EVALUATION OF ELDERLY PATIENTS HOSPITALIZED FOR HYPONATREMIA: IS HYPONATREMIA A REAL INDEPENDENT RISK FACTOR AFFECTING MORTALITY IN THESE PATIENTS?

Abstract

Introduction: Hyponatremia is a significant and common electrolyte disorder in elderly patients that affects in-hospital mortality. We herein aimed to assess the effect of hyponatremia on mortality of elderly patients hospitalized with the diagnosis of hyponatremia from the emergency department.

Materials and Method: Medical records of 7659 patients aged 65 and over hospitalized in Antalya Education and Research Hospital Internal Medicine Clinics between 1 January 2010 and 31 June 2015 were retrospectively screened. Laboratory values, age, sex, comorbidities, medications, complaints at admission, duration of hospital stay and outcomes of 856 patients diagnosed with hyponatremia according to International Classification of Diseases (ICD) system were evaluated. Total 138 pure hyponatremia patients without major diagnosis other than hyponatremia were analyzed.

Results: Among a total of 7659 geriatric patients hospitalized during the study period, all-cause and pure hyponatremia prevalences were 11.1% (856/7659) and 1.8% (138/7659), respectively. The 3 most common causes of hyponatremia were diuretic use (47/138, 34%), syndrome of inappropriate antidiuretic hormone secretion (27/138, 19.5%), and reduced oral intake (18/138, 13%). The average duration of hospital stay was 5 days and in-hospital mortality was 5.8% (8/138).

Conclusion: The most common causes of hyponatremia in elderly patients requiring hospitalization were diuretic use, syndrome of inappropriate antidiuretic hormone secretion and reduced oral intake. The mortality of patients hospitalized with purely hyponatremia is not different from the normal population.

Keywords: Hyponatremia; Geriatric Assessment; Mortality.
INTRODUCTION

Hyponatremia is defined as a decrease in serum sodium to levels below 135 mEq/L. It has critical implications as the most commonly observed electrolyte abnormality in hospitalized patients. In geriatric patients, defined as those aged ≥65 years, hyponatremia may result from increased exposure to drugs, diseases associated with hyponatremia, and aging-related impairment in water excretion capacity (1). The majority of these patients has mild hyponatremia and is clinically asymptomatic. Therefore, they are usually not hospitalized. However, even mild hyponatremia can cause falls, unsteadiness, bone demineralization, fractures, and cognitive problems in the geriatric patients, leading to serious consequences in the long term (2). The major clinical presentation of acute hyponatremia is neurologic dysfunction induced by cerebral edema that is proportional to the degree of hyponatremia (3). Nausea and malaise are the earliest symptoms and may be observed at serum sodium concentrations below 125–130 meq/L. Headache, lethargy, obtundation, and eventually seizures, coma, and respiratory arrest can occur if serum sodium concentration falls below 115–120 meq/L (4, 5). As hyponatremia was shown to be an independent risk factor, increasing hospital mortality by 40%, its early recognition is critical (6). The reported prevalence of hyponatremia varies between studies and is estimated to increase up to 20% in hospitalized patients (7); however, it is observed substantially more frequently in geriatric patients, and can directly affect mortality (8). However, the relationship between hyponatremia with hospital morbidity and mortality remains controversial, mainly because of the methodology and design of studies (9). Specifically, differences in serum sodium cut-off values, small number of patients, and absence of control groups contribute to the conflicting results (10). It is also unclear whether the relationship between hyponatremia and adverse outcomes is associative or causative. Age, comorbidities, severity and etiology of hyponatremia, treatment failure, and rate of onset were determinants of clinical outcomes in hospitalized hyponatremic geriatric patients (9, 11). In this study, we investigated whether these factors were associated with outcomes in geriatric patients who were hospitalized with the major diagnosis of hyponatremia.

MATERIALS AND METHOD

Study Population

Medical records of geriatric patients (age, ≥65 years) who were hospitalized at Internal Medicine Clinics of Antalya Training and Research Hospital between January 1, 2010 and June 31, 2015 were retrospectively screened. Among a total of 7659 geriatric patient admissions, 856 patients diagnosed with hyponatremia (serum sodium ≤ 135 meq/L) according to ICD (International Classification of Diseases) system were evaluated. Patients diagnosed with decompensated heart failure (HF), decompensated cirrhosis, treatment resistant and/or end stage malignancy, severe diarrhea, acute cerebrovascular disease (CVD), and myxedema were excluded. The records of remaining 168 geriatric patients in whom major hospitalization diagnosis was hyponatremia were further evaluated in detail, and those who developed hyponatremia during hospitalization, those with incomplete clinical and laboratory data in medical records, and those with repeated admissions were also excluded. Finally, 138 (41 males, 97 females) pure hyponatremia patients without major diagnosis other than hyponatremia were included in the study.

