



HANTAVIRUS: A GLOBAL OVERVIEW

Medical Microbiology

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ABSTRACT

Hantaviruses are rodent-borne pathogens that can cause severe diseases in humans, primarily presenting as hemorrhagic fever with renal syndrome in Asia and Europe, and hantavirus pulmonary syndrome in the America. This review synthesizes global data on hantavirus infections, highlighting epidemiological trends, clinical manifestations, and preventive strategies.

KEYWORDS

INTRODUCTION

Hantaviruses, member of the Bunyaviridae family and genus Orthohantavirus, are enveloped, tri-segmented, negative-sense RNA viruses. They are predominantly transmitted to humans through contact with rodent excreta, including urine, saliva, and feces. While many infections are asymptomatic, some can lead to severe, life-threatening conditions. The genome of Hantaviruses contains three segments of single stranded, negative ribonucleic acid (RNA) molecules with a terminal sequence at their 3' end. These genome segments are named according to their nucleotide sequence length as small (S), medium (M), and large (L). Hantaviruses are enveloped viruses with a spherical structure of about 80 to 120 nm length in diameter. The envelope membrane is composed of bilayer of exterior lipids secreted from Golgi complex. The complex and unusual symmetry of the spikes is considered rarely common in enveloped viruses. Variation and genetic alterations in M and S segments can disturb the virulence and antigenicity of virus.

Pathogenesis

Hantaviruses basically infect rodents and are also found in small insectivorous mammals and bats. They cause asymptomatic infections in rodents, and are transmitted to humans through rodent bite, inhalation of aerosolized virus particles and via inhalation of dried feces, urine and saliva of rodents. Hantavirus infection in humans mainly affects the endothelial cells in lungs and kidneys. The infection begins with contact of surface proteins with β -integrin receptors, yet how hantaviruses spread in the human body is still not fully known. Given that they express 3-integrin receptors and are found close to epithelial cells, immature dendritic cells likely play a crucial role. Platelet dysfunction, immunological responses, and the disruption of endothelial cell barrier capabilities likely have a role in the pathological process of Hantavirus.

Epidemiology

Asia: China reports the highest incidence of hemorrhagic fever with renal syndrome (HFRS) globally, with approximately 150,000 to 200,000 cases annually. Between 1950 and 2007, an estimated 1.5 million cases and 46,000 deaths occurred nationwide. The primary causative agents are Hantaan virus (HTNV) and Seoul virus (SEOV). In 2021, 8,502 cases were documented across 29 provincial-level administrative divisions, resulting in 54 deaths, marking a 9.1% increase in cases compared to 2020.

Europe: Over 10,000 cases of HFRS and thousands of nephropathia epidemica (NE) cases are reported annually, primarily caused by Puumala virus (PUUV), Dobrava-Belgrade virus (DOBV), and Saaremaa virus (SAAV). Germany, Finland, and other European countries have documented significant case numbers, with Germany reporting over 2,800 cases in 2012. The severity varies, with case

fatality rates ranging from less than 1% to 12%, depending on the specific virus strain.

America: Hemorrhagic fever with renal syndrome (HPS) is primarily associated with Andes virus (ANDV) and Sin Nombre virus (SNV). Since its identification in 1993, the United States has reported 864 cases by the end of 2022, with a case fatality rate of approximately 35%. Cases are predominantly located west of the Mississippi River. Other countries, including Canada, Argentina, Brazil, and Chile, have also reported HPS cases, with varying incidence rates and mortality. The case fatality rate averages around 40%.

Transmission And Risk Factors

Hantavirus Is Mainly Transmitted Through:

- Aerosols and droplets: Containing rodent excretions
- Contaminated food: Consuming food contaminated with infected rodent excretions
- Bites and scratches: From infected rodents
- Environmental factors: Rainfall, temperature, and humidity can influence transmission

People At Higher Risk Of Infection Include:

- Farmers and forestry workers: Those who work outdoors and are exposed to rodents
- Hikers and campers: Individuals who spend time in areas with rodent infestations
- Rodent breeders and pet owners: People who handle rodents regularly

Clinical Manifestations

Hantavirus infections present differently across regions:

HFRS: It has five phases:

1. **Febrile phase: Characterized by fever and headache**
2. **Hypotensive phase: Marked by low blood pressure**
3. **Oliguria phase: Reduced urine production**
4. **Polyuria phase: Excessive urine production**
5. **Recovery phase: Gradual recovery**

It is characterized by fever, hemorrhagic manifestations, and renal failure.

