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Hyponatremia in Chagas disease heart failure: Prevalence, clinical characteristics, and prognostic importance☆

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ABSTRACT

Background: The prevalence, the clinical characteristics and the impact of hyponatremia on the prognosis of patients with chronic heart failure secondary to Chagas cardiomyopathy is unknown.
Methods: All patients with positive serology for Chagas disease and a left ventricular ejection fraction <55% on echocardiography routinely followed at the cardiomyopathy service of the university hospital from January, 2000 to December, 2008 were screened. The work-up consisted of anamnesis, physical examination, standard laboratory tests, 12-lead resting ECG, and 2-D echocardiography. Hyponatremia was defined as serum sodium levels <135 mEq/L.
Results: 246 patients were entered in the study; 30 (12%) patients were found to have hyponatremia. A multivariate stepwise logistic regression analysis revealed that the need of inotropic support [hazard ratio (HR) = 2.97; 95% Confidence Interval (CI) 1.24 to 7,18; p = 0.01], left ventricular systolic diameter (HR = 1.05; 95% CI 1.0 to 1.1, p = 0.03), and diastolic blood pressure (HR: 0,96; 95% CI 0,92 to 0,99; p = 0.04) were independent predictors of hyponatremia. A Cox regression analysis showed that the need of inotropic support (HR = 1,84; 95% CI 1,24 to 2,72; p = 0,0002), hyponatremia (HR = 2,05; 95% CI 1,25 to 3,38; p = 0.005), Betablocker therapy (hazard ratio = 0,33; 95% Confidence Interval 0,22 to 0,50; p < 0,0005), and digoxin use (HR = 2,79; 95% CI 1,42 to 5,46; p = 0003) were independent predictors of all-cause mortality.
Conclusion: Hyponatremia is an independent predictor of all-cause mortality of patients with chronic heart failure secondary to Chagas cardiomyopathy in the contemporary era of syndrome management. Hyponatremia can be predicted by variables consistent with syndrome severity.

1. Introduction

In the 21st century, Chagas disease still is a major health problem in Latin America, where about 10 million people are carriers of the disease, and about 10,000 people die of the disease annually [1]. Owing to international immigration, Chagas disease has spread throughout the world, and the global costs associated with this disease are about US 7, 2 billion each year, higher than that observed in several types of cancer [2].

The disease is caused by *Trypanosoma cruzi*, a protozoan transmitted to humans through the feces of a sucking bug. Infection usually occurs in infancy. Many years later on, about 30% of infected patients develop chronic cardiomyopathy. Ventricular dysrhythmias, conduction disturbances, sudden cardiac death [3], chronic systolic heart failure [4] cardiac thrombosis [5], thromboembolism [6], and precordial chest pain [7] are the protean clinical manifestations of the disease.

Chronic heart failure secondary to Chagas cardiomyopathy has a dismal prognosis not only in patients with moderate heart failure [8], but also in patients awaiting heart transplantation [9]. Its outcome is poorer than that observed in patients with ischemic cardiomyopathy [10], hypertensive cardiomyopathy [11], and idiopathic dilated cardiomyopathy [12,13].

Hyponatremia can be found in about 7% to 20% of outpatients with chronic non-Chagas disease heart failure [14–17]. New York Heart Association Class, higher urea serum levels, treatment with diuretics, and lower systolic blood pressure have all independently been associated with hyponatremia in non-Chagas disease heart failure [15]. Hyponatremia overshadows the outcome of patients with chronic non-Chagas disease heart failure [15,18].

Plasma serum levels are one of the independent predictors of all cause-mortality for patients with chronic systolic heart failure secondary to Chagas cardiomyopathy [8]. The prevalence, the clinical characteristics

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and the impact associated specifically with hyponatremia on patients with this condition is unknown at this time. Accordingly, the present study was undertaken to clarify the clinical aspects of hyponatremia in patients with chronic systolic heart failure secondary to Chagas cardiomyopathy.

2. Methods

2.1. Patients

All patients with positive serology for Chagas disease and a left ventricular ejection fraction <55% on echocardiography routinely followed at the cardiomyopathy service of the university hospital from January, 2000 to December, 2008 were screened for potentially taking part in the investigation. Patients with a concomitant disease that could potentially cause heart disease by itself were excluded.

The work-up consisted of anamnesis, physical examination, standard laboratory tests, 12-lead resting ECG, and 2-D echocardiography. New York Heart Association functional Class (NYHA), heart rate, and systemic arterial pressure were observed at study entry. Hyponatremia was defined as serum sodium levels <135 mEq/L, as previously established in the MAGGIC study [18].

All patients received evidence-based treatment for chronic systolic heart failure, according to international guidelines of the time. Thus, treatment with angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blocks (ARB) and Betablockers (BB) at targeted or maximal tolerated doses was considered for all patients. Those with pitting edema received furosemide, while those in the NYHA Class III/IV with a left ventricular ejection fraction <30% were treated with digoxin.

Patients usually visited the outpatient service each 4 months, and a senior heart failure specialist (RBB) supervised the treatment given. Patients were followed until the close study; they were also censored at heart transplantation or death.

