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HANTAVIRUSES AS EMERGENT ZOONOSES

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ABSTRACT: Hantaviruses belong to the Bunyaviridae family, which consists of vector-borne viruses. These viruses can provoke two infection types: hemorrhagic fever with renal syndrome (HFRS) – which occurs in the Old World – and hantavirus cardiopulmonary syndrome (HCPS) – an emergent zoonosis that can be found in many countries of the western hemisphere. Rodents are hantavirus reservoirs and each species seems to host a different virus type. Humans acquire the infection by inhaling contaminated aerosol particles eliminated by infected animals. The factors involved in the emergence of hantavirus infections in the human population include ecological modifications and changes in human activities. The most important risk factor is contact between man and rodents, as a result of agricultural, forestry or military activities. Rodent control remains the primary strategy for preventing hantavirus diseases, including via health education and hygienic habits.

KEY WORDS: hantaviruses, rodents, control, public health.

CONFLICTS OF INTEREST: There is no conflict.

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INTRODUCTION

The *Hantavirus* genus is widely distributed throughout the globe and causes two types of infections: hemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS) (1).

Several rodent species are reservoirs for hantavirus. These animals, when infected, do not necessarily show any clinical signs of the disease, although they can carry the virus for long periods. Humans acquire the infection by inhalation of contaminated excretory particles, mainly from feces and urine. Over twenty hantavirus serotypes have been described and each virus appears to have a specific rodent as its reservoir (23).

In Brazil, the viruses identified were: Juquitiba (26), Araraquara, and Castelo dos Sonhos (16). In 2000, two new viruses were isolated in Maranhão State, by the Evandro Chagas Institute, in Belém, Pará State. The first was named Anajatuba, after the city located in an area known as flooded Baixada Maranhense, and its reservoir was the wild rodent *Oligoryzomys fornesi*. The other was denominated Rio Maerim, after the main river of the region, its host being the small aquatic rodent *Holochilus sciureus* (9).

Hantaviruses are widely distributed in various continents, primarily in Asia, where they were originally described, in Europe and, more recently, in several countries of the Americas, where they are considered an emerging public health problem (4).

In 1951, during the Korean War, 3,000 soldiers of the United Nations were affected by HFRS associated with a virus. In 1978, this virus was isolated from wild rats on the banks of the Hantaan river, identified as Hantaan virus and classified among the Bunyavirus family (18).

The disease is disseminated in eastern countries – including China, Japan and and Russia (19) – and remains endemic in Korea, though the annual number of cases has decreased (25).

In Europe, HFRS is endemic in Finland, Sweden, Norway, Germany, France, Slovenia, Croatia, Serbia and Greece. The most serious cases have been reported in France and were caused specifically by Dobrava-Belgrade viruses (25).

In the Americas, the virus is distributed from southern Canada to southern Argentina, near Patagonia. In South America, cases of HCPS have been confirmed in Argentina, Brazil, Chile, Paraguay and Uruguay (22).

The factors responsible for the emergence of hantavirus infections in humans include changes in both ecological factors and human habits. The most important risk factor is contact with rodents as a result of human activities (21). So the main strategy of preventing hantaviruses is rodent control (1).

ETIOLOGICAL ASPECTS

These RNA viruses, belonging to the *Hantavirus* genus, Bunyaviridae family, are spherical viral particles, 90-100 nm in diameter, possessing envelope with double lipid layer that surround three nucleocapsids of helical symmetry. Their RNA is composed of three segments: large (L), medium (M) and small (S) (1). The S segment encodes the nucleocapsid protein (N), the M segment encodes G1 and G2 protein, and the L segment encodes viral RNA dependent on RNA polymerase (7).

This genus contains several virus types that differ antigenically from the Hantaan prototype. Each virus has a different type of rodent as main reservoir, with variable clinical and pathological effects in humans. Table 1 presents the main Hantaviruses that cause diseases in humans, as well as their reservoirs and geographic distribution (1).

