Clinical and laboratory findings related to a favorable evolution of hantavirus pulmonary syndrome

Características clínicas e laboratoriais associadas com boa evolução clínica na síndrome cardiopulmonar por hantavírus

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ABSTRACT

The medical records of 27 patients with hantavirus pulmonary syndrome were analyzed according to the need for invasive mechanical ventilation in relation to the following data up on hospital admission: age, gender, fever, cough, dyspnea, systolic arterial blood pressure, heart rate, levels of hemoglobin, hematocrit, leukocytes, lymphocytes, platelets, creatinine and arterial blood gases. The volume infused during the first 24 hours after admission, the use of inotropic agents, the use of corticosteroids and the patient outcomes were also evaluated. A favorable outcome was related to systolic blood pressure ³ 100mmHg, heart rate lower than 100 beats per minute, creatinine below 1.6mg/dl, arterial blood pH ³ 7.35, bicarbonate higher than 15mEq/dl, oxygen saturation higher than 84.1%, lower rehydration volume in the first 24 hours of hospitalization and no use of inotropic agents. Absence of clinical and laboratory signs of circulatory shock up on admission was associated with a favorable outcome of the patients.

***Key-words**: Hantavirus pulmonary syndrome. Prognostic. Clinical outcome. Hantavirus.*

RESUMO

Pouco se conhece sobre os fatores determinantes de bom prognóstico na síndrome cardiopulmonar por hantavírus. Foram revisados os prontuários médicos de 27 pacientes com diagnóstico confirmado de síndrome cardiopulmonar por hantavirus com o objetivo de avaliar dados clínicos e laboratoriais eventualmente associados com bom prognóstico dos pacientes. Os seguintes fatores foram associados com evolução clínica favorável quando analisados na admissão hospitalar: pressão arterial sistólica maior ou igual a 100mmHg (p=0,07); freqüência cardíaca abaixo de 100/minuto (p=0,01); níveis de creatinina sérica abaixo de 1,6mg/dl (p=0,03); pH do sangue arterial igual ou maior que 7,35 (p=0,03); bicarbonato sanguíneo igual ou maior que 15mEq/dl (p=0,03); saturação de oxigênio arterial maior que 84% (p=0,02); menor volume infundido (p=0.008) e ausência de indicação de aminas vasoativas (p< 0,001). Dessa forma, ausência de sinais clínicos e laboratoriais de choque circulatório na admissão hospitalar foi associada com bom prognóstico nos pacientes com síndrome cardiopulmonar por hantavirus.

***Palavras-chaves**: Síndrome cardiopulmonar por hantavírus. Prognóstico. Evolução clínica. Hantavírus.*

Two different diseases are caused by hantavirus: hemorrhagic fever with renal syndrome (HFRS) occurring in Asia and Europe and the hantavirus pulmonary syndrome (HPS) occurring in the Americas[10].

Hantavirus is a genus of the family *Bunyaviridae*, which comprises enveloped spherical viruses having 3 single-stranded and negative RNA polarity fragments[5 10]. In contrast to most of the *Bunyaviridae*, which are arboviruses, *Hantavirus* is transmitted to humans by the inhalation of aerosols containing the urine and feces of rodents. In the Americas, *Hantavirus* transmission is related to wild rodents, mostly occurring in association with agricultural or recreational activities in rural

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areas. However, *Hantavirus* infections have been reported in urban areas, also related to domestic activities[6 13].

Initially described in June 1993 in southeastern United States, HPS cases were later reported in North, Central and, principally, South America[8]. In Brazil, human hantavirus infections were first reported in November and December 1993, when 3 individuals from the rural area of Juquitiba, close to São Paulo City, presented acute febrile illness evolving to pneumonitis with respiratory failure[12]. Since then, HPS has become an emerging disease in Brazil, with approximately 400 HPS cases being reported from 1993 through 2004, with a 45% fatality rate.

Almost 10% of the Brazilian HPS cases occurred in the Ribeirão Preto region. The economy of the inland region of Ribeirão Preto, São Paulo State, with 3,500,000 inhabitants, is based on the sugar cane agroindustry and the area has been almost completely deforested, with important consequences for the environment and for wild rodent ecology. HPS cases in the region are caused by the Araraquara virus and the wild rodent *Bolomys lasiurus* is believed to be the most important reservoir of this hantavirus[3].

