

Twenty years of hantavirus pulmonary syndrome in Brazil: a review of epidemiological and clinical aspects

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Abstract

Hantavirus infection is transmitted to humans by wild rodents and the most common clinical form in Brazil is the Hantavirus Pulmonary Syndrome (HPS). The first serological evidence of the disease was identified in 1990, in Recife, Pernambuco State, and later in 1993 in Jucituba, State of São Paulo. Since then there has been a progressive increase in case notification in all regions of the country. The clinical aspects of the disease in Brazil are characterized by a prodromal phase, with nonspecific signs and symptoms of an acute febrile illness. After about three days, respiratory distress develops, accompanied by dry cough that turns progressively productive, evolving to dyspnea and respiratory failure with cardiogenic shock. Although the majority of patients receive hospital care in intensive care therapy units, case-fatality rate in Brazil ranges from 33% to 100% depending on the region. Besides it has to be added the problem of differential diagnosis with other prevalent diseases in the country, like dengue and leptospirosis. Questions about the impact of uncontrolled urbanization and other environmental changes caused by human action have been raised. Due to increasing incidence and high case-fatality, there is an urge to respond to such questions to recommend preventative measures. This article aims to review the main acquisitions in clinical and epidemiological knowledge about HPS in Brazil in the last twenty years.

Key words: Hantavirus infection; hantavirus pulmonary syndrome; epidemiology; Brazil

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Introduction

Hantaviruses are responsible for a zoonotic disease acquired predominately by inhalation of aerosols contaminated by excreta from wild rodents. It is widely distributed in the world, being considered an emerging disease and an important public health problem. The first reports of the disease were published in the early 50's when more than 3,000 cases of a new acute hemorrhagic fever affected US soldiers during the Korean War [1].

The first serological evidence of this disease in humans in the Americas was reported during an outbreak of leptospirosis in 1990 in the Brazilian city of Recife, Pernambuco State, when serological diagnosis of two cases were done during a leptospirosis epidemic [2]. In South America the main affected countries are Brazil, Argentina, Chile and Paraguay, and Hantavirus pulmonary syndrome (HPS) is the predominant clinical manifestation [3].

The causative agent of HPS is a Hantavirus, a spherical and enveloped single-stranded RNA virus belonging to the family *Bunyaviridae* which has about two dozen subtypes described as causing the syndrome, and whose nomenclature usually derives from the region where the viruses were first identified [4,5]. Each viral subtype frequently infects one species of rodent and in Brazil reservoirs belong to the subfamily *Sigmondontinae* [6].

This review aims to describe the clinical and epidemiological features of HPS with emphasis on the Brazilian experience through the review of scientific publications and the communication instruments of the Public Health Surveillance of the Ministry of Health.

Types of Hantavirus in Brazil and their epidemiological determinants

The first cases of HPS diagnosed in Brazil occurred in 1993 in the region of Jucituba, São Paulo State in the southeast Region, when three previously

healthy brothers, residents in the rural area, had the disease and two of them died of respiratory failure and cardiogenic shock [7]. From this point forward, other Brazilian States also started to detect cases of HPS in their territories. According to a recent analysis of cases notified to the National System of Disease Notification (SINAN), 14 of the 27 Brazilian States have already notified cases of HPS encompassing all regions of the country [8].

Epidemiological data show that the number of cases is increasing each year, as well as the number of viral variants described. Until October 2001, 134 cases of the disease were confirmed in the country evolving to 1,252 cases in December 2009, an increase of more than 800 % in an eight-year period. The occurrence of cases is seen throughout the year, but the seasons with the highest frequency are winter and spring [8,9].