Table 1. Hantaviruses and human diseases: highlighting viral type, clinical manifestations, reservoirs and distribution

Virus	Disease	Main reservoirs	Virus distribution
Hantaan	HFRS	*Apodemus agrarius*	China, Russia, Korea
Dobrava-Belgrado	HFRS	*Apodemus flavicollis*	Baltic region, Europe
Seoul	HFRS	*Rattus norvegicus*	The entire world
Puumala	HFRS	*Clethrionomys glareolus*	Europe, Russia, Scandinavia
Sin Nombre	HCPS	*Peromyscus maniculatus*	USA, Canada
New York	HCPS	*Peromyscus leucopus*	USA
Black Creek Canal	HCPS	*Sigmodon hispidus*	USA
Bayou	HCPS	*Oryzomys palustris*	USA
Andes	HCPS	*Oligoryzomys longicaudatus*	Argentina, Uruguay
Araraquara	HCPS	Unknown	Brazil
Bermejo	HCPS	*Oligoryzomys chacoensis*	Bolivia
Choclo	HCPS	*Oligoryzomys fulvescens*	Panama
Lechiguana	HCPS	*Oligoryzomys fulvescens*	Argentina, Uruguay
Laguna Negra	HCPS	*Calomys laucha*	Bolivia, Paraguay
Oran	HCPS	*Oligoryzomys longicaudatus*	Argentina
HU396904	HCPS	Unknown	Argentina
Aún sin denominar	HCPS	*Calomys laucha*	Paraguay
Anajatuba	HCPS	*Oligoryzomys fornesi*	Brazil
Rio Maerim	HCPS	*Holochilus schiureus*	Brazil

EPIDEMIOLOGY

All hantaviruses isolated worldwide were transmitted to humans through inhalation of viral particles of excreta from infected rodents. The human disease occurs due to contact with rodents that eliminate the virus via urine, feces and saliva. The infection occurs mainly when persons inhale aerosol containing the agent. There are other forms of transmission, less important, such as rodent bites, the ingestion of food contaminated with infected rodent feces or urine, and also contact with a virus-contaminated site followed by application of the hand to the nose or mouth (22, 25, 26).

The transmission can occur in any place infested by rodents including warehouses for storing grains, basements or attics of abandoned houses, buildings next to forests

or other environments where wild rodents could live. The infection occurs when viral particles are inhaled, usually during activities that disseminate these particles, such as cleaning of floors containing rodent excreta, demolition of buildings infested with these animals or in cases of grain removal from silos or warehouses. The transmission can also occur when humans use buildings that have been closed for weeks or months for leisure activities, such as hunting and fishing, or professional activities, including reforestation. No domestic animals – cows, chickens, sheep, dogs or cats – are considered carriers of the virus. There is no evidence that hamsters and mice, sometimes considered pets, can be virus hosts. Often dogs and cats hunt infected rodents and bring them into houses, which is a risk factor for human infection (4, 22, 25, 26).

Certain professional groups are more affected by hantavirus diseases, such as farmers, agronomists, veterinarians, zootechnists, geologists, civil construction workers (who operate in rural areas) and biologists (at least those devoted to the study of small mammals) (22). The professionals who work in activities like deforestation and reforestation are also exposed to wild reservoirs that eliminate the virus in the environment, in tents or in buildings used as accommodation.

There is also the possibility of interhuman transmission, as seen in Argentina and Chile. This infection route is rare and has been documented only for the Andes virus (30, 31).

Several rodent species have been implicated in the transmission of hantavirus to humans. In the Old World, members of Murinae and Arvicolinae subfamilies represent the most important transmitters of these viruses, particularly those that belong to the *Apodemus* and *Clethrionomys* genera. In the Americas, the wild rodents that transmit hantaviruses belong to the Sigmodontinae subfamily. The *Rattus* genus, including *R. norvegicus* and *R. rattus* species, transmit the Seoul hantavirus, which causes HFRS (10, 12).

