Hantavirus Pulmonary Syndrome in Florida: Association With the Newly Identified Black Creek Canal Virus

Ali S. Khan, MD, *Atlanta, Georgia,* Milton Gaviria, MD, *Miami, Florida,* Pierre E. Rollin, MD, *Atlanta, Georgia,* W. Gary Hlady, MD, MS, *Tallahassee, Florida,* Thomas G. Ksiazek, DVM, PhD, Lori R. Armstrong, PhD, *Atlanta, Georgia,* Richard Greenman, MD, *Miami, Florida,* Eugene Ravkov, PhD, *Atlanta, Georgia,* Michael Kolber, MD, PhD, Howard Anapol, MD, Eleni D. Sfakianaki, MD, MSPH, *Miami, Florida,* Stuart T. Nichol, PhD, Clarence J. Peters, MD, Rima F. Khabbaz, MD, *Atlanta, Georgia*

Hantavirus pulmonary syndrome (HPS) is a recently recognized viral zoonosis. The first recognized cases were caused by a newly described hantavirus, Sin Nombre virus (previously known as Muerto Canyon virus), isolated from *Peromyscus maniculatus* (deer mouse). We describe a 33-year-old Floridian man who resided outside the ecologic range of *P maniculatus* but was found to have serologic evidence of a hantavirus infection during evaluation of azotemia associated with adult respiratory distress syndrome. Small mammal trapping conducted around this patient's residence demonstrated the presence of antihantaviral antibodies in 13% of *Sigmodon hispidus* (cotton rat). Serologic testing using antigen derived from the Black Creek Canal hantavirus subsequently isolated from this rodent established that this patient was acutely infected with this new pathogenic American hantavirus. HPS is not confined to the geographical distribution of *P maniculatus* and should be suspected in individuals with febrile respiratory syndromes, perhaps associated with azotemia, throughout the continental United States.

Hantavirus pulmonary syndrome (HPS) is a recently recognized viral zoonosis characterized by a febrile prodrome progressing to severe noncardiogenic pulmonary edema.[1-3] This emerging infectious disease is caused by at least two newly described hantaviruses: the first is Sin Nombre virus (SNV), which caused an outbreak of acute respiratory failure in the southwestern United States during the summer of 1993, and the viral sequence of the second was identified in lung tissue from a patient in Louisiana.[4,5] Field investigations have identified *Peromyscus maniculatus* (deer mouse) as the rodent reservoir for SNV in the southwestern United States, and efforts are ongoing to identify the rodent reservoir for the Louisiana virus.[6] We report the first case of HPS from the southeastern United States due to Black Creek Canal virus (BCCV), the recently isolated hantavirus from Florida cotton rats (*Sigmodon hispidus*), in a patient with noncardiogenic pulmonary edema and acute renal insufficiency.[7,8]

From the Division of Viral and Rickettsial Diseases (ASK, PER, TGK, LRA, ER, STN, CJP, RFK), National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; University of Miami, School of Medicine (MG, RG, MK, HA), Miami, Florida; Communicable Disease Epidemiology (WGH), Tallahassee, Florida; Miami Veterans Affairs Medical Center (RG), Miami, Florida; and Dade County Public Health Unit, Department of Health and Rehabilitative Services (EDS), Miami, Florida.

Requests for reprints should be addressed to Dr. Ali Khan, Centers for Disease Control and Prevention, Mailstop A-26, 1600 Clifton Road, Atlanta, Georgia 30333.

Manuscript submitted October 7, 1994 and accepted in revised form March 30, 1995.

CASE REPORT

A 33-year-old previously healthy black male was hospitalized in October 1993 with diagnoses of sepsis, acute renal failure, acute rhabdomyolysis, and suspected disseminated intravascular coagulation after a 4-day prodrome of fever, chills, myalgias, abdominal pain, emesis, and malaise. Three days after onset of his illness, his temperature was 102°F, his blood pressure was 74/50 mm Hg, his respiratory rate was 24, and his hematologic and chemical profiles were abnormal (ie, he had 30% bands, 76,000 platelets, and a creatinine of 4.6 mg/dL) (**Table I**).