2.2. Statistical analysis

Continuous variables are presented as mean ± standard deviation, whereas categorical variables are given as number (percentages). Continuous variables were compared by the unpaired T-test, while categorical variables were compared by Fisher exact test. The Spearman test was used to establish correlation between continuous variables. A Cox proportional hazards model was used to evaluate the ability of hyponatremia to independently predict all-cause mortality.

In the multivariable model, only variables with a p value <0.05 in the univariate model were entered a forward stepwise approach to establish independent predictors of mortality. In addition, continuous variables underwent the Spearman test to establish correlation among them. The variable who correlated with others and with the highest Wald coefficient remained in the model, whereas the other were ruled out. Thus, each variable entered the multivariable model in a proportional to 10 events in an attempt to avoid overfitting.

A separate binary logistic stepwise regression analysis was used to determine independent variables associated with hyponatremia. Survival probabilities were estimated by the Kaplan–Meir method. A p value <0.05 was considered statistically significant in all circumstances.

3. Results

A total of 246 patients fulfilled the inclusion criteria and were entered in the study. About 30 (12%) patients were found to have hyponatremia. Table 1 shows the clinical characteristics, whereas Table 2 gives the electrocardiographic and echocardiographic features of patients with and without hyponatremia. In comparison to patients without hyponatremia, patients with hyponatremia had clinical signs compatible with more severe chronic heart failure. In fact, such patients were found to have higher NYHA Class III/IV at presentation, more need of inotropic support, more need of hospitalization to compensate for acute HF, a lower proportion of patients on Betablockers; a higher proportion of patients on digoxin, diuretics, and spironolactone. Furthermore, they had lower systemic blood pressure at admission, higher creatinine serum levels, higher frequency of ventricular premature contractions in the 12-lead ECG, larger diastolic and systolic left ventricular diameters, larger diameter of the right ventricle, and lower left ventricular ejection fraction than patients with no hyponatremia did.

A multivariate stepwise logistic regression analysis revealed that the need of inotropic support (hazard ratio = 2.97; 95% Confidence Interval 1.24 to 7.18; p = 0.01), left ventricular systolic diameter (hazard

Table 1
Clinical characteristics of patients with chronic systolic heart failure due to Chagas cardiomyopathy with (n = 30) and without hyponatremia (n = 216).

Variable	Hyponatremia	No Hyponatremia
Age (years)	53 ± 13	55 ± 14
Male	20 (67%)	141 (67%)
Class III/IV	17 (57%)	61 (28%)*
Hospitalization	26 (87%)	129 (60%)**
Inotropic support	17 (57%)	51 (24%)***
ACEI/ARB	29 (97%)	200 (93%)
Betablockers	10 (33%)	118 (55%)****
Digoxin	28 (93%)	148 (68%)#
Diuretics	26 (87%)	177 (82%)
Spironolactone	26 (87%)	139 (64%)##
Amiodarone	14 (47%)	83 (38%)
Heart Rate (beats/min)	74 ± 20	70 ± 14
SBP (mmHg)	100 ± 13,4	108.7 ± 16.4
DBP (mmHg)	65 ± 8.6	71.4 ± 11.2###
K (mEq/L)	4.4 ± 0.7	4.4 ± 0.6
Creatinine (mg/dL)	1.4 ± 0.6	1.2 ± 0.4
Hemoglobin (g/L)	13.8 ± 1.7	13.4 ± 1.6

ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor block; HR = heart rate; SBP = systolic blood pressure; and DBP = diastolic blood pressure.
* P = 0.02.
** P = 0.004.
*** P < 0.001.
**** P = 0.03.
\# P = 0.005.
\#\# P = 0.01.
\#\#\# P = 0.01.

Table 2
Electrocardiographic and echocardiographic findings in patients with chronic systolic heart failure due to Chagas cardiomyopathy with (n = 30) and without (n = 216) hyponatremia.

Variable	Hyponatremia	No hyponatremia
Electrocardiography		
Atrial Fibrillation	9 (30%)	60 (28%)
Pacemaker	17 (57%)	107 (49%)
LBBB	7 (23%)	34 (16%)
RBBB	10 (33%)	89 (41%)
LAFB	14 (47%)	85 (39%)
Low Voltage of QRS	1 (3%)	11 (5%)
VPC	19 (63%)	94 (43%)*
2D-Echocardiography		
WMA	8 (27%)	83 (38%)
LVEF <35%	21 (70%)	92 (43%)**
LVDD (mm)	69.9 ± 9.9	63.8 ± 8.5***
LVSD (mm)	60.3 ± 10.7	52.6 ± 10.1***
RVD (mm)	29,7 ± 7.7	24.9 ± 7.3#
LVEF (%)	28.9 ± 10.2	36.1 ± 13##

LBBB = left bundle branch block; RBBB = right bundle branch block; LAFB = left anterior fascicular block; VPC = ventricular premature contraction; WMA = wall motion abnormalities; LVEF = left ventricular ejection fraction; LVDD = left ventricular diastolic diameter; LVSD = left ventricular systolic diameter; and RVD = right ventricular diameter.
* P = 0.04.
** P = 0.01.
*** P < 0.01.
\# P < 0.05.
\#\# P = 0.04.