Hantavirus

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Sin Nombre virus (SNV), an emerging pathogen in the United States, was identified in 1993. This hantavirus, a member of the *Bunyaviridae* family of RNA viruses, is transmitted by its reservoir host *Peromyscus maniculatus,* the deer mouse. Transmission is by inhalation of aerosolized feces, urine, or saliva from the infected mice. The illness that pursues, hantavirus pulmonary syndrome (HPS), is characterized initially by mild flu-like symptoms, followed by rapid progression to respiratory distress. There is no established therapeutic regimen and treatment is only supportive. Preventive methods include attempts to minimize contact with the rodents since elimination of the virus is not realistic.

ABBREVIATIONS: BUN = blood urea nitrogen; DIC = disseminated intravascular coagulation; ECMO = extracorporeal membrane oxygenation; ELISA = enzyme linked immunosorbent assay; EPA = Environmental Protection Agency; HFRS = hemorrhagic fever with renal syndrome; HPS = hantavirus pulmonary syndrome; IHC = immunohistochemistry; NO = nitric oxide; PT = prothrombin time; PTT = partial thromboplastin time; RNA = ribonucleic acid; RT-PCR = reverse transcriptase polymerase chain reaction; SNV = Sin Nombre virus

INDEX TERMS: hantavirus; hantavirus pulmonary syndrome.

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Focus Continuing Education Credit: *see pages 50 to 53 for learning objectives, test questions, and application form.*

Learning Objectives

1. Identify the geographical area in which the initial endemic of HPS occurred.
2. Identify the primary means of transmission for hantavirus.
3. Describe the four phases of clinical manifestations of HPS.
4. Discuss the pathology and pathophysiology of HPS.
5. Describe the three diagnostic laboratory tests for HPS established by CDC.
6. Identify three characteristic hematological and six chemical findings associated with HPS.
7. Discuss the treatment of and steps to avoid infection with hantavirus.

In the age of HIV, cancer, and a plethora of emerging infectious diseases, a new virus has brought deadly havoc in the United States and other parts of the world. In 1993, the first documented cases of hantavirus infections appeared in the Four Corners Region of the U.S. Because of mysterious deaths due to adult respiratory distress syndrome (ARDS), the Sin Nombre virus (SNV), an RNA virus that belongs to the *Bunyaviridae*, has silently ascended the mortality charts.[1] The initial endemic area, which includes the northeast corner of Arizona, the southeast corner of Utah, the southwest corner of Colorado, and the northwest corner of New Mexico, reported additional deaths in that same year. Since its first occurrence, studies have exposed a proliferation of the organism and the disease it produces, hantavirus pulmonary syndrome (HPS).

The greatest incidence continues to occur in the Four Corners region, but individuals who live in states that harbor the reservoir host, deer mouse, *Peromyscus maniculatus*, are susceptible to HPS.[2] Although closely related to other known hantaviruses, genetic studies of rodent and human tissue demonstrated that this was a new virus.[3,4] The expedient identification of SNV was facilitated by results from research studies of the other hantaviruses.[5,6] Retrospective studies of patient specimens from 1959 revealed that HPS had previously occurred, but was not recognized until 1993.[5,7,8] The prototype virus, Hantaan, was isolated from mice near the Hantaan River in South Korea in 1976.[8,9] Hantaan virus and other pathogenic species known before 1993, Seoul, Dobrava, and Puumala, produce disease referred to as hemorrhagic fever with renal syndrome (HFRS).[8]

CLINICAL MANIFESTATIONS

Following an incubation period of one to five weeks, HPS consists of four phases: febrile, cardiopulmonary, diuretic, and convalescent.[6,7,10,11,12,13] The febrile stage, the prodromal period, ranges from one to twelve days but averages three to five days. The typical characteristics of the febrile phase include fever, myalgia, malaise, headache, dizziness, anorexia, nausea, vomiting, and diarrhea. Gastrointestinal symptoms, which can mimic other less severe viral infections, may also be present. Thus, diagnosis of HPS during this period may be difficult. At the end of the prodromal phase and the onset of pulmonary edema, nonproductive cough and tachypnea ensue. Physical examination may yield rales or signs of pleural effusion.[6,10,12]

The cardiopulmonary phase tends to progress rapidly (four to twenty-four hours). The characteristic presentation is shock and pulmonary edema, accompanied by hypotension, oliguria, and sometimes weakness and delirium. Although non-cardiogenic in origin, tachypena, exertional dyspnea, and nonproductive cough result from pulmonary edema. The capillary wedge pressure is normal as well as the heart size on x-ray. Another common feature is hypoxemia with an oxygen saturation of hemoglobin less than 95%. There is a progressive leakage of high protein fluid from circulating blood into the lung interstitium and alveoli resulting from hypovolemia. Progressive leak and myocardial failure also contribute to shock. Once pulmonary edema is present, the disease progresses rapidly; patients usually die within 48 hours from hypoxia and or circulatory compromise.[6,12]