Evaluation on hospitalization also revealed elevated serum lactate dehydrogenase, creatine kinase, aspartate aminotransferase, alanine aminotransferase, prothrombin time, and partial thromboplastin time, in addition to hypoxemia on an arterial blood gas (PaO_2 = 55 on room air) and radiographic evidence of mild interstitial pulmonary edema with a normal cardiac silhouette consistent with noncardiogenic pulmonary edema. A urine analysis at that time was significant for 1+ proteinuria with 5–10 RBC/hpf but no detectable casts, his spot urine sodium was 76 mmol/L, osmolality was 300 mOsm/kg, and his fractional excretion of sodium was 3.5%; the calculated serum osmolality was 295 mOsm/kg.

He was admitted to the intensive care unit and was placed on broad-spectrum antibiotics and supplemental oxygen and was aggressively hydrated. Although his azotemia resolved over the next 48 hours, he started to develop progressive shortness of breath with radiographic evidence of increasing interstitial pulmonary edema and moderate alveolar pulmonary edema with small pleural effusions. He required mechanical ventilation for 12 days before improvement

TABLE I

Laboratory Test Results

Laboratory Tests	Normal Values*	Day -48†	Day 4	Day 5	Day 7	Day 9	Day 22‡
Blood urea nitrogen (mg/dL)	10–20	8	41	63	20	21	16
Creatinine (mg/dL)	0.9–1.5	1.3	4.6	4.7	1.00	1.4	0.8
Aspartate aminotransferase (U/L)	5–40	16		411	211	231	57
Alanine aminotransferase (U/L)	7–56	13		293	132	144	99
Lactate dehydrogenase (U/L)	313–618	137§		3,535	2,575	4,784	
Total protein (g/dL)	6.0–7.7	6.8		5.3			
Albumin (g/dL)	3.0–4.7	4.4		2.9			
Creatine kinase (U/L)	57–374			1,926	2,932	5,427	211
Hemoglobin (g/dL)	14.0–18.0	15.5	15.5	14.4	10.3	11.3	12.0
Platelets (10^3/mm^3)	140–440	212	76	42		150	633
White blood cell count (mm^3)	4.0–11.0	5.5	4.6	7.2	8.1	15.8	14.5
segs (%)	36–56	32	38	20	29	56	48
bands (%)	5–11		30	25	37	29	18
lymphocytes (%)	24–44	45	24	48	20	10	16
monocytes (%)	2–6	8	8	4	12	2	13
Prothrombin time (sec)	9.2–13.0			11	11.4	10.6	
Partial thromboplastin time (sec)	23–40			41	41	34	
Thrombin time (sec)	16–18			25			
Fibrin/fibrinogen degradation product	negative			positive			
Fibrinogen (mg/dL)	200–400			170			

*For laboratory tests of sera drawn on days 5–22.
†Serum collected as part of medical evaluation prior to illness onset.
‡Platelet value from day 21 and creatine phosphokinase value from day 23 shown.
§Normal value 60–200 U/L.

of his diffuse combined interstitial and alveolar infiltrates. He also required a 3-day period of intravenous vasopressors for severe hypotension (blood pressure 77/45 mm Hg) unresponsive to additional fluid administration on the same day of intubation.

An echocardiogram performed 5 days after admission while the patient was normotensive on intravenous dopamine showed a moderate pericardial effusion without hemodynamic compromise and normal left ventricular systolic function. Bronchoscopy performed 12 days after admission showed normal airways, all orifices patent, no endobronchial lesions, no purulent secretions, and minimal airway erythema; no transbronchial biopsy was performed. His hospital course was complicated by progressive peripheral edema with a positive fluid balance of 20 liters before he spontaneously diuresed; this diuresis heralded an improvement in his respiratory status. He was discharged home in good condition 5 days following extubation.

