2006 HUMAN HANTAVIRUS INFECTIONS IN LOS ANGELES COUNTY RESIDENTS

BACKGROUND

Hantavirus pulmonary syndrome (HPS) was first recognized in 1993 after an outbreak of acute respiratory failure in young people in the Four Corners area of southwestern United States (U.S.). The case fatality rate among these cases was 76% [1]. Fortunately, recent Centers for Disease Control and Prevention (CDC) surveillance data reports a decline in the case-fatality rate of 30 to 40% [2]. HPS is characterized by a febrile illness associated with bilateral diffuse interstitial edema of the lungs developing within 72 hours of hospitalization in a previously healthy person. The causative agent of HPS is Sin Nombre virus, a previously unknown hantavirus that was both documented in individuals with HPS in New Mexico and rodents within their dwellings [1]. Sin Nombre virus (SNV), a lipid enveloped single stranded RNA virus of the family Bunyaviridae, is genetically distinct from other known hantaviruses that cause hemorrhagic fever with renal syndrome in Europe and in Asia [3].

Several hantaviruses that are pathogenic for humans have been identified in the U.S. [3]. In general, each virus has a single primary rodent host. The deer mouse *Peromyscus maniculatus* (*P. maniculatus*) is the primary rodent host and reservoir for Sin Nombre virus (SNV). *P. maniculatus* has been found in almost every state and province in the U.S. and Canada, except in the southeastern U.S. and the Atlantic seaboard.

Hantavirus infection is invariably related to contact with rodent reservoirs, but the duration of contact with infectious materials and dose necessary for disease transmission are not well understood. Most human infection is felt to be acquired through inhalation of aerosolized feces, urine or saliva from the infected mice. Case-control studies have found that the most commonly associated risk of hantavirus infection is contact with rodent excreta. Because most contact with infectious materials results from the ubiquitous presence of rodents, determination of the exact exposure can be difficult. The estimated incubation period has ranged from 1 to 5 weeks [4].

Since HPS was first identified in 1993, the CDC has confirmed 438 cases of HPS reported from 30 states among residents of 32 states through March 2006 [2]. Most cases have been reported in the Southwest especially New Mexico, Colorado, and Arizona. However, 43 cases have been reported to the CDC from California (CA) as well. Most cases in CA have been documented on the CA-Nevada border in the Sierra Nevada mountain range. However, environmental surveillance data has shown *P. maniculatus* serologically positive for SNV infection throughout southern and northern CA. There are usually from 0 to 5 cases documented each year in CA. Although Los Angeles County (LAC) residents have been previously identified with SNV infection, the cases were thought to have acquired infection outside of LAC.

In 2006, two cases of fatal SNV infection were documented in LAC residents. The first case was most likely acquired in Mono County, CA in an area where the human HPS had been previously documented. The second case of HPS was most likely acquired in the Antelope Valley of LAC. Although hantavirus infection had been documented in deer mice from past annual environmental surveillance data in the Antelope Valley, no human cases of HPS had been previously documented.

CASE REPORTS

Case 1: A 52 year-old male with history of hypertension, sleep apnea, and morbid obesity presented to a medical center in Reno, Nevada (NV) with complaints of progressive shortness of breath, wheezing, coughing and increased sputum production for the past three weeks. Prior to seeking care in Reno, this patient had spent one month camping in the family trailer with his wife at Robinson Creek campground, located in the Sierra-Nevada Mountain Range within Mono County, California.

Upon initial evaluation at the medical facility in Reno, the patient was noted to have an O_2 saturation at 90% on 10L of oxygen with a chest radiograph showing hypo-inflation with atelactasis versus infiltrates.

The patient's admitting diagnoses included: chronic obstructive pulmonary disease, pneumonia, and rule-out myocardial infarction. Within five days of his hospitalization, it was apparent that both his renal and pulmonary functions were deteriorating. He developed renal failure, creatinine of 2.4 mg/dl with hematuria and also required mechanical ventilation. Additionally, he developed thrombocytopenia with a platelet count of 61,000. The patient was placed on broad spectrum antibiotics initially and cared for in the intensive care unit. In addition to routine blood, urine, and sputum culture, additional infectious disease work-up was requested to include: hantavirus serological testing, blood smears for *Borrelia* sp., urinary *Legionella* antigen, and serological testing for West Nile virus and Rocky Mountain Spotted Fever. All blood, urine, and sputum cultures showed no growth and serological testing was negative with the exception of hantavirus serology which was strongly positive. Acute hantavirus (SNV specific) titers initially performed at the State of Nevada Public Health Laboratory were notable for an IgG $\geq$ 1:6400 and IgM $\geq$ 1:6400, consistent with acute hantavirus pulmonary syndrome. No additional convalescent hantavirus titers were obtained on this patient. These serological results were additionally confirmed at State of California Viral and Ricketsial Disease Laboratory (VRDL). The patient ultimately died of fulminant respiratory failure within 11 days of admission. No autopsy was conducted on this case.

