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Hantavirus pulmonary syndrome: prognostic factors for death in reported cases in Brazil

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ABSTRACT

Hantavirus pulmonary syndrome (HPS) was described for the first time in Brazil in 1993 and has occurred endemically throughout the country. This study analysed clinical and laboratory aspects as well as death-related factors for HPS cases in Brazil from 1993 to 2006. The investigation comprised a descriptive and exploratory study of the history of cases as well as an analytical retrospective cohort survey to identify prognostic factors for death due to HPS. A total of 855 Brazilian HPS cases were assessed. The majority of cases occurred during spring (33.5%) and winter (27.6%), mainly among young male adults working in rural areas. The global case fatality rate was 39.3%. The mean interval between the onset of symptoms and hospitalisation was 4 days and that between hospitalisation and death was 1 day. In the multiple regression analysis, adult respiratory distress syndrome and mechanical respiratory support were associated with risk of death; when these two variables were excluded from the model, dyspnoea and haemoconcentration were associated with a higher risk of death.

1. Introduction

Hantavirus pulmonary syndrome (HPS) was first recognised in May 1993 in southwestern USA when epidemiological, serological and genomic detection studies allowed the identification of its aetiology associated with viruses of the genus *Hantavirus*, whose natural reservoirs are wild rodents from the subfamily Sigmodontinae.[1]

In the Americas, hantaviruses have since been found in Canada through to regions close to the south of Argentina. In South America, the disease occurs in Brazil, Argentina, Chile, Paraguay, Uruguay, Bolivia and Venezuela.[2–4]

In Brazil, five hantavirus variants had been detected until 2006 (Juquitiba, Araraquara, Castelo dos Sonhos, Anajatuba and Rio Mearim). The first three were identified as being associated with HPS, and four probable reservoirs were identified.[5,6]

Hantavirus infections may present a broad clinical spectrum according to the viral genotype involved, ranging from asymptomatic or oligosymptomatic forms to the classical picture of HPS.[1,7–11]

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HPS is a severe clinical presentation with high lethality. It has four clinical stages (prodromes) characterised by: (i) an acute febrile disease that lasts 3–6 days; (ii) a cardiopulmonary stage, characterised by acute respiratory insufficiency and circulatory collapse; (iii) if the patient survives the second phase, he or she enters the diuretic stage characterised, by profuse diuresis and excretion of liquids from extravascular spaces; and (iv) the convalescent stage, with slow recovery of the patient's haemodynamic abnormalities and respiratory function.[4]

The first cases of HPS diagnosed in Brazil occurred in November 1993.[12] Up to December 2006, 855 cases had already been reported. This study analysed the clinical and laboratory features of HPS as well as factors associated with confirmed cases during this period.

2. Materials and methods

The population of this study consisted of confirmed cases of HPS in Brazil, according to the national definition (http://portal.saude.gov.br/portal/arquivos/pdf/Guia_Vig_Epid_novo2.pdf), notified to the Ministry of Health's Sistema de Informação de Agravos de Notificação (SINAN) from 1993 to 2006.

The inclusion criterion was all cases clinically compatible with HPS plus at least a positive laboratory confirmatory test (IgM ELISA, RT-PCR or real-time PCR). The criterion for exclusion was all cases that presented negative results in the laboratory confirmatory tests (as above), except those that were clinically and epidemiologically compatible with the definition of HPS.

The variables in this study were: sociodemographic features (gender, age, occupation and race); clinical characteristics (signs and symptoms); laboratory and radiological aspects; treatment (hospitalisation and type of therapeutic support); and evolution (recovery or death).

The investigation was developed in two phases. The first phase was a descriptive and exploratory study of various cases. The second phase consisted of an analytical retrospective cohort study that aimed to identify the prognostic factors for death caused by HPS.

First, a description of HPS patients' features was performed. For the comparative analysis, Pearson's χ^2 test and Fisher's exact test were used for categorical variables and Kruskal–Wallis's test was used for continuous variables.

To analyse the association between the dependent variable (death caused by HPS) and independent variables, the relative risk (RR) and 95% CI was used as a measure of association.

To investigate factors associated with the severity of HPS, death was considered the dependent variable and the exposures of interest were the independent variables. The association between the dependent variable and the exposures of interest was assessed by unadjusted estimations of the RR (95% CI).

