Review Article

A Review on Hantavirus

Hemant K Khairnar*, Rajesh J Oswal and Rishikesh V Antre

Medicinal Chemistry Research laboratory, JSPM`s Charak College of Pharmacy & Research, Wagholi, Pune, Maharashtra, India.

ABSTRACT

Hantaviruses are a group of viruses that are carried by many different kinds of wild rodents (mainly wild rats and mice), all over the world. Other small mammals could also be infected, but they are much less likely to spread the virus to other animals or peoples.Hantaviruses cause two types of serious illness when transmitted from their rodent reservoirs to humans: hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS). Members of the genus *Hantavirus*, family *Bunyaviridae*, have a tri-segmented, negative-sense, single-strand RNA genome enclosed within a membrane derived from the Golgi apparatus.

The disease caused by hantavirus-hantavirus pulmonary syndrome (HPS) begins as a flu-like illness. Hantavirus pulmonary syndrome is usually characterized by pulmonary rather than kidney disease. The initial phase usually lasts for 3 to 5 days; the clinical signs during this period are similar to the prodromal stage of HFRS, and may include fever, myalgia, headache, chills, dizziness, malaise, lightheadedness, nausea, vomiting and sometimes diarrhea. There are two drugs which are being clinically tested, Ribavirin and Bradycor. Ribavirin, used in other parts of the world to treat viral infections such as hepatitis and herpes, seems to decrease mortality and duration of symptoms in severe hantavirus

Keywords Hantavirus, Hantavirus-hantavirus pulmonary syndrome.

INTRODUCTION

Hantaviruses are a group of viruses that are carried by many different kinds of wild rodents (mainly wild rats and mice), all over the world. Other small mammals could also be infected, but they are much less likely to spread the virus to other animals or peoples.Hantaviruses cause two types of serious illness when transmitted from their rodent reservoirs to humans: hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS). These viruses are harbored by both Old-World and New-World rodents, and hence, their epidemiology reflects the geographical restriction imposed by the host range of the rodent vector[1]. Hantaviruses first came to the attention of western medicine in the early 1950s when more than 3000 US troops fighting in the Korean war became ill with Korean hemorrhagic fever, which later came to be known as HFRS. The wave of HFRS cases presumably resulted from a high contact rate with rodents chronically infected with Hantaan virus (HTNV) as soldiers lived and fought in the open fields. The second category of illness, HPS, was first recognized in 1993 when an outbreak of severe respiratory disease struck in the Four Corners region of the US[2]. The hantavirus responsible for this disease, Sin Nombre virus (SNV), is harbored by the deer mouse (*Peromyscus maniculatus*)[3].

This mysterious disease starts like the flu with fever, coughing, and chills. However, the victims of this disease die a painful death, their lungs filling with fluids. This was the situation when Hantavirus Pulmonary Syndrome (HPS) first appeared in the United States. Quick response by medical investigators from the Federal Center for Disease Control and Prevention (CDC) identified the Southwest outbreak as a new strain of the hantavirus, which had been previously reported in other countries. Investigating scientists with the CDC immediately suspected that, as with other

hantaviruses, the likely carrier of the disease was a rodent. Preliminary tests conducted on rodents in the region indeed revealed the presence of the virus[4].

Classification, structure and replication strategy[1]

Members of the genus *Hantavirus*, family *Bunyaviridae*, have a tri-segmented, negative-sense, single-strand RNA genome enclosed within a membrane derived from the Golgi apparatus.The three gene segments, L, S, and M encode the L protein, nucleocapsid protein (N), and envelope glycoproteins (Gn and Gc; previously G1 and G2), respectively. Hantaviruses enter host endothelial cells via interaction of the larger viral glycoprotein (Gn) with the host's cell surface receptor(s); β_1 and β_3 integrins. Following entry, the precise steps are unknown, however, it is presumed that the virus is uncoated to liberate the three nucleocapsids that contain genomic RNA complexed with N and L proteins. Transcription, replication and assembly occur within the cytoplasm with L and S transcripts translated on free ribosomes, while the Gn/Gc precursor is co-translated on the rough endoplasmic reticulum. For the Old-World hantaviruses, experimental evidence clearly shows that the viral envelope derives from budding into the Golgi apparatus, while New-World viruses may mature at the plasma membrane. The molecular determinant(s) responsible for differences in the clinical course of the two diseases are unknown.