Study Parameters

All records of hyponatremic patients were reviewed for the following parameters: laboratory values, age, gender, comorbidities, medications, complaints at admission, duration of hospital stay and patient outcomes. The cause of hyponatremia was categorized into the following 3 groups based on the volume status of patients at admission: hypovolemic, normovolemic, and hypervolemic. In cases where this categorization was not defined in the medical records, clinical symptoms and findings of the physical examination, including symptoms related to hydration status, skin turgor, presence of edema, and blood pressure were used to categorize the volume status. Laboratory parameters at admission, which included serum sodium, serum potassium, urine sodium, blood urea nitrogen (BUN), serum osmolarity, urine osmolarity, and whole blood count, were also noted. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) was diagnosed based on the guidelines (12).

Statistical Analysis

Student’s t test or Mann–Whitney U test were used to compare quantitative data from 2 independent groups. The relevance of normal distribution of continuous variables was investigated with the one sample Kolmogorov–Smirnov test. Chi-square test or Fisher’s exact probability test was performed to test correlations between groups of qualitative data. In correlation analysis for variables with normal distribution, Pearson correlation analysis was used, whereas Spearman corre-
lation analysis was used for abnormally distributed variables. Results were expressed with a 95% confidence interval (CI) and were considered statistically significant if \( P \) values were <0.05. All statistical analysis were performed using the Statistical Package for Social Sciences (SPSS; Chicago, IL, USA) software, version 16.0. The study protocol was conducted in accordance with the ethical principals stated in the Declaration of Helsinki and was approved by the local Research Institutional Ethics Committee (reference, 62/10).

RESULTS

Patient characteristics are shown in Table 1. The prevalences of all-cause hyponatremia and pure hyponatremia cases without major diagnosis other than hyponatremia were 11.1% (856/7659) and 1.8% (138/7659), respectively. The mean age of geriatric patients hospitalized with the pure diagnosis of hyponatremia (\( n = 138 \)) was 75.28. Of these, 97 (70.3%) were female and 41 (29.7%) were male. The average duration of hospital stay was 5 days. The mean serum sodium level was 118 meq/L (range, 103–132 meq/L) and serum osmolarity was 253.72 ± 20.26 mOsm/L, which was compatible with the sodium level. Hypertension (66.7%) was the leading concomitant systemic disease and was followed by neurological diseases (35.5%), diabetes mellitus (DM) (28.3%), HF (17.4%), and chronic kidney disease (CKD) (10.1%) (Table 1).

The distribution of neurological/psychiatric disorders in 49 patients were as follows: 15 patients (30.61%) had CVD, 12 patients (24.49%) had dementia, 8 patients (16.33%) had depression, 5 patients (10.2%) had Parkinson’s disease, 1 patient (2.04%) had bipolar disorder, 3 patients (6.12%) had epilepsy, 3 patients (6.12%) had schizophrenia, and 2 patients (4.08%) had malignancy (Table 2).

According to the volume status, hypovolemia, hypervolemia, and normovolemia were observed in 68 (49.3%), 26 (18.8%), and 44 (31.9%) patients, respectively (Table 3). The cause of hyponatremia was diuretic use in 47 patients (69.1%), lack of oral intake in 18 patients (26.5%), and vomiting related...
In 3 patients (4.4%). The cause of hypervolemia was HF in 11 patients (42.3%), CKD in 7 patients (26.9%), cirrhosis in 3 patients (11.5%), hypoalbuminemia in 1 patient (3.8%), and idiopathic etiology in 4 patients (15.4%). In the normovolemic group, 27 patients (61.4%) had SIADH, 10 patients (22.7%) had hypothyroidism, 6 patients (13.6%) had hypopituitarism, and 1 patient (2.3%) had polydipsia. Of the 138 patients included in the final analysis, 27 patients (19.6%) had a diagnosis of SIADH. The specific etiologies of SIADH were medications (63%), central nervous system (CNS) pathology (14.8%), pulmonary system pathology (14.8%), and idiopathic (7.4%).

Complaints of patients at first admission were as follows: nausea and vomiting in 36 patients (26.1%), altered mental status in 32 patients (23.2%), fatigue in 23 patients (16.7%), general poor condition in 11 patients (8%), dyspnea in 11 patients (8%), edema in 9 patients (6.5%), reduced oral intake in 6 patients (4.3%), headache in 6 patients (4.3%), seizures in 2 patients (1.4%), anorexia in 1 patient (0.7%), and inability to walk and talk in 1 patient (0.7%) (Table 4).