Later, a logistic regression analysis was performed. Variables that presented an association in the univariate analysis were used, except for adult respiratory distress syndrome (ARDS) and mechanical respiratory support because they could mean a late evolution of the disease. The model was adjusted following a step-by-step progressive procedure, and the variables were included according to an increasing order of the OR values. The significance of the variables was then assessed through the likelihood ratio test. For the final model, $p < 0.05$ was considered statistically significant.

3. Results

From November 1993 to December 2006, there were 855 cases of HPS in Brazil; 684 (80.0%) were male. The mean age was 33 years for males and 31 years for females, and 647 (75.7%) were aged 20–39 years. The disease affected mainly White individuals (635; 74.3%) with 4–7 years of education. HPS occurred in all regions of the country [in 14 (51.9%) of the 27 Federated Units]. The Southern Region presented the highest number of cases (44.2%), followed by the Southeastern Region (30%) and the Central-Western Region (20.2%). The Northern and Northeast Regions together had <6% of cases. There was no significant difference regarding the location in which the infection occurred.

Cases were reported in all months of the year, but the highest numbers of cases were registered during spring (33.5%) and winter (27.6%). The majority of cases occurred in individuals with professional activities related to agriculture and deforestation.

The most frequent clinical manifestation was fever, which occurred in 783 individuals (91.6%), followed by dyspnoea, headache and myalgia, all reported by >80% of cases. Cough, nausea and vomiting were common and occurred in >70% of patients. More than 50% of cases presented dizziness (57.5%), thoracic pain (54.7%) and abdominal pain (54.2%). ARDS affected 49.1% of individuals. An increase in the serum level of creatinine was detected in 42.5% of cases, and acute renal insufficiency was diagnosed in 18.9%. Other less reported clinical manifestations were odynophagia, diarrhoea, and haemorrhagic and neurological manifestations (Figure 1).

The most frequent haemorrhagic manifestations were epistaxis (18.8%), purpura (18.8%), haematemesis (14.1%) and haemoptysis (10.4%). Among the laboratory findings, the most important were thrombocytopenia (78.6%), haemoconcentration with haematocrit >50% (57.3%), leukocytosis with a left shift (50%) and the presence of atypical lymphocytes (23.7%).

Chest radiographs showed a bilateral interstitial infiltrate in 675 (78.9%) of the cases.

During their clinical course, 815 (95.3%) of the patients were hospitalised and 378 (46.4%) required mechanical respiratory support.

The first consultation with a doctor occurred within an average of 3 days after the onset of symptoms and 707 (82.7%) of the patients consulted a doctor within 5 days of the onset of symptoms.

The global case fatality rate (CFR) was 39.3% (336/855). The CFR ranged from 89% to 100% from 1995 to 1996; between 43.0% (n = 368) and 45.0% (n = 385) from 2001 to 2003; and was 35.0% (n = 299) each year during 2004–2006. The CFR was 100% in the Northeast Region and 33.1% in the Southern Region. The Mid-Western, Northern and Southeast Regions showed CFRs of 40.9%, 42.5% and 46.5%, respectively. The distribution of CFRs according to sex

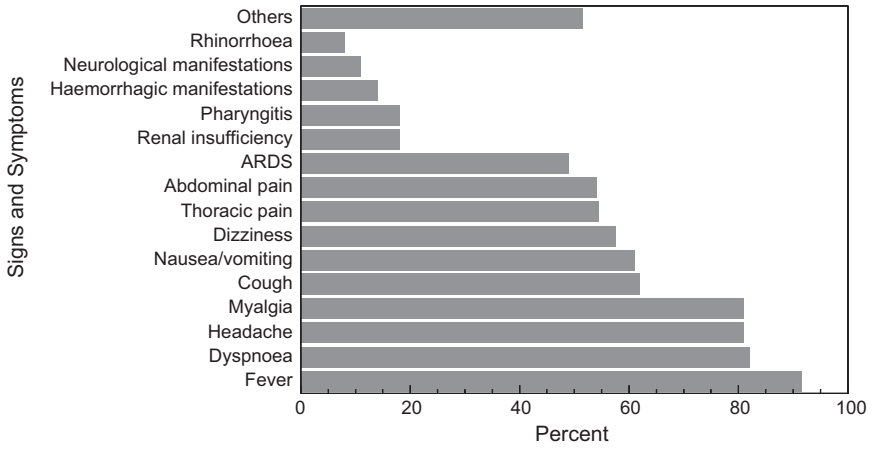

Figure 1. Percentage of individuals with the main signs and symptoms observed in hantavirus pulmonary syndrome, Brazil, 1993–2006. ARDS: adult respiratory distress syndrome.

was higher among females (45.6%) compared with males (37.7%).