Case 2: On July 22, 2006, a previously healthy sixteen year-old Hispanic male was initially seen at an outpatient clinic with a one-day history of high fever and headache. His evaluation consisted of blood cultures, complete blood count, blood chemistries and a computerized tomography head scan. All tests were normal and the patient was discharged home. The patient was seen again on July 24, 2006 due to persistent fevers, progressive shortness of breath, and severe headache. His evaluation revealed a bilateral pneumonia, thrombocytopenia, elevated hemoglobin and severe hypotension. He was subsequently admitted to an inpatient medical center with a diagnosis of sepsis and pneumonia and later requiring mechanical ventilation. On July 26, 2006, he was seen by an infectious disease specialist who placed him on broad spectrum antibiotics and also treated with a new "sepsis" drug (Xigris). The working diagnoses included: adult respiratory distress syndrome (ARDS), septic shock, and rule out meningitis. A spinal tap was not performed due to low platelet counts. On July 26, 2006, the infection control practitioner from the inpatient medical center reported the case as an "unusual occurrence" to the Los Angeles County Department of Public Health Acute Communicable Disease Control (ACDC) Program. After reviewing the medical chart and additional discussion with the infectious disease specialist on this case, additional infectious disease work-up was recommended which included testing for: WNV, HIV, Hantavirus, and urinary *Legionella* antigen. All labs were unrevealing including blood cultures, serologic testing for WNV, HIV, other viral pathogens, as well as *Legionella*. The patient's serum specimen was sent to the state of California VRDL and acute serological results were strongly consistent with acute SNV infection with IgM $\geq$ 1:1600 and IgG $\geq$ 1:6400. Despite aggressive medical care, the patient died 19 days after his admission to the medical center.

During the six week period before the onset of his illness the patient completed his junior year of high school, and worked at a nearby fast food restaurant. He had quit his job at a local fast food restaurant the first week in July. His parents could not recall the patient complaining of seeing with rodent dropping or rats or mice during his time working. However, during the first week in July, his last days on the job were spent cleaning the store room behind the kitchen. Other summer activities included rabbit hunting, visits to a regional park and odd jobs gardening and painting were confined to the Antelope Valley. During this period he resided with his family in a mobile home and at a nearby friend's home, where no infestations of rodents were reported.

METHODS

Medical chart review was completed on the two reported cases of suspected HPS. The family of Case #2 was extensively interviewed by a physician from ACDC and investigators from the LAC Environmental Health Vector-borne Disease Surveillance Unit for possible sources of exposure to hantavirus. Serological testing for both human and rodents for hantavirus infection was conducted at the State of CA VDRL using ELISA methodology.

Case Definition: A confirmed case of HPS is a febrile illness characterized by bilateral interstitial pulmonary infiltrates and respiratory compromise usually requiring supplemental oxygen and clinically

resembling acute respiratory disease syndrome (ARDS). The typical prodrome consists of fever, chills, myalgia, headache, and gastrointestinal symptoms. Typical clinical laboratory findings include hemoconcentration, left shift in the white blood cell count, neutrophilic leukocytosis, thrombocytopenia, and circulating immunoblasts [5].

The appropriate laboratory criteria for diagnosis are:

- detection of hantavirus-specific immunoglobulin M or rising titers of hantavirus-specific immunoglobulin G, or
- detection of hantavirus-specific ribonucleic acid sequence by polymerase chain reaction (PCR) in clinical specimens, or
- detection of hantavirus antigen by immunohistochemistry

A field investigation was conducted by California Department of Health Services (CDHS) Vector-borne Disease Section to determine the source of hantavirus-infected deer mice surrounding infection in Case #1. The LAC Environmental Health Vector-borne Disease Surveillance Unit conducted rodent trapping in multiple locations within the Antelope Valley that Case #2 frequented. Investigation consisted of trapping of rodents and obtaining serum from deer mice, *P. maniculatus*, and completing serological testing and PCR testing for hantavirus infection.

RESULTS

Human Serological Results: Only acute serological evaluations were obtained from both Case #1 and #2 during their initial evaluation. Both cases had strongly positive acute IgM and IgG consistent with recent hantavirus (SNV-specific) infection. The first case was found to have an IgM $\geq$ 1:6400 and IgG $\geq$ 1:6400 and the second had an IgM $\geq$ 1:1600 and IgG $\geq$ 1:6400.

Autopsy Findings and RT- PCR Evaluation: No autopsy was performed on Case #1. Autopsy on Case #2 revealed severe pulmonary edema consistent with ARDS and cerebral edema. Both pulmonary and renal tissues obtained at autopsy did not reveal hantavirus RNA upon RT-PCR.