Clinical and laboratory data of 27 patients with SIADH were compared with those of non-SIADH patients. Age, frequency of hypertension, and diuretic use were significantly lower (P-values; 0.006, 0.006, and 0.001, respectively) and neurological disease rate was significantly higher (P < 0.001) in the SIADH group. There were no statistically significant differences in sex distribution, BUN, serum potassium and sodium levels, urine sodium level, serum and urine osmolality, hemoglobin level, length of hospital stay, and diabetes, HF, and CKD prevalence between the two groups (Table 5).

### Table 4—Admission Complaint Distribution of the Patients

<table>
<thead>
<tr>
<th>Admission complaint</th>
<th>Number</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>36</td>
<td>26.08</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>32</td>
<td>23.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23</td>
<td>16.6</td>
</tr>
<tr>
<td>Impaired general condition</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Edema</td>
<td>9</td>
<td>6.5</td>
</tr>
<tr>
<td>Poor intake orally</td>
<td>6</td>
<td>4.3</td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
<td>4.3</td>
</tr>
<tr>
<td>Seizures</td>
<td>2</td>
<td>1.4</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Inability to talk and walk</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>138</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

### Table 5—Comparison of the Patients with SIADH to Those Without SIADH

<table>
<thead>
<tr>
<th></th>
<th>SIADH (+) n:27</th>
<th>SIADH (-) n:111</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.70±6.40</td>
<td>76.15±7.72</td>
<td>0.006*</td>
</tr>
<tr>
<td>Female % (n)</td>
<td>55.56 (15)</td>
<td>73.87 (82)</td>
<td>0.062**</td>
</tr>
<tr>
<td>Serum sodium (mEq/L)</td>
<td>118.0 (20)</td>
<td>118.0 (33)</td>
<td>0.207***</td>
</tr>
<tr>
<td>Urine sodium (mEq/L)</td>
<td>86.93±56.71</td>
<td>62.66±48.95</td>
<td>0.110*</td>
</tr>
<tr>
<td>Serum osmolarity (mOsm/L)</td>
<td>247.44±17.02</td>
<td>255.81±21.10</td>
<td>0.290*</td>
</tr>
<tr>
<td>Urine osmolarity (mOsm/L)</td>
<td>370.7±269.28</td>
<td>187.59±105.48</td>
<td>0.064*</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>18.0 (11.0)</td>
<td>22.0 (121.0)</td>
<td>0.055***</td>
</tr>
<tr>
<td>Serum potassium (mEq/dL)</td>
<td>4.21±0.49</td>
<td>4.47±1.01</td>
<td>0.062*</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.43±1.71</td>
<td>10.85±1.67</td>
<td>0.113*</td>
</tr>
<tr>
<td>Duration of hospital stay (day)</td>
<td>5.0 (17.0)</td>
<td>5.0 (36.0)</td>
<td>0.362***</td>
</tr>
<tr>
<td>Hypertension % (n)</td>
<td>44.44 (12)</td>
<td>72.07 (80)</td>
<td>0.006**</td>
</tr>
<tr>
<td>Diabetes Mellitus % (n)</td>
<td>25.92 (7)</td>
<td>28.83 (32)</td>
<td>0.764**</td>
</tr>
<tr>
<td>Heart failure % (n)</td>
<td>7.41 (2)</td>
<td>19.82 (22)</td>
<td>0.102**</td>
</tr>
<tr>
<td>Chronic kidney damage % (n)</td>
<td>11.11 (3)</td>
<td>9.91 (11)</td>
<td>0.543**</td>
</tr>
<tr>
<td>Neurological disorder % (n)</td>
<td>70.37 (19)</td>
<td>27.03 (30)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Diuretic use % (n)</td>
<td>22.22 (6)</td>
<td>57.66 (64)</td>
<td>0.001**</td>
</tr>
</tbody>
</table>

Mean ±SD, median (range) or % (n) are reported for continuous and categorical variables regarding their distribution status.

* Student’s test was used.
** Chi-Square test was used.
*** Mann whitney U test was used.
Hospital mortality rate of the patient cohort included in final analysis was 5.8% (8/138). There were no significant differences in any of the clinical and laboratory values between these 8 patients and others.

When we examined associations between serum sodium level and other variables, we observed a positive correlation of serum sodium level with serum osmolality (r=0.742, p<0.001), serum potassium (r=0.178, p=0.041), and serum BUN (r=0.218, p=0.013). There were no correlations between serum sodium level and other variables.