In Brazil, knowledge about Hantavirus infection and familiarity with the clinical presentation of HPS has increased among doctors working in some areas where cases have been reported. This has led to the diagnosis of an increasing number of HPS cases, many of them showing mild forms of the disease. However, in spite of the growth of milder HPS reports, little has been written about factors related to a favorable evolution of the disease. In the present study, clinical and laboratory data associated with a favorable evolution of HPS were evaluated in patients from the Ribeirão Preto region.

PATIENTS AND METHODS

The medical records of 27 HPS patients from the Ribeirão Preto region, hospitalized from 1998 through 2004, were analyzed. All patients were given an HPS diagnosis confirmed by detection of the Hantavirus genome by the reverse transcription-polymerase chain reaction (RT-PCR) in blood and/or by detection of IgM antibodies specific to Sin Nombre virus by ELISA. The patients were divided into 2 groups. Group I included 10 patients who did not require mechanical ventilation and Group II included 17 patients who required invasive mechanical ventilation.

Patients of both groups were compared regarding the following clinical and laboratory data checked at the time of admission to the hospital: age, gender, days of disease, presence of fever, cough and dyspnea, arterial blood pressure, heart rate, and levels of hemoglobin, hematocrit, leukocytes, lymphocytes, platelets, creatinine and of arterial blood gases (pH, pO_2, pCO_2, bicarbonate and O_2 saturation). The rehydration volume infused into the patients during the first 24 hours after admission, the use of inotropic pressor agents and corticosteroids and patient outcomes were also evaluated.

The data were analyzed statistically by the Fisher exact test and Student t test, with the level of significance set at 5%.

RESULTS

The data for the HPS patients studied are shown in Table 1 and Table 2. A significant difference between the groups was observed regarding death ($p < 0.001$), with no deaths being observed in Group I patients and 13 deaths occurring in Group II patients; a 76.4% case fatality rate. The following

Table 1 - General data and clinical parameters of Group I and Group II HPS patients obtained at the time of hospital admission.

	Group I (number)	Group II (number)	p (*t* or Fisher exact test *)
Gender (M)	9	11	
	(10)	(17)	0.16*
Fever	9	13	
	(9)	(13)	-
Cough	6	8	
	(7)	(9)	0.70*
Dyspnea	8	15	
	(9)	(15)	0.37*
Systolic arterial pressure ≥ 100mmHg	3	13	
	(7)	(13)	**0.007***
Heart rate > 100 beats/min.	3	12	
	(6)	(12)	**0.001***
Volume infused during the first	2056±1084	3 694±1.203	**0.008**
24h (L)	(8)	(10)	
Use of corticosteroids	3	5	
	(10)	(12)	0.45*
Use of inotropic agents	0	12	
	(10)	(13)	**<0.001***
Death	0	13	
	(10)	(17)	**<0.001***

p values indicating significant differences between groups are shown in bold.

Table 2 - Laboratory data of Group I and Group II HPS patients obtained at the time of hospital admission.

	Group I (number of patients)	Group II (number of patients)	p (*t* or Fisher exact test *)
Hemoglobin (g/dl)	17.5 ± 4.1	16.9 ± 3.4	
	(9)	(14)	0.70
Hematocrit (%)	52.1 ± 9.6	52.4 ± 10.7	
	(9)	(14)	0.94
Leukocyte (mm^3)	15 080 ± 8423	19 293±11 186	
	(10)	(15)	0.34
Lymphocytes (%)	17.1 ± 8	22.5±12,5	
	(9)	(14)	0.28
Platelets (mm^3)	85 175 ± 39 718	92 230 ± 78 723	
	(8)	(13)	0.81
pH < 7,35	2	8	
	(9)	(11)	**0.03***
PO_2 < 60 mmHg	6	6	
	(10)	(12)	0.48*
O_2 saturation (%)	88.9 ± 4.8	77.8 ± 13.4	
	(10)	(11)	**0.02**
HCO≤15	1	6	
	(9)	(10)	**0.03***
Creatinine (mg/dl)	1.0 ± 0.17	1.5 ± 0.41	
	(9)	(12)	**0.003**
Creatinine ≥1,6 mg/dl	0	7	
	(9)	(12)	**0.006***

p values indicating significant differences between groups are shown in bold.