The highest CFR (50.5%) was reported among individuals aged 50–59 years. Of the 336 patients with a fatal outcome, 272 (81%) died within 7 days of the onset of symptoms; 307 of the 336 deaths (91.4%) occurred within 4 days of hospitalisation.

The variables associated with death caused by HPS in the univariate analysis were dyspnoea (RR = 3.54, 95% CI 2.31–5.44), cough (RR = 1.28, 95% CI 1.03–1.59), thoracic pain (RR = 1.23, 95% CI 1.01–1.51), renal insufficiency (RR = 1.60, 95% CI 1.29–1.97), haemorrhagic manifestations (RR = 1.62, 95% CI 1.31–2.01) and ARDS (RR = 2.85, 95% CI 2.29–3.56). The laboratory and imaging findings associated with death were haematocrit >50% (RR = 2.42, 95% CI 1.90–3.08), leukocytosis with a left shift (RR = 1.47, 95% CI 1.18–1.83), increase of the serum level of blood urea nitrogen and creatinine (RR = 1.40, 95% CI 1.11–1.78), presence of pulmonary interstitial infiltrate (RR = 2.16, 95% CI 1.51–3.10) and mechanical respiratory support (RR = 3.36, 95% CI 2.61–4.34) (Table 1).

Table 1
Variables associated with risk of death from hantavirus pulmonary syndrome by univariate analysis, Brazil, 1993–2006

Variable	RR	95% CI	p-value
Signs and symptoms			
Dyspnoea	3.54	2.31–5.44	<0.001
ARDS	2.85	2.29–3.56	<0.001
Haemorrhagic manifestations	1.62	1.31–2.01	<0.001
Renal insufficiency	1.60	1.29–1.97	<0.001
Cough	1.28	1.03–1.59	0.023
Thoracic pain	1.23	1.01–1.51	0.042
Laboratory findings			
Haematocrit >50%	2.42	1.90–3.08	<0.001
Leukocytosis with left shift	1.47	1.18–1.83	<0.001
Increase of BUN and creatinine	1.40	1.11–1.78	0.005
Radiological findings			
Bilateral interstitial infiltrate	2.16	1.51–3.10	<0.001
Therapeutic procedures			
Mechanical respiratory support	3.36	2.61–4.34	<0.001

RR: relative risk; ARDS: adult respiratory distress syndrome; BUN: blood urea nitrogen.

Table 2
Measures of association for risk of death from hantavirus pulmonary syndrome by multiple regression analysis, Brazil, 1993–2006

Variable	OR	95% CI	p-value
Signs and symptoms			
ARDS	3.74	1.94–7.20	<0.001
Dyspnoea	1.76	0.71–4.35	0.222
Thoracic pain	1.18	0.64–2.19	0.302
Haemorrhagic manifestations	1.13	0.46–2.79	0.791
Cough	0.80	0.41–1.56	0.504
Renal insufficiency	0.76	0.33–1.75	0.526
Laboratory findings			
Haematocrit >50%	1.75	0.91–3.38	0.095
Leukocytosis with left shift	1.08	0.58–2.04	0.805
Increase of BUN and creatinine	0.66	0.33–1.33	0.245
Radiological findings			
Bilateral interstitial infiltrate	1.46	0.61–3.51	0.395
Therapeutic procedures			
Mechanical respiratory support	5.99	3.08–11.67	<0.001

ARDS: adult respiratory distress syndrome; BUN: blood urea nitrogen.

Of the 855 HPS cases analysed, only 264 (30.9%) reports presented information on all the variables individually associated with death caused by HPS and necessary for the adjusted analysis. In the multiple regression model, only the occurrence of ARDS (OR = 3.74, 95% CI 1.94–7.20) and mechanical respiratory support (OR = 5.99, 95% CI 3.08–11.67) were independently associated with risk of death caused by HPS regardless of the other investigated exposures (Table 2).