If the patient survives the cardiopulmonary phase, two additional phases follow. The third phase is the diuretic phase, which is characterized by a rapid resolution of pulmonary edema, shock, and fever. Diuresis usually precedes this process.[6,12]

The final phase is the convalescent phase. This phase may last up to two months and patients appear to recover; however, there is not enough evidence yet to determine the long-term recovery.[10,13,14] Current findings show that pulmonary dysfunction seems to be short-term.[13]

TRANSMISSION

SNV is transmitted by rodents, in particular the deer mouse, *Peromyscus maniculatus*. Infected mice shed the virus in their urine, saliva, and droppings. Humans acquire the virus primarily by aerosol inhalation, usually during spring and summer. Other ways the virus may be acquired include: rodent bites, cross contamination between nose and mouth, articles that have been contaminated by rodent body fluids or feces, and contaminated food. Person-to-person transmission of classical SNV has not been reported in the U.S.; however person to person transmission, as well as occurrence of childhood disease have been reported in South America.[10,12,14]

RISK FACTORS

SNV is nondiscriminatory and will affect anyone that comes into contact with it, regardless of age, gender, race, or health. Activities that enhance one's contact with rodent body fluids, feces, or nesting materials, pose a higher risk. Several factors such as 1) poorly ventilated rooms, 2) housecleaning activities, 3) hiking or camping, 4) construction and utilities work, 5) any activity that stirs up dust, or 6) being in an area where a large number of rodents reside can increase one's risk of acquiring the virus.[9,12-15]

PATHOLOGY AND PATHOPHYSIOLOGY

In SNV infections, consistent histopathological features have been observed.[6,7,8,10,16,17] The viral antigens of SNV have been shown by immunohistochemistry analysis to be distributed primarily within the endothelium of capillaries throughout various tissues. The most notable accumulations of viral antigens are seen in the pulmonary microvasculature and in the dendritic cells within the lymphoid follicles of the spleen and lymph nodes. The basic histopathological findings in the lungs are interstitial pneumonitis with mononuclear cell infiltrates, congestion, and both interstitial and intra-alveolar edema.[10] In the spleen, large immunoblasts in the red pulp are consistently found. Endothelial cells have been shown to have a high viral load, with the viral antigens regularly seen in the capillary endothelial cells in various tissues throughout the body. Pulmonary endothelial involvement is far greater in SNV than seen in other hantaviral syndromes.[10]

The microvasculatures of the kidney show SNV antigens in the medulla and glomeruli, but minute amounts are noted in the tubular epithelial cells. In cardiac tissue, there is no evidence of tissue damage but large quantities of hantaviral proteins are observed in the microvasculature. In other hantaviral infections, lesions are observed on the organs, but in SNV infections there are no notable lesions.[10,12-14] Due to this information, it is believed that hantaviruses may induce altered endothelial function without overt cell death. Pulmonary edema plays an essential role in the fatality of the disease, and vascular endothelium dysfunction appears to be the major cause of the pathogenesis. This alteration is thought to be mostly the result of the immune response to the virus. Lymphoid infiltrates in the lungs consist of a mixture of T lymphocytes, particularly those expressing CD8, and macrophages. Cellular immunity mediated by activated cells may be the cause of lung injury in HPS.[10]

DIAGNOSIS

Radiological findings

Characteristic radiologic findings are also seen in HPS.[5-7,9,10,12,13] These findings begin with minimal changes of interstitial pulmonary edema and progress into alveolar edema with severe bilateral involvement. Pleural effusions are often large enough to be seen radiographically. The common findings are Kerley B lines (short linear opacities which are perpendicular to the pleural surfaces), peribronchial cuff, and alveolar interstitial fluid in the basal segments.[10,12,14] About one-third of the patients show evidence of pulmonary edema in the initial radiograph, and nearly all patients demonstrate interstitial edema 48 hours after the initial radiograph and two-thirds have developed extensive bibasilar or peripheral airspace disease.[13]

The clinical manifestations, laboratory results, and radiologic findings can mimic other conditions; therefore, HPS must be part of the differential diagnoses.

Laboratory findings

Characteristic hematological and chemical findings are associated with SNV infection.[7,8,10,12,13,18] In approximately 80% to 98% of the cases, thrombocytopenia with platelet counts less than $15x10^9$/L is observed.[10] Initially, the white blood count may be normal or elevated with progression to very high levels. Typically, a left shift is seen. Immature granulocytes, up to 50%, immunoblasts, and hemoconcentration are commonly seen at the onset of pulmonary edema.