It is known that at least two species of rodents are infected in the southern, southeastern and western regions of Brazil. One of them, *Bolomys lasiurus* – distributed throughout the states of São Paulo, Minas Gerais, Bahia, Goiás, Mato Grosso and Mato Grosso do Sul –, is the predominant rodent species in these areas. In the southern states, the transmitter appears to be *Oligoryzomis nigripes* in few cases described in Paraná, Santa Catarina and Rio Grande do Sul. In Maranhão, a water-dwelling rodent, belonging to the *Holochilus* genus, was identified as being

infected by the virus and regarded as a probable transmitter of the disease in this state. In countries that present vast dimensions, like Brazil, other wild rodent species can be carriers of hantaviruses with zoonotic potential (8).

Studies on serum samples, carried out in recent decades, have demonstrated the presence of anti-hantavirus antibodies in populations of northern Brazil, and Hantaan virus was isolated in household rats (17). Serological evidence of the disease caused by Seoul virus was detected in Recife, Pernambuco State, Brazil, in patients with primary suspicion of leptospirosis (12). The first Brazilian patients with HCSP were diagnosed in 1993, in Juquitiba, São Paulo State; three brothers acquired the disease in a deforestation area, two of whom died. Since this first description, the Brazilian virus has been known as Juquitiba (26). From that moment on, other cases of hantavirus infection have been described in various Brazilian states (Table 2).

Table 2. Frequency of cases (per year) and lethality caused by hantavirus in Brazil (1993 to 2007)

Year	Cases	Lethality (%)
1993	3	66.7
1995	1	100
1996	3	100
1998	11	72.7
1999	29	48.3
2000	55	34.5
2001	79	40.5
2002	74	50
2003	84	45.2
2004	163	37.4
2005	166	34.9
2006	187	34
2007	55	38.2

Source: Health Vigilance Secretary, Brazilian Health Ministry; preliminary data.

Until the beginning of June, 2007, 55 cases of the disease had been confirmed in Brazil and the lethality rate was 38.2% (considered high). There were 15 cases in Santa Catarina, 12 in São Paulo, seven in Minas Gerais, six in Mato Grosso, five in the Federal District, four in Paraná, three in Goiás and one in Rondônia (3). These data indicate the emergence of hantaviruses in Brazil and the importance of health surveillance actions for their detection and control.

Some cases of hantavirus infection registered in the states of Santa Catarina and Paraná, in 2005, occurred due to a phenomenon known as “ratada", which takes place, on average, every 30 years and is caused by drought and consequent flourishing of “taquara-lixa” (*Merostachys fistulosa*), a bamboo species that serves as food for rodents. When there is an excess of “taquara-lixa” seeds, the rodent population also undergoes an increase. Since these animals reproduce quickly, within a few months there is a lack of food and the rats invade homes and grain-storage areas, thus increasing the human risk for infection (24).

PATHOGENY

The physiopathological mechanisms of hantavirus infections that lead to HFRS or HCPS seem to be related to exaggerated immune response to the virus (20, 32). The viruses do not provoke the destruction of the cells that they infect and, by themselves, do not lead to the increase of the capillary permeability. The severity of the disease increases after the installation of the immune response. Clinical and anatomical pathological tests suggest the occurrence of functional changes in pulmonary capillary permeability and renal failure, reversible after appropriate clinical treatment (6, 32). In HCPS, immunohistochemical studies of lung tissue showed the extensive distribution of viral antigens in endothelial cells, without evidence of cell necrosis. The viral antigens are also present at other sites, such as heart and lymphoid tissue (29). In the lungs, there is considerable infiltration of CD8 lymphocytes, which are also present in peripheral blood in the form of atypical lymphocytes.