factors were related to non requirement of mechanic ventilation in Group I patients: systolic blood pressure equal to or higher than 100mmHg (p=0.007), heart rate lower than 100 beats per minute (p 0.001), creatinine levels below 1.6mg/dl (p=0.003), and arterial blood pH equal to or higher than 7.35 (p .03), bicarbonate equal to or higher than 15mEq/dl (p=0.03), oxygen saturation higher than 84.1%, average 88.9% (p=0.02). Aspects of HPS management were also associated with non requirement for mechanical ventilation in Group I patients: rehydration volume in the first 24 hours of hospitalization of 2,056ml ± 1,084ml (p=0.008) and no use of inotropic pressor agents (p <0.001).

DISCUSSION

Most of the HPS patients presented severe disease that started after 3 to 6 days of a prodromic phase characterized by nonspecific symptoms such as fever, malaise, headache, myalgias and, occasionally, gastrointestinal disorders. The disease evolved from dry cough to respiratory failure due to capillary leaking syndrome into the pulmonary interstitium, evidenced by chest radiographs showing peribronchial haze and Kerley B lines that subsequently progressed to alveolar flooding. Hemoconcentration as a consequence of capillary leaking syndrome and thrombocytopenia due to platelet destruction were observed in the majority of cases. HPS also included circulatory shock, with cardiovascular depression in many cases. The disease presented a high fatality rate, 48%, in agreement with data reported by others[2 7].

Padula et al[9], analyzing HPS cases from 5 South American countries, observed that fatality rates decreased from 70% to 30% after a decade of HPS reports. This reduction was probably related to improved knowledge regarding the disease by clinicians, who immediately suspect HPS, offer an adequate initial therapy and recommend hospitalization in intensive-care units. However, 30% is still a high case fatality rate and suggests the participation of other factors, such as the circulation of more than one hantavirus, with different virulence, in the same region[3 9].

In the present study, 3 Group 1 patients (30%) presented a light or mild form of the disease. In these patients, after prodromic clinical manifestations, the disease progressed to interstitial pneumonia with transitory dyspnea that did not require invasive mechanical ventilation in 2 cases, and 1 case presented no dyspnea. Mild or light forms of HPS are probably more frequent than severe forms and are also probably undiagnosed. This possibility is supported by the high prevalence of antibodies to Hantavirus described in the Ribeirão Preto region. In 2001, a serologic survey carried out in the region on the adult population of Jardinópolis County, showed that the blood samples of 14.3% of the participants presented antibodies for Hantavirus independent of sex, profession or history of contact with rodents[1]. A similar high (13.3%) prevalence of hantavirus infections was observed in Anajatuba, Maranhão State, in the North of Brazil[6]. A high prevalence of antibodies for Hantavirus has also been described in other South American countries, reaching 66% in individuals older than 53 years in the indigenous communities of Paraguay[3].

In this context, some clinical and laboratory factors observed in 10 HPS patients that did not develop severe respiratory failure were evaluated in order to permit an early determination of cases that would show a favorable clinical evolution. These factors, obtained at the time of admission to the hospital, were: blood pressure equal to or higher than 100mmHg, heart rate lower than 100 beats per minute, serum creatinine levels below 1.6mg/dl, and arterial blood pH equal to or higher than 7.35, bicarbonate equal to or higher than 15mEq/dl, and oxygen saturation higher than 84.1%. Riquelme et al[11] studied 25 HPS patients from Chile and found cyanosis, tachypnea, tachycardia, high levels of urea and creatinine, an APACHE score of 12, and a low $PaO2/FiO_2$ ratio, as factors associated with death in HPS . In the present study, Group I patients did not present circulatory shock or severe respiratory failure and consequently did not need to use inotropic pressor agents or corticosteroids. This is probably the reason why absence of the use of these drugs was associated with a favorable evolution of HPS. Likewise, the absence of circulatory shock in Group I patients probably led to a rehydration volume of less than 3,140ml in the first 24 hours of hospitalization and was associated with a favorable evolution of HPS. However, it is known that the use of massive quantities of fluids in HPS patients may aggravate pulmonary edema and contribute to a fatal outcome[3].

These clinical and laboratory parameters of a favorable evolution of HPS, determined on the basis of significant differences from those observed in patients presenting severe HPS, could be used to indicate a prognosis of light or mild evolution of the disease.

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