Other laboratory findings include elevated creatinine, elevated blood urea nitrogen (BUN), proteinuria, abnormal urinary sediment, elevated hepatic enzymes with normal bilirubin levels, hypoalbuminemia, metabolic acidosis, slightly elevated aspartate aminotransferase, elevated lactate dehydrogenase, and in severe cases, lactic acidosis.[12-15] In most severe cases of HPS, disseminated intravascular coagulation (DIC) develops. Therefore, abnormal partial thromboplastin time, prolonged thrombin time, decreased fibrinogen, elevated fibrin split products, and elevated prothrombin time (PT) may be observed. The prognosis is poor when metabolic acidosis, prolonged PT, partial thromboplastin time (PTT), and rising serum lactate levels develop.[18]

According to the Centers for Disease Control and Prevention (CDC)), a laboratory diagnosis of HPS is based on 1) a positive serological test result, 2) evidence of viral antigen in tissue by immunohistochemistry, or 3) the presence of amplifiable viral RNA sequences in blood or tissue, with a compatible history of HPS.

IgM capture enzyme-linked immunosorbent assay (ELISA), a widely used serological test, detects antibodies to SNV in acute infection.[8-10,13,14,15] The ELISA methodology also detects IgG antibody detection; therefore, acute and convalescent phase infections can be identified by a four-fold rise in IgG titer. The ELISA IgG has been found to be the most appropriate serological test in epidemiological investigations of the disease, because patients who have recovered from HPS retain the antibody for many years.

The Western Blot assay uses recombinant antigens and isotype-specific conjugates for IgM-IgG differentiation.[14] The results of this test have been in agreement with the IgM capture assay. A new investigational prototype assay is the rapid immunoblot strip assay (RIBA) that identifies serum antibody to recombinant proteins and peptides specific for SNV.[14] Traditionally, neutralizing plaque assays have been the serologic confirmatory test for other hantaviral diseases; however, this test is not commercially available for SNV. Routine virus isolation is not an option at this time because the virus has not been recovered from humans.[7]

Immunohistochemistry (IHC) has been proven to be very valuable and plays an important role in diagnosis when serum samples and frozen tissues are unavailable.[14] IHC tests formalin-fixed tissues with specific monoclonal and polyclonal antibodies to detect SNV antigens. This method has been proven to be a sensitive method for laboratory confirmation, and is also useful in the retrospective assessment of disease prevalence in a specified geographic location.

Reverse transcriptase-polymerase chain reaction (RT-PCR) can detect SNV RNA in fresh-frozen lung tissues, blood clots, nucleated blood cells, or buffy coats.[10,12-14] This method has a downfall, however, because it is very susceptible to cross-contamination and should be limited to a research or experimental environment.[12]

TREATMENT

There is no established therapy or treatment for SNV infections.[10] The major challenge in treating SNV infection is the delay in diagnosis; by the time the virus is identified, the patient has already progressed to the end stages of the disease or is in respiratory distress. The antiviral drug, ribavirin, has been shown to be effective in treating patients infected with hemorrhagic fever with renal syndrome (HFRS), but the efficacy in for HPS is unclear.[13] If ribavirin is to be used in HPS, it must be administered early in the prodromal phase. Because early diagnosis of HPS is difficult, all suspected HPS patients should be given a broad spectrum antibiotic until the causative agent is confirmed.[10] The only available treatment is supportive in nature. It has been shown that early intensive care management is very important. Once in the intensive care unit, patients are intubated and given oxygen therapy which helps them through the period of severe respiratory distress. Electrolyte, pulmonary, and hemodynamic abnormalities should be corrected promptly and crystalloid or colloid fluids should be given to patients who are hypotensive. A major problem in treating HPS occurs when the patient develops a severe pulmonary capillary leak along with myocardial insufficiency and shock which requires increased cardiac filling pressure. As the pulmonary capillary pressure increases, fluid begins to pour into the alveolar space. The use of flow-directed catheterization of the pulmonary artery will correct this situation and aids in monitoring and clinically managing the patient. Extracorporeal membrane oxygenation (ECMO) and inhaled NO have been used as salvage options, but the efficacy of these methods have not been fully determined.[12-14]

PREVENTION

The key to preventing SNV is to minimize human-rodent contact. A sanitary environment is of utmost importance; seal food in rodent-proof containers, keep garbage receptacles tightly fastened and distant from the house, and place adequate rodent traps in suspected areas. Other preventive methods include the use of EPA approved rodenticides, securing any possible rodent entry holes, removing debris from areas around building foundations, and elevating wood piles and trash receptacles. Although elimination of the rodent population is not feasible, these methods are effective in reducing man-rodent contact.[14]

CONCLUSION

Disease caused by the Sin Nombre virus or HPS is a serious viral zoonotic infection because of its quick mortality. Epidemiology of HPS parallels the ecology of the rodent host, and most infected patients have associated risk factors for exposure during spring or summer. Laboratory diagnosis is primarily by serology, although antigen detection in tissue by immunohistochemistry and amplification of any RNA in blood and tissue can be used. Treatment is only supportive, and the best prevention is to minimize contact with rodent excreta.

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