A second multiple regression model was tested without the variables mechanical respiratory support and ARDS because they could mean a late evolution of the disease. Under this model, the presence of dyspnoea (OR = 2.75, 95% CI 1.25–6.06) and haematocrit >50% (OR = 1.95, 95% CI 1.15–3.31) were independently associated with the risk of death caused by HPS.

4. Discussion

This is the first study presenting analyses of the clinical history of HPS cases and the prognostic factors for death caused by the disease in Brazil. The profile of HPS

patients in Brazil does not differ from those observed in other American countries, namely predominantly male, of working age, and working on agricultural activities. A similar distribution according to sex and age has been reported from Canada to Argentina.[3,4,10,13] This association of cases with rural areas and agricultural activities is acknowledged in Central America and especially in South American countries.[4,13,14]

Hantavirus infections may present various clinical forms. In the historical series analysed in this study, the proportion of non-specific signs and symptoms such as fever, myalgia and nausea/vomiting was high. However, the presence of cough and dyspnoea in >70% of cases demonstrates that there was a predominance of the classical clinical presentation recognised as HPS, which demanded high rates of hospitalisation and mechanical respiratory support and was associated with a high CFR. A similar pattern of clinical presentation has been also described in several investigations.[4,8,14–17] Extrapulmonary manifestations such as renal insufficiency and haemorrhagic manifestations were also frequent. In South America renal involvement was reported in up to 50% of cases caused by the Andes virus,[13] whereas in North America this manifestation was rare in HPS patients infected by Sin Nombre virus.[15] Haemorrhagic manifestations observed in this study, such as epistaxis, haematemesis and haemoptysis, have been reported in other studies.[18]

The diversity of clinical and laboratory findings in this study has also been described by several authors and leads to the conclusion that hantavirus infections present a broad spectrum of clinical disease ranging from mild clinical forms to the classical pulmonary involvement characteristic of HPS.[7,8,14,15,19]

In Brazil, the global CFR of HPS over the 14 years was 39.3%. The CFR by geographic region showed great variability, ranging from 33.1% to 100%. Several authors have reported similar variation in these rates, ranging from 12% to 54% according to the region and period surveyed. Other studies should be carried out in Brazil to identify the associated risk factors for the different geographic regions.[13–16,20] Analysis of the CFR by different hantavirus lineages could provide information on whether factors such as virulence, accessibility and quality of hospitalisation, early recognition of cases, and availability of emergency care units for inpatient treatment are associated with risk of death. Patients who received mechanical respiratory support in the intensive care unit due to their critical condition at the time of hospitalization tended to have a higher risk of death.

Regarding the rate of lethality by sex, although females comprised only 20% of cases and 23.8% of deaths, the CFR was approximately 20% higher than that observed for males ($p = 0.22$).

The median period between the onset of symptoms and hospitalisation and that between hospitalisation and death of the patients analysed in this study was similar to the average period in a report of the 100 first cases in the USA.[15] Regarding the time of hospitalisation of the survivors, the median period was shorter than the time observed in Canada.[17]

Of the factors associated with death due to HPS in Brazil in the univariate analysis, non-specific laboratory findings such as leukocytosis, thrombocytopenia and haemoconcentration were also related to the most severe course in Chile and Canada.[8,20] As observed in the current study, haemorrhagic phenomena were associated with a poor prognosis in research carried out in Chile.[7]

When ARDS and mechanical respiratory support (variables that were strongly associated with the evolution to death, but which possibly mean a late evolution of HPS) were excluded from the multiple regression model, dyspnoea and haemoconcentration were independently associated with a higher risk of death. Although these data need to be validated by other studies, they suggest that these variables may be used as markers for early identification of severe cases of HPS.

The clinical and epidemiological information obtained in this study shall contribute to due revision of the surveillance system of hantavirus infection in Brazil, including case definition as well as epidemiological, laboratorial and clinical criteria to confirm an HPS case and criteria for inpatient transference to the emergency room. Similarly, it is expected that these findings may contribute to a reduction in the CFR observed in this country.

Authors' contributions: MRE, WSM, EHC and PFCV conceived and designed the study; MRE, EAW, EHC and JPD analysed and interpreted the data; MRE, EAW and PFCV drafted the manuscript. All authors critically revised the manuscript for intellectual content and read and approved the final version. PFCV is guarantor of the paper.

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