Etiologic Agent[4,5]

Hantaviruses (genus *Hantavirus*, family Bunyaviridae) are single-stranded RNA viruses belonging to the bunyavirus family. Numerous hantavirus species exist. They are a group of antigenically distinct viruses carried in rodents and insectivores (shrews). Each hantavirus is endemic in one, or at most, a few specific rodent or insectivore hosts, to which it is well adapted. At least 20 hantaviruses have been identified, but estimates of the exact number of viruses vary. Newly identified hantaviruses are often named for the location where the virus is found; however, some of these viruses are later reclassified. The Laguna Negra, Rio Mamore, Oran, Lechiquanas and Pergamino viruses, which were once thought to be separate hantaviruses, are now considered to be variants of Andes virus, and the New York virus and Monongahela virus are currently classified as variants of Sin Nombre virus. One variant of Dobrava virus (DOBV-Aa) is also called Saaremaa virus; whether this is a separate virus or a less pathogenic variant of Dobrava virus is controversial. Some hantaviruses have not yet been named."Nephropathia epidemica" is sometimes used for a mild form of HFRS, which is often caused by Puumala virus or Saaremaa virus.

Clinical Signs and Symptoms[5]

Depending on the virus, hantavirus infections vary from asymptomatic to severe. Flu-like symptoms with fever, chills, muscle pain, and cough are the primary symptoms.

Fever, fatigue, and muscle aches are the first symptoms of HPS

Hemorrhagic Fever with Renal Syndrome

The severity of HFRS varies with the causative agent. Hantaan, Dobrava and Amur virus infections usually cause severe symptoms. Seoul virus generally results in more moderate disease, while Puumala and Saaremaa (Dobrava Aa) virus infections are typically mild. Classically, the course of the disease has been divided into febrile, hypotensive/ proteinuric, oliguric, diuretic and convalescent stages; these stages are usually more evident in severe disease, and may not be seen in mild cases.

The onset of HFRS is usually abrupt; the initial clinical signs may include fever, chills, prostration, headache and backache. Gastrointestinal signs including nausea, vomiting and abdominal pain may also be seen; in some cases, the pain can be severe enough to mimic appendicitis. Patients may also develop injected mucous membranes, photophobia, temporary visual impairment, a flushed face and conjunctivae, or a petechial rash, which usually occurs on the palate or trunk. This prodromal stage typically lasts for a few days to a week, and is followed by the onset of renal signs. The first stage is the proteinuric stage. Hypotension may develop during this phase of the disease and can last for hours or days. Nausea and vomiting often occur, and death may result from acute shock. In severe cases, this is typically followed by an oliguric phase then a diuretic/polyuric phase as kidney function improves. Death can occur at any point, but it is particularly common during the hypotensive or oliguric phases. In severe cases, kidney failure may be seen.

Hantavirus Pulmonary Syndrome

The disease caused by hantavirus-hantavirus pulmonary syndrome (HPS) begins as a flu-like illness. Hantavirus pulmonary syndrome is usually characterized by pulmonary rather than kidney disease. The initial phase usually lasts for 3 to 5 days; the clinical signs during this period are similar to the prodromal stage of HFRS, and may include fever, myalgia, headache, chills, dizziness, malaise, lightheadedness, nausea, vomiting and sometimes diarrhea. Arthralgia, back pain and abdominal pain are occasionally seen. As the disease progresses, fluid builds up in the lungs, making it difficult to breath. Respiratory distress and hypotension usually appear abruptly, with cough and tachypnea followed by pulmonary edema and evidence of hypoxia. Cardiac abnormalities can occur, and may include bradycardia, ventricular tachycardia or fibrillation. After the onset of the cardiopulmonary phase, the disease usually progresses rapidly; patients may be hospitalized and require mechanical ventilation within 24 hours. Kidney disease can also be seen, but it tends to be mild; kidney damage occurs more often with the Andes, Bayou and Black Creek viruses. Hemorrhagic signs are rare in patients with HPS in North America, but more common in South America. Although recovery is rapid and patients usually recover full lung function, convalescence may last for weeks or months. Asymptomatic or mild infections appear to be rare with Sin Nombre virus, but may be more common with some South American hantaviruses. Andes virus infections tend to cause severe disease, while Choclo virus infections are usually milder.

Diagnostic Tests[5]

A definitive diagnosis can be made if the hantavirus is isolated from the patient; however, recovery is not always successful. In addition, some hantaviruses (including Sin Nombre virus) have never been isolated in cell culture. If viruses are found, they can be identified by virus neutralization. Hantavirus infections are often diagnosed by serology. Either the presence of specific IgM in acute phase sera or a rise in IgG titer is diagnostic. Serological tests include the immunofluorescent antibody test (IFA), enzyme-linked immunosorbent assays (ELISA), immunoblotting and virus neutralization. Commercial ELISA and/or immunoblot assay kits have been developed for Dobrava, Hantaan, Puumala, Seoul, Sin Nombre and some other viruses. Rapid immunochromatographic IgM antibody tests have been described in the literature for acute Dobrava, Hantaan and Puumala virus infections. Hantaviruses can cross-react in some serologic assays.

