Hyponatremia in Patients with Heart Failure: a Prognostic Marker

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Due to the high prevalence of cardiovascular diseases and better treatment strategies, with increased survival, heart failure is a condition with increasing prevalence, especially in developed countries. Heart failure patients often present electrolytic disorders, the most frequent one being hyponatremia. The objective of the study was to evaluate the frequency of hyponatremia in patients with chronic heart failure hospitalized in the Internal Medicine Clinic of the Clinical Emergency Hospital of Bucharest and to assess the clinical and paraclinical correlations, as well as prognostic implications of hyponatremia in these patients. We performed an observational retrospective study on 400 chronic heart failure patients hospitalized between January 1st 2014 and August 31st 2015. From these patients, 60 patients have been diagnosed with hyponatremia (defined as a serum natrium <135 mEq/L) and represented our group of study. The values of the serum natrium at admission in the study group ranged between 110-132 mmol/L. Most patients had advanced heart failure, according to NYHA classes' classification. The proportion of patients discharged with persistent hyponatremia was 48.33%, lower than the patients discharged with corrected serum sodium (51.67%), indicating an effective treatment of hyponatremia during hospitalization. The mortality rate during hospitalization in patients with corrected hyponatremia was 8.33%, smaller than the mortality rate in patients with persistent hyponatremia despite the correct administration of hydroelectrolytic rebalancing treatment (18.33%). Persistent hyponatremia may be considered a marker of a poor prognosis in hospitalized heart failure patients.

Key words: hyponatremia, heart failure, electrolytic disorders, diuretics, mortality

The majority of cardiovascular diseases will progress to heart failure, as the final stage of evolution in patients who survive after an acute cardiac event. Due to the high prevalence of cardiovascular diseases and better treatment strategies, with increased survival of these patients, heart failure is a condition with increasing prevalence, especially in developed countries. Heart failure patients often present electrolytic disorders, the most frequent one being hyponatremia [1-3]. Hyponatremia is the most common electrolyte disorder in hospitalized patients, being associated with higher mortality in different pathologies [4-6]. The OPTIMIZE-HF study (Organized Program To Initiate Life-Saving Treatment in Hospitalized Patients With Heart Failure) has demonstrated that 19.7% of patients admitted for acute decompensated heart failure present hyponatremia, with a serum sodium less than 135 mEq/L [7]. This analysis was made on a high number of patients: 47,647. The hyponatremic patients admitted for acute decompensated heart failure had worse outcomes than those with normonatremia, requiring more often dialysis and inotropic agents [7, 8]. The mortality rate during hospitalization was higher in hyponatremic patients than in patients with normal serum sodium [7]. Lee et al have found that chronic hyponatremia in more than 4000 patients hospitalized for heart failure was associated with an increased mortality at 30-days (by 53%) and at 1-year (by 46%) [9]. It is not well known yet if the increased mortality in heart failure patients with hyponatremia is directly related to hyponatremia or if the natrium abnormality is a marker of a more severe cardiac disease, with a poor prognosis *per se*. Severe hyponatremia and it's management can lead to neurological events, from cerebral edema, ischemia to brain herniation, therefore worsening the prognosis of this patients with the necessity of supplementary therapeutic management [10].

There are multiple mechanisms to explain the high incidence of hyponatremia in heart failure patients. These mechanisms include the non-osmotic release of arginine vasopressin due to low cardiac output, decreased renal blood flow, and baroreceptor stimulation due to low blood pressure. In heart failure patients, with reduced cardiac output, the hypovolemic hormones (renin, antidiuretic hormone, and norepinephrine) react [11]. Although patients with heart failure and edema have high volemia, the low cardiac output decreases the carotid sinus baroreceptors' pressure of perfusion and the body perceives volume depletion. The neurohormonal activation of patients with heart failure limits natrium and water excretion, by antidiuretic hormone release that increases water reabsorption in the collecting tubules (fig. 1).

There are 3 types of hyponatremia, depending on the volume status: hypovolemic, euvolemic and hypervolemic. Patients with heart failure often present hypervolemic hyponatremia; the body fluid volume exceeds the total natrium content, resulting in low natrium level. Diuretics, which are the cornerstone therapy in the management of heart failure symptoms, increase the urinary excretion of water and natrium, leading to hyponatremia. Thiazide diuretics are the most frequently associated with hyponatremia, by blocking the sodium-chloride transport in the distal tubules and connecting segment [6,12,13]. In some cases, reset osmostat secondary to intracellular