Environmental Health Investigation

Case #1: On August 3, 2006 staff of the CDHS Vector-borne Disease Section (VBDS) initiated a site inspection and rodent surveillance at Robinson Creek Campground in Mono County. The first stop was the Bridgeport District Ranger Station on August 3. VBDS staff consulted with the District Ranger and campground hosts and informed them of the purpose of the visit. Several campground visitors expressed concern to VBDS staff about rodents that they had observed entering their campers or recreational vehicles. VBDS staff observed fresh mouse droppings under the sofa-bed of one guest's vehicle. VBDS staff offered safety tips on avoiding exposure to SNV to many campers.

Ninety folding traps were set at several campsites and inside buildings. A total of 81 rodents were collected. Serum specimens for SNV serologic testing were collected from 41 deer mice (*P. maniculatus*) and 2 mountain voles (*Microtus montanus*). Seven of the deer mice were trapped within the two campsites the case-patient occupied. Serum antibodies to SNV were detected in 19 of 41 deer mice and 1 of 2 voles, including 4 of the 7 trapped from the case-patient's campsites.

Case #2: On August 14-16, 2006, staff of the LAC Vector-borne Disease Surveillance Unit (VBDSU) visited the case-patient's residence to conduct visual evaluation and rodent surveillance. No rodents were captured in 20 traps set over-night at the patient's residence. Eight rodents, including three *P. maniculatus*, were captured in 53 traps set nearby at a friend's residence. Visual inspection of the friend's mother's worksite, and a regional park where the patient reportedly frequented revealed no evidence of rodent activity. Visual evaluation of the patient's worksite demonstrated nine surrounding habitats conducive to deer mouse presence.

LAC VBDSU conducted a second round of rodent surveillance on August 21-23, 2006. Six rodents, including one *Peromyscus* sp., were collected in 40 traps set in a field near the friend's residence. Two rodents, including one *Peromyscus* sp., were captured in 10 traps set near the patient's work site. No rodents were collected in 20 and 22 traps set at the patient's residential mobile home park and school, respectively.

Serum specimens from five *Peromyscus* sp. were collected and tested at VDRL. Only one of the five collected specimens was positive for hantavirus. The positive specimen was collected in a field adjacent to the residence of the patient's friend and was also found to positive for hantavirus by RT-PCR evaluation of pulmonary tissue of the deer mouse.

DISCUSSION AND PREVENTION

In 2006, two cases of hantavirus infection were confirmed in LAC residents. Both cases had onset dates in late spring and summer which is the usual peak period for hantavirus infection. The first case, most likely acquired in hantavirus exposure in Mono County, while the second case probably acquired infection within the Antelope Valley. Previous CA hantavirus pulmonary syndrome cases have been documented to have been acquired in Mono County, CA, however, this is the first time that human hantavirus infection has ever been documented within LAC.

The first case was documented in a known endemic area for hantavirus infection in the CA- Nevada border in the Sierra-Nevada Mountain Range. We can speculate that with the first case, exposure was probably peridomestic, likely associated with live deer mice and their excreta during a camping trip at Robinson Creek campground in Mono County. The second case was most likely acquired in the Antelope Valley area of LAC. Exposure probably occurred from rodents located at the patient's friends' residence. Field surveillance data documented one of five trapped deer mice (*Peromyscus* sp) had been infected with hantavirus by both serological and PCR testing. Although only one deer mouse was trapped that was positive after an extensive investigation, it is very possible that exposure could have been 4 to 8 weeks prior to the field investigation when the infected deer mouse population was at a much higher level.

Unfortunately, both cases were fatal. There is still no established antiviral therapy that has proven effective in the treatment of HPS. Treatment remains supportive with aggressive management in the intensive care unit with ventilator support and fluid management and use of ionotropic pressers agents as needed. Therefore, prevention of hantavirus exposure is critical. The best available approach to disease control and prevention is risk reduction through environmental modification and hygiene practices that deter rodents from colonizing the home and work environment, as well as safe cleanup of rodent waste and nesting material. Rodent control in and around the home remains the primary strategy in preventing hantavirus infection by undertaking such measures as keeping food and water covered and stored in rodent-proof container and keeping pet food and trash in rodent-proof containers. Additionally, various precautions outside the dwelling include disposing of trash, placing woodpile and stack of lumber at least 100 feet from the dwelling, and removing excess brush and shrubbery close to the home. Making homes rodent-proof is also an important preventive strategy. All gaps and holes inside and out of the home ≥¼ inch should be sealed. Gaps and holes are common around windows and doors and between the foundation of the home and ground. Further guidance to workers, campers and hikers with frequent exposure to rodents can be found in a recently MMWR devoted to HPS risk reduction [6].

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