HPS: It has three phases:

1. **Prodromal phase: Early symptoms like fever and muscle pain**
2. **Cardiopulmonary phase: Respiratory distress and cardiac issues**
3. **Recovery phase: Gradual recovery**

It begins with flu-like symptoms, progressing rapidly to severe respiratory distress and potential organ failure.

Diagnosis

Initial diagnosis can be performed by observing the symptoms associated. Screening tests such as Complete Blood Count (CBC) and peripheral smear can also be used. Serology is used to detect IgG and IgM anti-hantaviral antibodies in the blood of the patient. The IgM antibodies appear extremely early during the course of the infection, whereas IgG antibodies appear later in the process. Enzyme Linked Immunosorbent Assay (ELISA) and the strip immunoblot detects viral antibodies, but is disadvantageous is the potential for cross reacting with other viral antigens, but are still extremely useful and important for diagnosis purposes. Indirect Immunofluorescence assay is more specific than Elisa but it is laborious. Neutralization tests are the most specific serological tests but are costly, laborious and require BSL-3 conditions. Immunochromatographic tests are readily performed and are cheap but cross reactivity minimizes precision of results obtained. Molecular methods include Real Time RT PCR, an important, sensitive and fast technique for detecting viral RNA in blood, blood clots or tissues. Next Generation Sequencing (NGS) is also used for virus detection and complete sequencing but it is expensive and requires complex bioinformatics tools. Virological methods include isolation in cell cultures which allows extensive functional and virological studies. Immunohistochemistry by enzyme immunoassay and immunofluorescent test allows diagnosis from infected tissues of organs.

Treatment

Hantavirus infections are managed mostly by managing the symptoms, providing supporting care and admitting patients to the Intensive Care Unit (ICU), providing patients with oxygen therapy, by administering an antiviral ribavirin, which has showed reduction in death rate of patients still in their initial stages of infection. Treatment for HCPS patients includes respiratory and cardiac monitoring and support which includes mechanical ventilation, hemofiltration and membrane oxygenation. Supportive treatment for HRFS includes electrolyte infusion and hydration to stabilize blood pressure, acute thrombocytopenia is managed with transfusing platelets, uremia is managed with intermittent hemodialysis and continuous renal replacement therapy is given to manage multi-organ pulmonary edema. Recent therapies against Hantavirus include:

- Blocking viral entry-The following candidate drugs have been shown to increase survival rate only in the initial stages of HTNV infection, but are ineffective in later stages.-Griffithsin, Coumarin, Lactoferrin, Virus fusion inhibitors (domain III and stem peptides), Hantavirus-binding receptor inhibitors (cyclic nonapeptides)
- Blocking viral replication- using drugs -Ribavirin, ETAR, Favipiravir, Baloxavir acid, siRNA based therapy.
- Bradykinin B2 receptor antagonists
- Immunotherapy- using monoclonal or polyclonal antibodies
- Corticosteroid therapy

Preventive Measures

Preventing hantavirus infections involves minimizing contact with rodents and their excreta:

- Implement rodent control strategies in and around living areas.
- Seal potential entry points to prevent rodent ingress.
- Use protective equipment when cleaning areas potentially contaminated with rodent excreta.
- Maintain good sanitation practices to deter rodents.

In China, the development of vaccines like Hantavax has contributed to a decrease in HFRS cases, with less than 20,000 reported by 2007. However, as of 2019, no hantavirus vaccines have been approved for use in Europe or the USA.

CONCLUSION

Hantavirus infections remain a significant public health concern worldwide, with distinct epidemiological patterns across different regions. Ongoing surveillance, public awareness, and preventive measures are essential to mitigate the impact of these infections.

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