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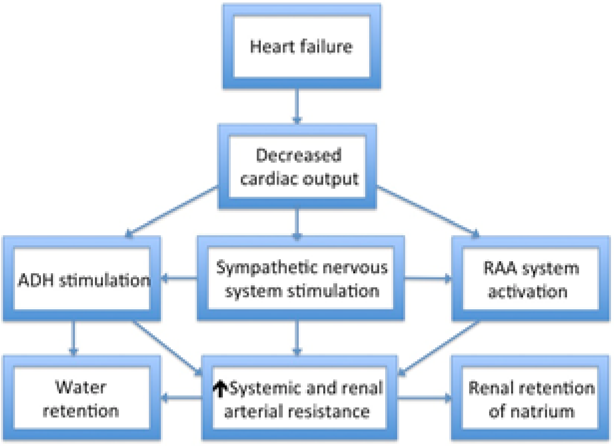

Fig. 1. The neurohormonal activation in patients with heart failure

potassium depletion may be responsible for hyponatremia, by normal dilution at a lower serum natrium level. Patients with chronic heart failure often present other comorbidities, such as depression, which require treatment with drugs that may lead to hyponatremia as a side effect (selective serotonin reuptake inhibitors, for example). Chronic heart failure can lead to kidney dysfunction with the necessity of long term renal replacement therapies associated with its own complications [14,15]. Micro- and macrovascular complicated diabetes mellitus [16,17] which is also a frequent comorbidity in heart failure patients, with uncontrolled values of hyperglycemia, may be responsible for hyponatremia [18,19].

Experimental part

The objective of the study was to evaluate the frequency of hyponatremia in patients with chronic heart failure hospitalized in the Internal Medicine Clinic of the Clinical Emergency Hospital of Bucharest and to assess the clinical and paraclinical correlations, as well as prognostic implications of hyponatremia in these patients.

We performed an observational retrospective study on 400 chronic heart failure patients hospitalized between January 1st 2014 and August 31st 2015. From these patients, 60 patients (15%) have been diagnosed with hyponatremia (defined as a value of serum natrium < 135 mEq/L) and represented our group of study. In the group of study, hyponatremia either was diagnosed at admission, either developed during hospitalization. We retrospectively analyzed the clinical and paraclinical data from the observation sheets of the patients and the electronic database of the hospital (Hippocrate), together with the treatment. The statistical analysis has been performed using the software IBM-SPSS (Statistical Package for the Social Sciences). The statistical tests (t-student, ANOVA) have been considered significant at a p value < 0.05.

Results and discussions

The distribution by gender in the study group was: 58% men and 42% women. The patients' average age was 72.21 years old.

The values of the serum natrium at admission in the study group ranged between 110-132 mmol/L. The standard deviation was 4.68, while the variation of the standard deviation was 22.33.

Most patients from the study group had advanced heart failure, according to NYHA classes' classification: 42% had NYHA class III and 45% NYHA class IV, the rest being in NYHA class 2.

The most common comorbidities in the group of study were represented by arterial hypertension (65%), chronic kidney disease (45% of cases), coronary heart disease (37.5%), diabetes mellitus (33.33%), heart rhythm disorders (especially permanent atrial fibrillation, in 36% of cases), anemia (27%), and hypercholesterolemia in 11.66% of the cases (fig. 2).

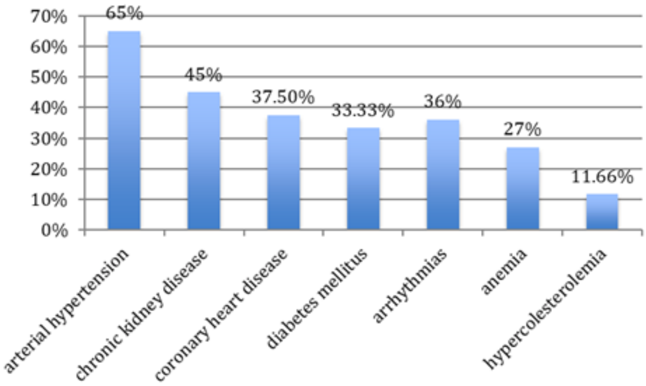

Fig. 2. The distribution of major comorbidities in the group of study

Hyponatremia was treated during hospitalization by water restriction, administration of hypertonic or isotonic saline solutions (sodium chloride) and diuretics. In cases of severe hyponatremia (defined as a serum natrium less than 125 mEq/L), it was achieved a natrium increase by 1.2 mmol/L/h to 4-6 mmol/L/h. After the initial correction, serum natrium was corrected with up to 8-12 mmol/L/24 h. 87% of the patients from the group of study, who were admitted for worsening heart failure, have been treated with a diuretic, in order to reduce congestion. In 64% of the cases, a combination of an aldosterone receptor antagonist with a loop diuretic (spironolactone + furosemide) has been used.

The proportion of patients discharged with persistent hyponatremia was 48.33%, lower than the patients discharged with corrected serum sodium (51.67%), indicating an effective treatment of hyponatremia during hospitalization.