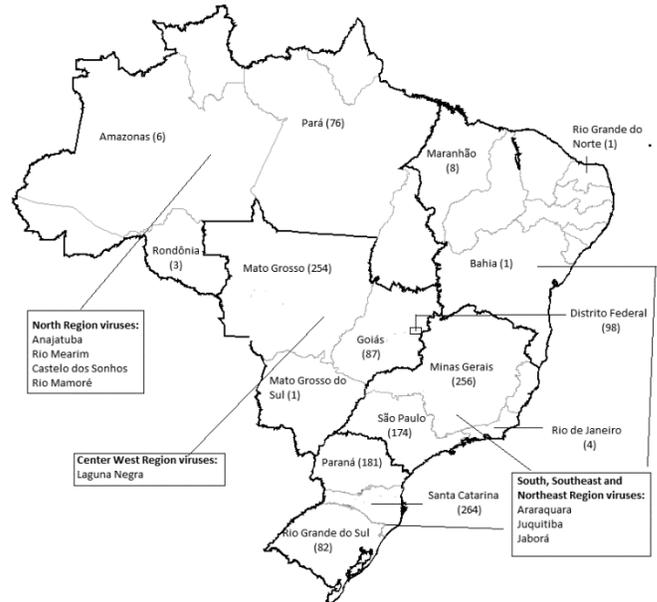
Disease transmission occurs by the inhalation of aerosols or dust particles formed by dry excreta of infected rodents, which are found in areas with a high rodent burden. Person-to-person infection has never been documented in Brazil, but in Southern Argentina, during an outbreak of HPS caused by the Andes virus in 1996, several cases showed epidemiological evidence suggesting this way of transmission [10].

Human transmission occurs when there is close contact between humans and the rodent reservoir of the disease. Any activity that causes dispersion of aerosols or dust such as cleaning, demolition or removal of grains stored in silos is reported as risk factors for acquiring the disease. In Brazil, environmental determinants involved in the disease transmission are not fully understood, reported cases occurred in areas with agricultural activities mainly located in the *cerrado* ecoregion and in the Atlantic forest biomes of the center-west, southeast and south regions [11-13].

In recent years, cases are also being reported in the periphery of cities of low and middle income countries, where the unordered growth of human settlements with low sanitation coverage and deforestation practices promoted rodent proliferation and wild rodents invasion of human dwellings [5,14,15]. Serologic surveys performed on inhabitants of urban areas with positivity ranging around 1%-4% also confirmed that the virus is circulating in these areas and probably the majority of infections have an asymptomatic course [16-18].

Published case reports show that HPS in Brazil primarily affects young adult males with an average age of 30 years and it is related to occupational activities affecting frequently veterinarians, farmers,

Figure 1: Total notified cases of hantavirus pulmonary syndrome in Brazilian states from 2001 to 2012 and geographical distribution of hantavirus variants in regions of Brazil.



agronomists and other related professions. Tourism to rural areas has also been implicated in disease transmission [9,19]. In all these settings, environmental alterations caused by human action constitute the most common predisposing factor described in epidemiological investigations regarding these cases [13,14,18].

Five hantavirus variants circulating in Brazil were related to the great majority of notified cases: Jucuitiba, Araraquara, Castelo dos Sonhos, Laguna Negra and Anatajuba [20-22]. Other described variants were related only to rodents: Jabora, Rio Mamore and Rio Mearim variants (Figure 1) [23,24].

Hantavirus Pulmonary Syndrome in Brazil

HPS is the most serious manifestation of hantavirus infection in the Americas and it is characterized by severe pulmonary involvement that leads to respiratory failure and cardiogenic shock. The incubation period ranges from 9 to 33 days, with a median of 14 to 17 days. Clinically, the disease is divided into three stages: the prodromal phase, the cardiopulmonary phase and the convalescent phase [25,26].

The prodromal phase is characterized by nonspecific clinical manifestations lasting from 3 to 6 days; the most common reported signs and symptoms in Brazilian patients are acute fever, chills, generalized myalgia, asthenia, headache and nausea; less often

described are vomiting, abdominal pain, chest pain, sweating and dizziness [5,27,28].

During the prodromal phase, mild respiratory symptoms (dyspnea, tachypnea and dry cough) are frequently reported, as well as discrete basal rales at pulmonary auscultation [27,28]. Respiratory manifestations evolve into the cardiopulmonary phase worsening the respiratory distress with progressive dyspnea, which represents the most prominent symptom of this stage. In a few hours the patient develops respiratory failure and dry cough can become productive with mucus bloody sputum. Along with respiratory distress and failure, the patient become hypotensive and tachycardic, and the cardiovascular shock soon ensues.