These cells, after activation, produce cytokines that will act directly on the vascular endothelium or will stimulate local macrophages to produce more cytokines that increase the vascular permeability, leading to massive transudation of liquids in alveolar space, which generates pulmonary edema and acute respiratory failure (13, 32). Antibodies, particularly IgM, emerge quickly in the course of infection and facilitate the diagnosis at an early stage of the disease (2). With regard to the infection caused by Andes virus, immunohistochemical studies in lung tissue have shown more extensive antigen distribution, which may explain the higher transmission rate by the respiratory route (22, 25, 32).

Hantavirus disease often leads to thrombocytopenia in over 80% of the cases. Its pathogenesis appears to be related to the virus' ability to be linked to the platelets, triggering the sequestration of movement (13, 22, 32).

CLINICAL MANIFESTATIONS

Hemorrhagic Fever with Renal Syndrome (HFRS)

The incubation period varies between seven and 42 days, and oligosymptomatic or subclinical infections are common. Classically, the clinical course is divided into five phases: febrile, hypotensive, oliguric, diuretic and convalescent. These periods can occur concomitantly and in mild cases be absent. The onset is sudden and the symptoms are: high fever, chills, headache, photophobia, myalgia, abdominal pain, nausea and vomiting. Diffuse cutaneous hyperemia affecting the face, neck and upper chest, petechias on the soft palate and in the underarms are common findings. The liver can be palpable in a significant number of cases. Many patients will recover from this stage, except in the case of some progress from hypotension to shock, which usually occurs before the fifth or sixth day. Bleeding is common at this stage, mainly in conjunctiva, skin, digestive-tract mucous membrane and central nervous system. There is loss of renal function, in general, 24 hours after hypotension, oliguria or even anuria. The recovery can be rapid, with emergence of diuresis and intense episodes of hypertension. The lethality rate is low, ranging from 1 to 10%. The infections caused by Puumala virus, prevalent in northern Europe, have the lowest lethality rate. Because of their clinical characteristics, they should be differentiated from leptospirosis and other viral hemorrhagic fevers (19, 20, 25).

Hantavirus Cardiopulmonary Syndrome (HCPS)

The HCPS is a febrile disease characterized by severe acute cardiovascular impairment (27). The incubation period is estimated to last up to 33 days, with an average of approximately 15 days. Early recognition based on initial signs is not easily accomplished and the infection can be mistaken for other endemic diseases prevalent in the same areas, such as dengue and leptospirosis (22).

The prodromic phase lasts between three and six days and precedes the appearance of pulmonary edema. At this stage, common symptoms are: fever, myalgia, nausea, diarrhea, headache, vomiting, abdominal and chest pain, sweating and dizziness. With the onset of the cardiopulmonary phase, the disease progresses

rapidly, requiring hospitalization and ventilatory assistance within the first 24 hours (11).

The cardiorespiratory phase is characterized by gradual infiltration of liquid and protein in the lung interstitium and alveoli, leading to tachypnea, hypoxia and tachycardia. Hypotension is common at thais stage and can provoke shock with severe myocardial depression, evidenced by the low cardiac output and increased systemic vascular resistance (27).

The involvement of other organs in the disease evolution may be due to Bayou virus, isolated in Texas, which evolves, in addition to pulmonary edema, renal failure and myositis (14). Bleeding has been rarely reported in these cases, but there are changes in clotting, which does not lead, however to disseminated intravascular coagulation (27).

The HCPS must be differentiated from many other acute infectious diseases that often occur in several western hemisphere countries, such as influenza, pneumococcal pneumonia, legionella, staphylococcal pneumonia, pneumonia caused by *Mycoplasma*, rickettsioses, respiratory anthrax, leptospirosis with respiratory involvement, dengue, malaria, acute histoplasmosis, Q fever and pneumocystosis. Still, some non-infectious diseases such as Goodpasture's syndrome, heart disease with acute pulmonary edema, mitral stenosis, acute myocardial infarction, bronchoalveolar cancer, among others, should be included in the differential diagnosis (5).