Hantaviral infection was suspected after multiple negative bacterial cultures and extensive nondiagnostic serologic studies including a convalescent leptospirosis titer of <1:50 by immunohemaglutination. The earliest serum sample available—obtained 11 days after onset of illness—showed the presence of immunoglobulin G (IgG) antibody to recombinant SNV nucleocapsid protein at a titer of 6,400 but no immunoglobulin M (IgM) antibody to native SNV antigens by an IgM capture enzyme-linked immunosorbent assay.[9] Serum samples collected 6 weeks and 3 months later showed no change in IgG titer to SNV (**Table II**).

TABLE II

Hantaviral Antibody Tests

	Seoul		Sin Nombre		Black Creek Canal	
	IgM	IgG	IgM	IgG	IgM	IgG
Day 11	50	50	50	6,400	>6400	25,600
Day 58	50	400	50	6,400	1,600	25,600
Day 87	50	100	50	6,400	400	25,600

These serologic results demonstrated prior infection with a hantavirus but did not establish recent infection.

ENVIRONMENTAL INVESTIGATION

In the 7 weeks before onset of his illness, the patient resided in a semirural part of south Dade County, and his residence was surrounded by grassy fields where rodents had been observed. The patient reported observing rodents in his residence and walking in the fields surrounding his residence. The occurrence of this HPS-compatible illness outside the known range of *P maniculatus* prompted an investigation to further characterize this patient's illness and the local rodent species.[8] Rodent trapping in south Dade County yielded 90 *S hispidus*, 74 *Mus musculus* (house mouse), 18 *Oryzomys palustris* (rice rat), 9 *Rattus rattus* (black or roof rat), and 7 *Rattus norvegicus* (brown or Norway rat).

Antihantaviral antibodies were detected in 12 (13%) of the *S hispidus* and none of the other rodent species. Nucleotide sequence analysis of hantaviral genetic material amplified by reverse transcriptase-polymerase chain reaction from lung tissues of 3 *S hispidus*

showed this viral material was consistent with a previously unrecognized hantavirus closely related to, but distinct from, both the hantavirus circulating in Louisiana[5] and SNV.[10] Subsequently, BCCV, a new hantavirus, was isolated from these rodents.[7] Repeat serologic testing of the patient using native BCCV antigen showed the presence of IgM antibodies at a titer of ≥6,400 in the 11-day serum; titers fell to 1,600 6 weeks later and to 400 3 months later. IgG to BCCV was also detected at a titer of 25,600 in all three sera.

DISCUSSION

The first pathogenic American hantavirus was identified in the United States in June 1993, after a cluster of unexplained respiratory deaths in the southwestern United States.[2] The clinical illness was designated HPS and is characterized by a typical prodrome consisting of fever, chills, myalgias, headaches, and gastrointestinal symptoms that rapidly progresses to severe hemodynamic dysfunction and bilateral noncardiogenic pulmonary edema simulating adult respiratory distress syndrome. Typical clinical laboratory findings included hemoconcentration, neutrophilic leucocytosis, left shift, circulating immunoblasts, thrombocytopenia, hypoalbuminemia, and mild transaminase and lactate dehydrogenase elevations. None of the first 17 reported cases had an elevation of creatinine greater that 2.5 mg/dL. The mortality rate is approximately 50%. HPS has now been confirmed by the Centers for Disease Control and Prevention (CDC) from 17 western and midwestern states known to harbor *P maniculatus*. In August 1993, genetic sequences suggesting the presence of another novel hantavirus were identified in tissues of a Louisiana resident who died of HPS-like illness.[5] Our data suggest that the etiologic agent of the Florida case was BCCV, a third new US pathogenic hantavirus, from a distinct rodent reservoir, *S hispidus*, which is found throughout the southeastern and southcentral United States.[11]