**Discussion**

As in many developing countries, the average life expectancy in Turkey has been increasing in the last decades. According to data from the Turkish Statistical Institute (www.tuik.gov.tr), the highest death rates were observed in the population who were >75 years of age, and the mortality rates among those ≥75 years were 48.6% and 47.1% in 2014 and 2013, respectively. Numerous etiologies, such as comorbid medical conditions, polypharmacy, and altered oral intake, may affect fluid and electrolyte imbalance in geriatric patients; thus, they are more likely to encounter associated morbid and potentially life-threatening conditions (13). Physiologic changes in regulation of water excretion that occur as part of normal aging also render geriatric patients more susceptible to the development of hyponatremia (14).

The results based on our hospital records revealed that the prevalences of all-cause hyponatremia and pure hyponatremia were 11.1% and 1.8%, respectively. These rates were lower than those reported by Sturdik et al. and Correia et al. (9, 15), which may be because of the early diagnosis and treatment of hyponatremic geriatric patients in whom serum sodium levels may not have yet required hospitalization depending on the clinical condition and evaluation in emergency department.

Nausea, headache, lethargy, confusion, muscle cramps, irritability, and seizures are general complaints related to hyponatremia. Depending on the magnitude and rate of decline of serum sodium levels, the severity of symptoms may be augmented. Coma, permanent brain damage, respiratory arrest, brain stem herniation, and death are symptoms of severe and rapidly developing hyponatremia (13). In our study, none of the patients exhibited these life-threatening symptoms.

Hyponatremia can be classified based on the volume status (16). Hypovolemic hyponatremia was the most common type in our study (47/138, 49.3%), which was reported by other studies as well (13,15). The vast majority of hypovolemic hyponatremia cases was the result of a side effect caused by diuretic usage. This finding was expected as diuretics were previously shown as one of the most common causes of severe hyponatremia (17). Both loop and thiazide diuretics can precipitate hyponatremia. In our study, of the 70 patients (50.7%) who used diuretics, 47 had hypovolemic hyponatremia. In contrast, SIADH and hypervolemic hyponatremia were observed in 6 and 17 patients, respectively.

There is also an association between hyponatremia and malnutrition (18). The geriatric patients, particularly those with neurological diseases, are at an increased risk of malnutrition. Reduced oral intake was the second most common cause of hypovolemic hyponatremia in our cohort, affecting 18 patients. Therefore, clinicians should be specifically careful when prescribing diuretics to geriatric patients with reduced oral intake.

Loss of water and sodium through vomiting is also a risk factor for hyponatremia. Unfortunately, it was very difficult to determine whether vomiting was the cause or the consequence. Although the complaint at admission was nausea and vomiting in 36 patients, only 3 patients had vomiting as the etiology of hypovolemia in this study.

We found that normovolemic hyponatremia (31.9%) was the second most common condition when patients were stratified according to their volume status. SIADH, a subtype of normovolemic hyponatremia, is the most common cause of hyponatremia in geriatric patients (19). In this study, 27 patients (19.6%) had SIADH, which was the most common pathological condition leading to hyponatremia. SIADH is a diagnosis of exclusion and is characterized by continued release of ADH (12). It should be suspected when hyponatremia is accompanied by hyperosmolar urine when compared with plasma. Many diseases of the geriatric population can cause SIADH (19). Almost all CNS disorders can lead to dysfunction of the hypothalamic system and induce ADH release. Risk for water retention and consequent hyponatremia may be apparent by this way (20). In our study, 4 patients in the SIADH group had CNS pathology. In addition, certain drugs can cause hyponatremia as a side-effect by precipitating SIADH. Antipsychotic and antidepressant drugs, opiates, nonsteroidal anti-inflammatory agents, sodium valproate, and amiodarone are drugs that may cause SIADH (19). Seventeen patients with SIADH were associated with use of these drugs in our study. Malignancies and pulmonary pathologies can also cause SIADH by different mechanisms. In our study, 4 patients had lung malignancies. Drug-induced SIADH was the most common condition in this study, as only geriatric pati-
patients with the major diagnosis of hyponatremia were included. CNS pathologies, malignancies, and pulmonary diseases may demonstrate organ-specific symptoms and not hyponatremia. Of note, 2 patients had no apparent etiology related to comorbidities and drugs to explain SIADH.

When we compared the clinical and laboratory findings of SIADH patients with those of the non-SIADH patients, we found that the mean age of SIADH group (71.7 years) was significantly lower than that of the non-SIADH group (76.15 years; \( P = 0.006 \)), which was in contrast to that reported by Sweed (18). Advanced age itself may be a risk factor for hyponatremia, and SIADH was described in geriatric patients with idiopathic hyponatremia. Two patients with idiopathic SIADH in this study were 69 and 73 years old, whereas Miller et al. reported that the idiopathic form of SIADH could be observed in geriatric individuals who were generally older than 80 years of age (21).