Hantavirus infections can also be diagnosed by finding antigens in tissues with immunohistochemistry. Viral RNA can be detected in blood or tissues with reverse transcriptase- polymerase chain reaction assays (RT-PCR). PCR assays that can differentiate some hantaviruses have been described; one published assay identifies Dobrava, Hantaan, Seoul and Puumala viruses. Real-time RT-PCR has been described for some viruses.

Treatment[6]

There are two drugs which are being clinically tested, Ribavirin and Bradycor. Ribavirin, used in other parts of the world to treat viral infections such as hepatitis and herpes, seems to decrease mortality and duration of symptoms in severe hantavirus cases if given within five days of disease onset.

Antiviral therapy[1]

Ribavirin was tested for efficacy in HFRS patients in China and shown to have a statistically significant beneficial effect if initiated early in the disease course. Two double-blind, placebo-controlled efficacy trials have been performed in persons with HPS in the cardiopulmonary phase. The first was a trial of ribavirin conducted in the US and Canada by the NIAID-sponsored Collaborative Antiviral Study Group, and the second is an ongoing NIH-NIAID-sponsored controlled trial of intra-venous methylprednisolone in Chile. In the first trial, the majority of the patients were in the cardiopulmonary stage when they enrolled, and treatment with ribavirin had no clinical benefit, suggesting that its efficacy may depend on the phase of infection and the severity of disease when treatment is initiated and calling attention to the need for early intervention. Using clinical, radiological and peripheral blood smear criteria, over 90% of the subjects enrolled in these trials based on a presumptive diagnosis of HPS in the cardiopulmonary phase have subsequently had the diagnosis confirmed[7].

Immunotherapy

Administration of human neutralizing antibodies during the acute phase of HPSmight proves effective for the treatment and/or prophylaxis of hantaviral infections. Bharadwaj et al. measured antibodies at hospital admission and found that patients with lower titers of neutralizing antibodies often had severe disease, while those with higher titers had mild disease. The authors speculated that a strong neutralizing antibody response, or passive immunotherapy, might effectively reduce viremia and promote recovery. Reduced levels of viremia at hospital admission, as measured by numbers of viral genomes in plasma, were associated with reduced severity of HPS caused by SNV. At present, there have been no published reports of controlled clinical trials of immunotherapy for HFRS or HPS. However, studies in mice, hamsters and rats have indicated that passive transfer of neutralizing mAbs or polyclonal sera to HTNV can passively protect animals from challenge with the same virus. HTNV Gc-specific neutralizing mAbs, administered up to 4 days after challenge protected hamsters from infection, and up to 2 days after challenge protected suckling mice from lethal disease. Similarly, hamsters treated with immune plasma from ANDV patients and deer mice treated with plasma from SNV patients were protected against homologous virus challenge.Post-exposure administration of antibodies has been shown to confer protection[8,9]. Passive transfer of sera from rhesus macaques, vaccinated with a DNA vector expressing the ANDV M segment, protected hamsters against lethal challenge with ANDV(250 LD50) even when administered 5 days after challenge. Hamsters treated with immune serum 1 day before challenge with ANDV were either sterilely protected or developed HPS after several weeks; the late deaths were probably caused by the emergence of virus that was not eliminated by the passive antibody treatment. These data suggest that a post-exposure prophylaxis regimen consisting of passive immunoprophyaxis and active vaccination would be effective for HPS, as has been shown for other viral diseases such as rabies, hepatitis A and B, and varicella.

Vaccines

No FDA-approved vaccine for HPS is available in the United States. A killed-virus vaccine, similar to approaches used in China and Korea, is not being pursued for several reasons, including the dangers associated with the mass production of virus under high-containment (BSL-4 for large preparations of virus) and unresolved questions of the efficacy of killed-virus vaccines. However, a number

of laboratories have been working to develop vaccines that employ viral antigens delivered by DNA vectors or as recombinant proteins. A vaccinia virus-vectored vaccine containing the M and S genes of HTNV was found to elicit neutralizing antibodies in humans; however, pre-existing immunity to vaccinia (smallpox vaccination) lessened its efficacy. In another approach, HTNV glycoprotein genes were used to pseudotype vesicular stomatitis virus[8,9]. This vaccine elicited neutralizing antibodies in mice and protected against HTNV infection. For plasmid DNA approaches, the basic strategy of most vaccine efforts has involved the M segment products which elicit a protective neutralizing antibody response.