In the Brazilian literature there are some published case studies describing the main clinical manifestations of HPS concentrated in municipalities of Minas Gerais and São Paulo States, in the southeast Region of Brazil, where the Araraquara and Juitiba viruses cause the great majority of cases. The clinical picture described in each study is very similar with fever, dyspnea, cough, myalgia and headache reported as the most frequent manifestations. Hemorrhagic manifestations varied from 4 % to 37.5 % in Brazil, far less than observed in a case study conducted in Chile, where hemorrhage was described in 64 % of cases [3,19,29]. Table 1 shows the frequency distribution of the signs and symptoms observed in these case series.

HPS case-fatality rate in Brazil is very high and ranges from 33% to 100%, depending on the region.

Factors related to higher risk of death include the development of respiratory failure and the need for respiratory support [9]. Figueiredo *et al* suggested a link between mortality in patients with HPS and the virus type involved in the disease, being the Araraquara variant implicated in more severe cases of HPS if compared to the Juitiba variant infections; nevertheless, possible differences in pathogenesis are still unknown [31]. In another study, the Araraquara variant was also related to the severity of disease and the high case-fatality rate in Brazilian's cases [5].

The convalescent phase is usually prolonged and may last for weeks or months, especially in patients requiring mechanical ventilation. This may be due to nutritional deficiencies related to the severity of disease, alongside nosocomial pneumonias. It is noteworthy that the late diagnosis is associated to development of sequels, such as chronic fatigue and restriction of lung function, causing impact on the quality of life [26].

The differential diagnosis of HPS can be challenging in scenarios where dengue and leptospirosis epidemics occur often, as seen in a great number of Brazilian cities [2, 31-33]. Other conditions can also cause difficulties in diagnosis like severe respiratory disease caused by influenza and atypical pneumonias as well as acute febrile illness, like malaria, yellow fever and spotted fever, which also require the physician's attention, especially in tropical areas [34].

Table 1: Frequency distribution of signs and symptoms from Hantavirus pulmonary syndrome published in Brazilian literature as case series from 2000 to 2009

Signs/ symptoms	Ferreira <i>et al</i> 2000 ¹⁹ % (n=3)	Figueiredo <i>et al</i> 2001 ²⁰ % (n=8)	Silva-Vergara <i>et al</i> 2002 ¹⁵ % (n=8)	Limongi <i>et al</i> 2007 ¹⁶ % (n=23)	Campos <i>et al</i> 2009 ^{21*} % (n=43)
Fever	100 (3)	100 (8)	100 (8)	100 (23)	81.0 (35)
Dyspnea	66.7 (2)	100 (8)	100 (8)	100 (23)	34.0 (15)
Myalgia	100 (3)	37.5 (3)	100 (8)	78.0 (18)	18.0 (8)
Cough	100 (3)	50.0 (4)	87.5 (7)	74.0 (17)	44.0 (19)
Hypotension	-	75.0 (6)	87.5 (7)	65.0 (15)	2.0 (1)
Headache	33.3 (1)	62.5 (5)	62.5 (5)	65.0 (15)	34.0 (15)
Tachycardia	33.3 (1)	87.5 (7)	-	65.0 (15)	-
Nausea/vomiting	33.3 (1)	62.5 (5)	-	61.0 (14)	25.0 (11)
Chest pain	-	-	-	52.0 (12)	-
Abdominal pain	-	-	-	48.0 (11)	-
Chills	-	-	-	26.0 (6)	-
Sudoresis	-	-	-	22.0 (5)	-
Oliguria	-	-	-	22.0 (5)	-
Diarrhea	33.3 (1)	37.5 (3)	-	17.0 (4)	14.0 (6)
Hemorrhage	-	37.5 (3)	-	4.0 (1)	9.0 (4)
Chest rales	66.7 (2)	75.0 (6)	-	-	-

* The signs and symptoms described by this author refer to the prodromal phase.

Radiological findings

The chest X-ray is of a great importance for the HPS diagnosis, and it is also essential for monitoring disease progression. A typical bilateral pattern of diffuse interstitial infiltration may occur in more severe cases, early at the onset of fever and dyspnea. These changes evolve rapidly along with the worsening of respiratory distress to confluence of lung infiltrates, and resulting in alveolar consolidation. Pleural effusion is frequently reported, and often develops bilaterally. The infiltrates improve during the period of convalescence, but may persist in the lung bases. In less severe cases, there is only discrete diffuse interstitial infiltrate, with minimal alveolar opacification [5,25,34,35].