DIAGNOSIS

The diagnosis of hantavirus infection is primarily based on the completion of serological tests. Immunosorbent assay (ELISA) is the most widely used serological test and can differentiate between IgM and IgG antibody classes. The ELISA-IgM test is able to capture the antibody and avoid cross-reactions. Immunofluorescent antibody test (IFAT), neutralization, passive hemagglutination and western blotting can also be employed. The presence of IgM antibodies, which arise early, or four-fold IgG titles in paired serum samples confirms the clinical suspicion and the disease evolution. The IgG antibody level remains chronic and can be used in serological investigations (2).

Tissue immunohistochemistry can be performed in order to identify viral antigens and is an alternative to confirm the diagnosis. It is primarily employed in fatal cases, when it was not possible to obtain samples of serum during the disease evolution (22).

Reverse transcriptase-polymerase chain reaction (RT-PCR) consists of two steps, reverse transcription (converts an RNA cassette into cDNA) and amplification. The RT-PCR can be used to identify viral RNA in blood or tissue samples from suspected cases. This test usually identifies the viral RNA within seven to ten days of disease onset. Sometimes there are significant differences among viruses isolated from different regions or countries, thus decreasing the technique sensitivity and hindering its use (15, 22, 29).

TREATMENT

Treatment of HFRS is mainly supportive. During the febrile phase the patient must rest. Sedation, analgesic administration and hydric balance maintenance are indicated. Hypotension must be avoided. In the oliguric phase, hydric intake must be restricted and, when present, hypokalemia should be treated. In severe cases, hemodialysis is necessary. In the diuretic phase, hydroelectrolytic balance is the main point of concern (1).

In HCPS cases, pulmonary ventilation, careful monitoring of both hydroelectrolytic balance and blood pressure are recommended (1). Periodic patient assessment is indispensable to conducting the therapy, which must be rigid, or else the disease can be fatal.

PREVENTION AND CONTROL

Hantavirus prevention is based on measures that may avoid rodent presence and human contact with their excreta. The control of these natural virus reservoirs in a wild environment is not practical and can lead to ecological imbalance. However, the removal of these animals from areas adjacent to human habitation should be performed (10). The correct destination of waste, proper food storage and regular disinfection of environments are measures that reduce the occurrence of rodents in inhabited sites (28). Rural constructions, for human residence and for grain storage, must contain some protection against the entry of such animals (10).

Buildings closed for a long time must be opened first for ventilation and locations containing rodent excreta must be initially moistened with water containing detergent

or 10% sodium hypochlorite and, after 30 to 60 minutes, the place can be cleaned. Masks with a P3-type filter should be used during activities in contaminated environments (22).

Any population that resides in rural areas must be warned about the danger of acquiring the disease during domestic activities and should be encouraged to control the rodents on their properties through hygienic habits. Leisure activities undertaken in rural or forestry areas present risk of infection (8). In urban or rural domestic environments, the use of natural predators such as cats can facilitate the biological control of rodents.

Inter-human transmission, through breathing, has been registered only via Andes virus in Argentina and has not been observed in other countries. The measures recommended for patient management include the use of gloves and aprons, which prevent contact with secretions. The use of masks or general systems of air filtration is not necessary (22).

Epidemiological surveillance actions must be conducted and complemented by studies on zoonotic potential of different wild rodent species. In addition, health education measures must be practiced and directed chiefly to the main risk groups, emphasizing the epidemiological aspects including transmission and control possibilities of hantaviruses.

FINAL CONSIDERATIONS

Hantavirus infections are caused by viruses widely distributed in many parts of the world. Several wild rodent species are hantavirus reservoirs and humans acquire the disease by inhalation of contaminated aerosol particles.

The most important risk factor is close contact with rodents while control of these animals is the major form of prevention. Hygienic habits, health education, avoidance of places closed for a long time, before thorough cleaning, are other steps to decrease the infection risk of this emergent disease.

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