Incubation Period[7]

Since HPS is relatively uncommon, the incubation period has not yet been well-defined; Few cases have had clearly defined exposures in time and place. The incubation period of other hantavirus diseases is typically one to four weeks, although HFRS from Hantaan virus has apparently had an incubation period up to six weeks. In an effort to determine the incubation period of HPS-causing viruses in the United States, eight cases were identified with well-defined and isolated exposures. These findings suggested an incubation period ranging from 9 to 35 days from the time of probable infection to onset of symptoms. Incubation periods of one week to 39 days and nine to 33 days have been reported in patients with HPS from Andes virus and Sin Nombre virus, respectively.

Pathogenesis

The pathogenesis of HPS is related to a profound abnormality in vascular permeability. The capillary leak syndrome is virtually confined to the lungs, and chest radiograph series typically chronicle the rapid onset of diffuse, bilateral interstitial, and later alveolar, pulmonary edema. There is also evidence for myocardial failure as an important component of the shock syndrome observed.

At postmortem the lungs are massively edematous, but microscopic studies find little necrosis. There are scant to moderate hyaline membranes, intact pneumocytes, and scarce neutrophils. However, there is interstitial infiltration by T lymphocytes and activated macrophages. These findings differ from those of typical adult respiratory distress syndrome and much pneumonia. Hantaviral antigens are detected primarily in endothelial cells, and those in the lung are heavily involved[10].

Initial Treatment of Hantavirus Pulmonary Syndrome in the Emergency Room and During Transport

Initial treatment during the observation period should be directed to symptomatic and supportive measures, such as the control of fever and pain with paracetamol (avoiding the use of aspirin), antiemetics, and bed rest. The observation period could be managed at a primary care center. However, if there is a high suspicion of HPS according to the proposed HPS algorithm, patients should be immediately transferred to an emergency room (ER). Treatment in the ER should focus on maintenance of blood pressure and oxygenation while transfer to an intensive care unit (ICU) is organized.

Conclusion

HPS is a significant health threat in endemic areas because of the sporadic and unpredictable occurrence of disease in formerly healthy adults, its high case–fatality rate and absence of vaccines or drugs. Vaccination of individuals in endemic areas or those who could be exposed to the virus in military, clinical or research settings would be an important strategy toward reducing the incidence of disease. If vaccines are successfully developed and licensed, it is likely they would be used in populations at high risk of exposure, including persons in endemic regions performing tasks that put them in contact with rodent excreta (e.g. farm and forest workers, military personnel). Antiviral therapeutics offer an alternative strategy for dealing with outbreaks in areas previously unrecognized to harbor

disease, accidental exposure in laboratory workers or deliberate introduction through bioterrorism. Unfortunately, except for ribavirin, no potential antivirals have been reported to show efficacy in animal models of HFRS or HPS. Thus, it is imperative to develop countermeasures to treat unprotected persons who havebeen exposed to these virulent pathogens[1].

Discussion

Some aspects of the epidemiology of HPS have been discussed in the peer-reviewed literature. However, no studies have provided a comprehensive evaluation of the epidemiology of HPS in the United States. Most cases are from the western half of the U.S country. However, cases have been reported in 30 states, including one in a Massachusetts resident who acquired HPS in New York. By maintaining a registry and obtaining information in standardized manner, we were able to evaluate the epidemiologic characteristics of HPS in >500 cases over 19 years of data collection. Although HPS is a nationally reportable disease in the United States, maintenance of our registry has enabled us to obtain more detailed and standardized information on HPS than otherwise possible through other national surveillance mechanisms.

REFERENCES

1. Jonsson CB, Hooper J and Mertz G. Treatment of hantavirus pulmonary syndrome. Antiviral Research. J Antiviral. 2007;10:012.
2. Antoniades A, Grekas D, Rossi CA and LeDuc JW. Isolation of a hantavirus from a severely ill patient with hemorrhagic fever with renal syndrome in Greece. J Infect Dis. 1987;156:1010–1013.
3. Arikawa J, Yao JS, Yoshimatsu K, Takashima I and Hashimoto N. Protective role of antigenic sites on the envelope protein of Hantaan virus defined by monoclonal antibodies. Arch Virol. 1992;126;271–281.
4. www.mass.gov/Eeohhs2/docs/dph/disease.../guide/hantavirus.pdf
5. http://www.cfsph.iastate.edu/Factsheets/pdfs/hantavirus.pdf.
6. http://www.esa.org/education_diversity/pdfDocs/hantavirus.pdf
7. http://www.paho.org/english/ad/dpc/cd/tp47_07.pdf
8. www.cdc.gov/hantavirus/pdf/HPS_Brochure.pdf.
9. http://www.worksafebc.com/publications/health_and_safety/by_topic/assets/pdf/hantavirus.pdf.
10. http://www.mass.gov/Eeohhs2/docs/dph/cdc/factsheets/hantavirus.pdf.