The frequency of hypertension and diuretic use were significantly lower in the SIADH group than in the non-SIADH group in our study. Furthermore, concomitant neurological diseases in the SIADH group was significantly higher (\( P < 0.001 \)), in agreement with the literature. In contrast, gender, BUN, serum potassium and sodium levels, urine sodium level, serum and urine osmolality, hemoglobin level, length of hospital stay, diabetes, HF, and CKD prevalence were not significantly different between these 2 groups. The mean duration of hospitalization was 5 days for both SIADH and non-SIADH patients.

Hypothyroidism is a rare cause of normovolemic hyponatremia and can induce it via undefined mechanism. Reduced cardiac output and glomerular filtration are the default mechanisms that could lead to water uptake, subsequently reducing plasma sodium concentration by dilution (18). In our study, 10 patients (7.2%) in the normovolemic group had hypothyroidism. Although the literature regarding this subject was insufficient, it can be assumed higher.

Impaired pituitary–adrenal axis is linked to hyponatremia; glucocorticoid deficiency impairs water excretion in patients with hypopituitarism (22) because of altered ADH inhibitory and decreased mineralocorticoid activities of cortisol (23). In this study, 6 patients in the normovolemic group had hypopituitarism.

Compulsive water drinking or psychogenic polydipsia causes hyponatremia in individuals with chronic mental illness. These patients suffer from polydipsia and polyuria in the absence of identifiable underlying medical causes. Although the underlying pathophysiology of this syndrome is unclear, several factors have been implicated to induce polydipsia and symptomatic hyponatremia. These include a possible hypothalamic defect, SIADH, and neuroleptic medication (24). In this study, 1 patient with hyponatremia was diagnosed with polydipsia; she was 68 years old without any obvious etiology for hyponatremia and her condition improved following fluid restriction.

Several mechanisms mediate volume overload and hyponatremia in hypervolemic conditions. Both hyponatremia and fluid congestion share many common pathophysiological pathways, including activation of the sympathetic nervous system, the renin–angiotensin–aldosterone system, and arginine vasopressin (25). Hypervolemic conditions were the least common causes of hyponatremia in our study. In this group, 11 patients had HF, 7 patients had CKD, 3 patients had cirrhosis, 1 patient had hypoalbuminemia, and 4 patients were considered as idiopathic hyponatremia.

There was a significant correlation between serum sodium levels and serum osmolality in this study, as expected. However, the correlation of serum sodium with serum potassium and BUN was weak. There were no correlations between serum sodium levels and other variables in our study.

Our study is the first study in which the major diagnosis of hyponatremia at admission was investigated in elderly patients. The hospital mortality rate of hyponatremic geriatric patients in this study was found 5.8% (8/138) in this study. None of these patients had SIADH; 4 patients were hypervolemic and 4 were hypovolemic. Studik et al. showed that mortality rate of hyponatremic patients was significantly higher than that of non-hyponatremic patients (22% and 7%, respectively; \( P < 0.0001 \)) (9). Age, failure to correct hyponatremia, dilution, and reduced oral intake were predictors of increased hyponatremia-associated mortality in that study, and the severity of hyponatremia was not found to be a contributor to mortality (9). Because of the small number of mortalities in our study, there were no significant differences in the clinical and laboratory parameters between the deceased patients and survivors; however, we propose that the main factor affecting hyponatremia-related mortality in geriatric patients was underlying comorbidities.

In conclusion of this retrospective study, the prevalence rates of all-cause and pure hyponatremia at admission were 11.1% and 1.8%, respectively. The most relevant risk factor for hyponatremia was medications, through related side effects or via SIADH. Thus, clinicians must be particularly careful when prescribing diuretics and neurological drugs to geriatric patients. Studies investigating hyponatremia-related
mortality report conflicting results for numerous reasons. In this study, hyponatremia-related mortality was very low, raising the possibility that hyponatremia may not be a significant independent risk factor for mortality in geriatric patients, contrary to previous studies. Besides many conditions leading or facilitating hyponatremia in geriatrics, disturbed water regulatory mechanisms as a result of aging may be a benign predisposing factor of hyponatremia. In the light of above-mentioned findings and all other studies, perhaps hyponatremia can be a natural concomitant of aging in the near future. Thus, well organized, exhaustive, case-controlled trials with large number of patients are needed to address this issue.

REFERENCES