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Community-acquired hypernatremia in elderly and very elderly patients admitted to the hospital: Clinical characteristics and outcomes

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
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Summary

Background: The clinical features, outcome and cost burden of community-acquired hypernatremia (CAH) in elderly and very elderly patients are not well known. Our aim was to investigate the etiologies, reasons for admission, clinical courses, outcomes, complications, and cost assessments of the elderly patients with CAH.

Material/Methods: We conducted a retrospective study in our tertiary hospital. Elderly and very elderly patients evaluated in the emergency department (ED) from January 1, 2010 to December 31, 2010 (n=4960) were included. Totally, 102 patients older than 65 years and diagnosed with CAH were evaluated. The patients were divided into 2 main groups according to their age: elderly (65-74 years old) (group 1) (n=38), and very elderly (>74 years) (group 2) (n=64).

Results: Our overall observed prevalence of CAH was 2.0% (n=102, 102/4960). In particular, the prevalences of CAH in group 1 and group 2 were 1.0% (38/3651) and 4.8% (64/1309), respectively ($p<0.001$). Totally, 62 patients had been treated by renin-angiotensin system (RAS) blockers (ie, ACE-inhibitors). Alzheimer's disease had been diagnosed in 46.1% of the subjects. The mean Katz scores at the time of admission were 2.4±1.9 and 1.1±1.0 in group 1 and 2, respectively ($p<0.001$). The mean cost was higher in group 2 than in group 1 (2407.13±734.54 USD, and 2141.12±1387.14 USD, respectively) ($p<0.01$). The need for intensive care was significantly greater in group 2 as compared to group 1.

Conclusions: The important determinants of "CAH" in elderly subjects are accompanying Alzheimer's disease, oral intake impairment, and concomitant treatment with RAS blockers.

key words: elderly • community-acquired hypernatremia • morbidity • mortality • cost

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Background

Thirst is the ultimate defense against development of hypernatremia. Elderly people typically have decreased thirst, thus resulting in reduced water intake. The ability to concentrate urine also diminishes with advancing age. Numerous factors, including female sex, infections, hypertonic infusions, tube feedings, osmotic diuretics, laxatives, and mechanical ventilation, increase the susceptibility of elderly persons to hospital-acquired hypernatremia [1].

Hypernatremia is present in about 1% of hospitalized patients over 60 years of age [2–4]. On the other hand, the mortality rate, which is above 40% for hypernatremia, makes it a more important issue [5]. More than two fold of increase in the mortality in elderly patients with hospital-acquired hypernatremia has been detected as compared to non-elderly subjects [6]. However, data about the costs, clinical results, related factors and prevalence of community-acquired hypernatremia (CAH) are incomplete.

In Turkey, 7.2% of the total population is composed of people above 65 years of age (*http://www.tuik.gov.tr/PreHaberBultenleri.do?id=8428*), and by 2050 this age group is expected to increase by 730% (*http://www.tuik.gov.tr/PreHaberBultenleri.do?id=8428*). In this sense, the problems specific to elderly people, along with their management, should be well defined. The aim of this study was to explore the clinical features, results and cost of CAH in elderly subjects.

Material and Methods

We conducted a retrospective study in our tertiary hospital. Elderly and very elderly patients evaluated in the emergency department (ED) from January 1, 2010 to December 31, 2010 (n=4960) were recruited. Subjects with plasma Na^+ >145 mEq/L were accepted as hypernatremic. Serum Na^+ level between 145–160 mEq/L was defined as mild hypernatremia, and serum Na^+ level >160 mEq/L was defined as severe hypernatremia. The study included 102 patients older than 65, diagnosed with CAH. The records of each hypernatremic patient were reviewed.

We recorded blood pressure, volume status, mental and motor status, fluid prescription, and laboratory findings daily. The therapy and management of each patient had been determined by the patient's primary physician. In patients identified as hypernatremic, the onset, duration, and resolution of hypernatremia were determined on the basis of an upper limit of 145 mmol/L. Clinical characteristics, outcomes, accompanying problems, complications and cost assessments of each patient were obtained. The medical records of all patients were evaluated by one reviewer (KT).

The mean life expectancy in Turkey is 74 years. The patients were divided into 2 groups according to age. Group 1 was composed of "elderly" people aged 65 to 74 (n=38), and group 2 had "very elderly" subjects above age 74 (n=64). The study subjects had not been admitted by another hospital in the 2 weeks before admission at our center.

Demographic data

The volume and composition of intravenous fluids, nutrition, and oral water intake during hospitalization were recorded. Daily urine volume, based on the intake and output record, was recorded for each hypernatremic patient.