The mortality rate during hospitalization in patients with corrected hyponatremia was 8.33%, smaller than the mortality rate in patients with persistent hyponatremia despite the correct administration of hydroelectrolytic rebalancing treatment (18.33%).

The minimum value of the serum sodium at discharge was 122.67 mmol/L and the maximum value was 144.86 mmol/L. The difference between the minimum values at admission and discharge (110 mmol/L versus 122.67 mmol/L) indicates an improvement in natremia due to the treatment administered during hospitalization. The variation of the standard deviation was 19.36, with a standard deviation of 4.36. The sigma value is 0.1, indicating a correlation between values of serum natrium at admission and at discharge, due to effectiveness of natrium correction therapy during hospitalization.

The average value of the serum natrium in patients with symptoms corresponding to heart failure NYHA II class was 132 mmol/L, 131 mmol/L in NYHA class III and 126 mmol/L in patients with NYHA class IV. These differences indicate the inverse relationship between the severity of heart failure and the natrium values and the correlation of hyponatremia with the severity of heart failure. Also, in terms of natrium values at admission, the sigma value of $0.024 < 0.05$ reveals correlations between the admission value and NYHA class, a more severe hyponatremia being associated with more severe heart failure symptoms.

The initial diagnostic approach of a patient with heart failure and hyponatremia should include detailed history, physical examination, and laboratory tests. These are necessary in order to establish the correct mechanism of hyponatremia: hypotonic, isotonic, or hypertonic, with impact on the future therapeutic strategy. In diabetic patients with hyperglycemia, the level of the serum natrium should be corrected for the effect of glucose, to exclude a hypertonic hyponatremia. Other patients, who may have been treated with mannitol or glycerol, or may have lipemic serum or recent surgery with big volumes of electrolyte-poor irrigation fluids, should be evaluated for possible isotonic or hypertonic hyponatremia. The personal history and clinical examination should focus on determining the possible etiology of hyponatremia: electrolyte-rich fluid losses, low protein or high fluid intake, recent surgical interventions [20, 21], history of adrenal insufficiency [22], hypothyroidism, malignancy [23,24], pulmonary diseases, use of drugs like thiazide or thiazide-like diuretics, mannitol, antidepressants, antipsychotics etc. Most often, extensive laboratory tests are necessary for a correct diagnosis of hyponatremia etiology. These laboratory tests include complete blood count, other electrolytes (potassium, chloride, and calcium), bicarbonate, serum glucose, serum creatinine, liver function tests (alanine aminotranspherase, aspartate aminotranspherase, bilirubin, and albumin), kidney tests (blood urea nitrogen, creatinine), serum lipids, urine exam. The measurement of serum osmolality is not a usual part of the initial diagnostic approach of patients with hyponatremia, it is used mostly used only in specific cases. Natrium is the main determinant of the serum osmolality, which normally ranges from 275-290 mOsm/Kg.

In our study, the majority of hyponatremic patients admitted for heart failure had advanced stages (NYHA classes III or IV). They had clinical signs of hemodynamic congestion, such as peripheral edema and/or ascites, with hypervolemic hyponatremia. Heart failure patients with moderate to severe hyponatremia have near end-stage disease.

In the presence of heart failure and mild hyponatremia, patients undergoing surgery, like prostate resection, hysteroscopy, neuroendocrine tumor removal are at high risk of developing severe hyponatremia due to the changes in plasma osmolality over time [25-27].

Arterial hypertension was the most frequent comorbidity in our group of study, with 65% of the patients having different stages of arterial hypertension. Patients with arterial hypertension and heart failure are more likely to receive treatment with diuretics [28], which may further increase the risk of dyselectrolytemia.

The hemodynamic and neurohormonal changes of patients with heart failure induce renal impairment, which may progress over time to chronic kidney disease [29]. In our study, 85% of the patients with chronic heart failure and chronic kidney disease had moderate or advanced stages of kidney disease (stage 3 to 5). The association of chronic kidney disease further increases the risk of hyponatremia in patients with heart failure [30,31]. Hyponatremia is also considered to be a marker for poor long-term prognosis [32,33].

The number of patients discharged with hyponatremia was smaller than the number of patients discharged with corrected hyponatremia, indicating a reduced incidence of persistent hyponatremia in our group of study, most probably due to an efficient treatment.

Conclusions

The reduced in-hospital mortality rate of patients with corrected hyponatremia, as compared to those with persistent hyponatremia despite the correct treatment, indicate that persistent hyponatremia is a marker of a poor prognosis in heart failure patients. Hyponatremia is not only a marker of a poor long-term prognosis, but also a predictor of short-term increased mortality, especially in patients hospitalized for worsening heart failure, as in our study.

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Manuscript received: 21.12.2017