Diagnosis

The diagnosis of Hantavirus infection is done primarily by serology, which identifies specific antibodies of IgM and IgG class. Antibody detection may occur at early stages of disease, and contributes to prompt diagnosis. Specific positive IgM in the first sample examined, or quadrupling of IgG titers in paired samples are confirmatory. The levels of IgG are detectable throughout the life of the individual, allowing studies about the prevalence of HPS [36]. Diagnosis can also be done by PCR techniques, already performed in research centers in Brazil, but routine use of this technique is limited due to its costs [37,38].

In Brazil, diagnostic tests of Hantavirus infection are performed in seven reference laboratories distributed in the national territory, and each laboratory serves as reference for a group of states, testing the specimens by ELISA and polymerase chain reaction PCR [39]. This territorial distribution poses logistic and clinical concerns, since long distances from the area where the specimen was collected may cause difficulties in transportation and delayed results.

Non-specific laboratory findings include: increased hematocrit (usually greater than 45%), leukocytosis with a left shift, atypical lymphocytes in peripheral blood and thrombocytopenia. There may also be an increase in serum urea and creatinine caused by hypovolemia and impaired renal perfusion; and elevated liver enzymes. Arterial blood gas analysis may reveal severe hypoxemia and metabolic acidosis [19].

Treatment

Currently, there is no specific treatment for HPS, which consists essentially in the institution of life

support measures, preferably undertaken in intensive care units (ICU) settings, considering the high severity of disease often with a downhill course. The early clinical recognition of this disease enables a prompt treatment institution, which is considered the main factor that can positively influence the patient outcome [25].

The great majority of the patients assisted in Brazil with confirmed diagnosis of Hantavirus according to the disease definition of the Ministry of Health, was hospitalized (95.3%) [9]. Careful and continual monitoring of cardiorespiratory parameters is necessary, because these patients often evolve very fast to respiratory failure, hypotension and shock. In this scenario, immediate set up of ventilator support and administration of fluids and vasoactive drugs should be performed. Differential diagnosis with bacterial infections, especially pneumonia, along with the severity of HPS, have made the empiric prescription of antibiotics very frequent; another drug schedule often reported in case studies is the administration of corticosteroids [7,40-42].

Prevention

In Brazil, the transmission of Hantavirus occurs mainly in rural areas. In these settings wild rodents are especially attracted by the food stocked in silos during dry season, when it is also common the practice of field burning in order to clean them. The fire expels the rodents causing their migration to buildings where human activities take place. Public health surveillance recommendations consist mainly in changing the old agricultural practices and providing the good maintenance of buildings used for food storage and residential buildings in order to avoid rodent invasion. Individuals who are exposed, either through professional activities, sports, leisure, sightseeing or sporadic visits, should also be informed in order to avoid contact with aerosols contaminated with rodent excreta [39].

Another important environmental problem which favors invasion of human dwellings by rodents is the unplanned extension of the suburbs of big Brazilian cities on areas of native forest or farms. The two ecosystems most affected according to the Brazilian epidemiological investigations are the Atlantic forest in the southeastern region and the *cerrado* in the central-west region, mainly in the Central Plateau; these two regions account for more than 80% of the notified cases in Brazil [30]. In this epidemiological scenario the most important measures to prevent rodents invasion is to keep clean the *areas around the*

houses and the dwelling free of rodents through pest control measures.

Conclusions

The increasing incidence of HPS and its wide geographic distribution, affecting people from the majority of Brazilian states, in addition to the high lethality rate, turns the disease into an emerging infection in Brazil as well as an important public health problem. Besides clinical challenges, like the difficult differential diagnosis with different common acute febrile illnesses, other social and epidemiological factors add a high degree of complexity in the context of disease control in Brazil.

Crucial questions are raised in this scenario and urge to be answered, such as how the uncontrolled urbanization may affect the disease burden; whether urbane reservoirs play a role or not in disease propagation; what is the proportion between HPS cases and other clinical presentations of Hantavirus infection; and what would be the best epidemiological marker for disease monitoring. Further specific research would help to solve these issues of major concern.

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