented on May 8 to a hospital near his community with a 6-day history of fever, headache, nausea, myalgias, dyspnea, and productive cough. He was initially discharged home, although his symptoms persisted and he returned to the community hospital on May 11. He was found to be hypoxemic, with an oxygen saturation of 87% on room air, at which time he was admitted and subsequently transferred to an Edmonton hospital on May 12. It was noted that mouse droppings had been seen in the kitchen and on the stove burners, where urine and excrement may have been aerosolized with use. Although this man had not been at the residence of the first three cases, he was from the same community and he had spent time with Patient 3 two weeks before the onset of illness.

On arrival in Edmonton, examination revealed a temperature of 38.0°C and heart rate of 106 beats/min. Faint crackles were heard diffusely on pulmonary auscultation. Initial bloodwork revealed a leukocyte count of 10.3 × 10^9/L with 30% bands and 13% myeloids. His hemoglobin measured 149 g/L with a hematocrit of 0.41, platelets of 32 × 10^9/L, and a creatinine of 51 μmol/L. He was admitted to the pediatric ICU and treated empirically with cefotaxime and azithromycin. He remained stable on the ward and did not require intubation or hemodynamic support. SNV-specific IgM and IgG antibodies and PCR testing were subsequently reported as positive, confirming a recently acquired SNV infection.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Date</th>
<th>IgM titer</th>
<th>IgG titer</th>
<th>RT-PCR</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51</td>
<td>May 6, 2005</td>
<td>100</td>
<td>6400</td>
<td>Positive</td>
<td>Fatal</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>May 7, 2005</td>
<td>400</td>
<td>100</td>
<td>Positive</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>May 10, 2005</td>
<td>400</td>
<td>≥ 6,400</td>
<td>NT</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>May 12, 2005</td>
<td>100</td>
<td>400</td>
<td>Positive</td>
<td>Survived</td>
</tr>
</tbody>
</table>

Titters ≥ 400 were considered positive.
RT-PCR was performed on whole blood samples.
NT, not tested.
reported four case identified 11.5% (28 of 244) seroprevalence in Mani-
A large cluster of
The two neighboring provinces east of Al-
Intervals between many of the cases were consistent
studied 51 cases in south-
peridomestic area was subsequently carried out, and 15
infestation had been noted. An environmental study of the
area within the affected community. During
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(36.6%) of 41 deer mice had hantavirus antibodies.

Because this was the first time that a cluster of HPS cases had been reported in Canada, personnel from the Public Health Agency of Canada conducted a serologic survey of deer mouse populations within the affected community. In brief, deer mice were collected over six nights from May 16 to 21, 2005 using 225 Sherman live traps. Traps were operated in and around the patient’s residence and at 24 other localities within a 10-km² area within the affected community. During the 1,350 trap nights, a total of 234 deer mice were captured, with an average of > 17 deer mice per 100 trap nights of sampling effort. Antibodies against SNV were detected in 111 of 228 (48.7%) deer mice tested, and animals with SNV antibodies were detected at 88% of the localities sampled. Deer mouse abundance (8 deer mice per 100 trap nights) and prevalence of SNV antibodies (12 of 36; 33%) were significantly lower in a neighboring community, where parallel but less intense sampling (i.e., 450 trap nights of sampling effort) was conducted.

DISCUSSION

The youngest reported case of a child with SNV infection involved a 4-year-old boy from rural New Mexico in June 1993. This child developed bronchitis and nasal congestion; however, the illness was mild, and the authors stated that the case did not meet the CDC surveillance case definition for HPS. The child’s mother was subsequently diagnosed with HPS, and as such, the child was part of only the second reported household cluster of SNV infection. In the weeks preceding these illnesses, mice had been observed and trapped by the family in and around the home, and numerous signs of infestation had been noted. An environmental study of the peridomestic area was subsequently carried out, and 15 (36.6%) of 41 deer mice had hantavirus antibodies.

The first household cluster included the index cases in the
initial Four Corners outbreak during the spring of 1993. The cluster involved a 21-year-old woman and a 19-year-old man living in the same household in rural New Mexico. Both died of acute respiratory failure within 5 days of each other. Within 2 weeks, the women’s brother also experienced acute respiratory symptoms, as did his wife 5 days later. The peridomestic studies in the Four Corners region in 1993 found that 32 (30%) of 107 deer mice were seropositive for hantavirus.

The first case of HPS in Manitoba, Canada, in 2001, deer mouse seroprevalence studies in Manitoba and Saskatchewan—the two neighboring provinces east of Alberta—identified 11.5% (28 of 244) seroprevalence in Mani-

The prevalence of SNV antibodies in deer mice associated with our study was considerably higher (48.7%) than these earlier studies and likely contributed to the increased risk for exposure to SNV-infected animals.

Epidemiologically, SNV infections are not generally found in family clusters, and young children are less commonly infected and present with milder disease. In this report, we describe a cluster of four cases confirmed in May 2005 in the western Canadian province of Alberta. Three of these cases involved three generations of a single family. A fourth case, a relative from the same community, was later identified. All met the CDC clinical case definition for HPS, and in two cases, intubation and mechanical ventilation were required.

Clustering of SNV cases is uncommon, in contrast with frequent case clusters of ANDV infection. Furthermore, unlike SNV, it has been established that ANDV may be spread through person-to-person transmission. A large cluster of cases in Argentina in 1996 was notable for epidemicologic links between cases in the setting of low rodent population densities. Intervals between many of the cases were consistent with the typical incubation period of 2–3 weeks. Subsequent molecular evidence provided further evidence to support the view of person-to-person transmission.

Furthermore, Martinez and others reported four case clusters from 2002, with epidemiologic data consistent with interhuman transmission on three occasions. The molecular studies served to strengthen the link between geographically disparate cases. Lazaro and others studied 51 cases in south-

In contrast, the data surrounding this Canadian SNV case cluster points toward environmental exposures rather than person-to-person transmission. This latter mode of transmission has not been documented in outbreaks of SNV infection and is unlikely to have been a contributing factor in this cluster given the documented exposures and timing of clinical progression. The epidemiologic data provides strong evidence of multiple and distinct environmental exposures. In all four cases involved in this cluster, there had been heavy mouse infestation in and around the respective homes with individual exposures to deer mice and their excrement within the identified incubation period. In each case, there were significant exposures, and the varying localities were all shown to have high numbers of infected rodents.

The epidemiologic data are also supported by the molecular analysis identifying three SNV variants among the four cases. Genetic sequencing revealed a single nucleotide muta-
HANTAVIRUS PULMONARY SYNDROME CANADIAN CLUSTER