This patient's illness, although compatible with HPS, had prominent renal insufficiency early in the disease course, which has not been noted with SNV and is more characteristic of infections with Old World hantaviruses such as Puumala, Seoul, and Hantaan.[3,12] Although his markedly elevated creatine kinase is also atypical for HPS, there were no other indications of rhabdomyolysis. The patient's clinical course and elevated fractional excretion of sodium and other laboratory parameters are compatible with oliguric acute tubular necrosis and consistent with the transient renal impairment due to acute tubulointerstitial nephritis seen in Puumala infections. Prominent renal insufficiency was also noted in the Louisiana patient infected with an unnamed pathogenic hantavirus and suggests that these new American hantaviruses, at least in the southeastern United States, may be more nephropathic than previously assumed. Clearly, identification of additional patients will be necessary to confirm whether renal disease is caused by these new viruses. Although this patient had serologic evidence of recent BCCV infection, we were unable to obtain viral genetic material for sequence information from the patient's serum samples.

Definitive confirmation of the ability of this virus to cause human disease will require the isolation of the virus or viral sequences from human tissues. In addition to the rest of the continental United States, residents of the southeastern region should follow interim guidelines to reduce contact with rodents.[13] Physicians throughout the continental United States should consider HPS in patients with a syndrome of unknown etiology characterized by acute febrile noncardiogenic pulmonary edema, with or without acute renal insufficiency. Suspected patients should be reported to local and state health authorities who can arrange for specimens to be submitted to CDC for diagnostic testing.

ACKNOWLEDGMENT

We thank Anita Bock, Walter Livingstone, Myriam Ares, Lillian Rivera, Annie Neasman, Angel Muniz, and Greg Glass for invaluable assistance during this investigation and John O'Connor for editorial assistance.

REFERENCES

1. Centers for Disease Control and Prevention. Hantavirus pulmonary syndrome—United States, 1993. *MMWR*. 1994;43:45–48.

2. Nichol ST, Spiropoulou CF, Morzunov S, et al. Genetic isolation of a hantavirus associated with an outbreak of acute respiratory illness. *Science*. 1993;262: 914–917.

3. Duchin J, Koster F, Peters CJ, et al. Hantavirus pulmonary syndrome: a clinical description of 17 patients with a newly recognized disease. *NEJM*. 1994; 330:949–955.

4.Elliot LE, Rollin PE, Ksiazek TG, et al. Isolation of Sin Nombre virus, a new hantavirus from Peromyscus maniculatus. *Am J Trop Med Hyg*. 1994; 51:102–108.

5. Centers for Disease Control and Prevention. Update: Hantavirus disease—United States, 1993. *MMWR*. 1993;42:612–614.

6. Childs JE, Ksiazek TG, Spiropoulou CF, et al. Serologic and genetic identification of Peromyscus maniculatus as the primary rodent reservoir for a new hantavirus in the southwestern United States. *J Infect Dis*. 1994;169:1271–1280.

7. Rollin PE, Elliot LE, Ksiazek TG, et al. Isolation of Black Creek Canal virus, a new hantavirus from Sigmodon hispidus in Florida. *J Med Virol*. 1995; 46:35–39.

8. Centers for Disease Control and Prevention. Newly identified hantavirus—Florida, 1994. *MMWR*. 1994;43:99–105.

9. Feldmann H, Sanchez A, Morzunov S, et al. Utilization of autopsy RNA for the synthesis of the nucleocapsid antigen of a newly recognized virus associated with hantavirus pulmonary syndrome. *Virus Res*. 1993;30:351–367.

10. Spiropoulou CF, Morzunov S, Feldmann H, et al. Genome structure and variability of a virus causing hantavirus pulmonary syndrome. *Virology*. 1994;200: 715–723.

11. Cameron GN, Spencer SR. Sigmodon hispidus. *Mammalian Species*. 1981; 158:1–9.

12. McKee KT, LeDuc JW, Peters CJ. Hantaviruses. In: Belshe RB, ed. *Textbook of Human Virology*. 2nd ed. St. Louis, Mo: Mosby Year Book; 1991: 615–632.

13. Centers for Disease Control and Prevention. Hantavirus infection—southwestern United States: interim recommendations for risk reduction. *MMWR*. 1994:42(RR-11);1–13.