Neurologic examination had been performed in all subjects on admission. Motor examination had been performed by a neurologist via physical examination. Katz index, which identifies the patient's independency status in his/her daily activities, had been determined by a neurologist. In this sense, doing some activities themselves (eg, showering, dressing, fulfilling toilet needs, the ability of movement, and feeding were assessed. Scores above 6 were identified as "fully independent", 4 to 6 as "independent", 2 to 4 as "mildly dependent" and below 2 as "fully dependent" [7].

Mental status of the subjects had been assessed by a neurologist using Folstein's MMSE scoring system. MMSE score above 23 was defined as normal, 19 to 23 as borderline, and below 19 as impairment in the mental status [8].

Cranial nerves and cardiopulmonary functions were recorded in all subjects at the time of admission. Hypernatremia etiologies, features related with treatment course (eg, type of fluid used, and Na^+ level correction time), drugs which were discontinued, neurological findings and complications, clinical outcome, causes of death, costs, and factors related to these parameters were explored. The causal relation of hypernatremia with morbidity and mortality was determined during data analysis by the consensus of all investigators.

Laboratory tests

Values for serum sodium, potassium, chloride, total carbon dioxide, glucose, blood urea nitrogen, creatinine, calcium, and plasma osmolality were recorded daily by the patient's managing physician**.**

Serum Na^+, plasma glucose, serum blood urea nitrogen (BUN) and creatinine levels were measured using an Olympus AU 640 Chemistry Immunoanalyzer (Tokyo, Japan). Serum potassium, magnesium, chloride, calcium, phosphate, serum albumin and TSH (thyroid stimulating hormone) levels, as well as urine density and CRP levels, were measured by use of a Cobas Integra 800 Chemistry Analyzer (Basel, Switzerland). GFR (eGFR) was calculated with the "Modification of Diet in Renal Disease" MDRD formula, which can be shown as MDRD: eGFR = 170 × [Scr] – 0.999 × [age] – 0.176 × (0.762 if the subject is female) × (1.180 if the patient is black) × [BUN] – 0.170]. BUN/creatinine ratio was measured on admission for each subject. Cerebral computerized tomography and magnetic resonance imaging were performed if indicated.

Statistics

The Shapiro-Wilk test was used to test the numeric data in terms of its convenience for normal distribution. While parametric tests were used for the assessment of variables showing normal distribution, non-parametric tests were used if normal distribution was not detected. For the comparison of the 2 independent categoric groups in terms of

Table 1. Comparative clinical and laboratory features of both groups.

Features	Group 1 (n=38)	Group 2 (n=64)	p
Age (Year)	69.83±3.3	81.25±5.5	<0.05
Gender (male/female)	21/17	39/25	NS
Serum Na+ level on admission (mmol/L)	158.22±7.0	157.17±7.6	NS
Fasting plasma glucose(mg/dL)	101.16±31.36	99.46±31.36	NS
Potassium (mEq/l)	4.38±0.58	4.67±0.76	NS
Urea (mg/dl)	132.08±31.39	134.12±23.61	NS
Creatinine (mg/dl)	0.56±0.20	0.65±0.02	NS
Serum albumin (gr/dl)	3.7±1.2	3.3±1.4	<0.05
GFR(ml/minute)	76.3±8.1	72.1±7.3	<0.05
Systolic blood pressure(mmHg)	101.20±11.21	102.34±13.8	NS
Diastolic blood pressure (mmHg)	68.15±5.92	66.81±4.76	NS
Serum osmolality (mosm/kg-H_2O)	337.47±18.26	335.23±17.65	NS
Triglyceride (mg/dl)	127.89±60.72	131.23±43.87	NS
Total Cholesterol (mg/dl)	172.38±34.32	176.60±48.54	NS
Mechanical ventilator need (%)	25	75	<0.001
Intensive care need (%)	33	67	<0.001
Mean intensive care duration (days)	8.02±12	12.13±1.53	<0.001
Duration of hospitalization (days)	12.11±7.2	15.50±7.1	<0.05
Mortality (%) (n)	47.3 (18)	64.0 (41)	<0.001
Katz score*	2.4±1.9	1.1±1.0	<0.001
MMSE score*	21.1±8.1	12.5±7.5	<0.001

NS – not significant; * at the time of admission.

numeric variables, either Student's t test or Mann-Whitney U tests were used according to the distribution of the data. For the comparison of categoric variables where more than 2 independent groups were involved, one-way ANOVA test was used. Tukey HSD test was used to determine the pairwise differences between the subgroups when the omnibus test ANOVA showed significant statistical values. Pearson chi-square test was applied according to the assumptions gathered from the comparisons of 2 categoric variables. For testing a possible linear association between 2 numeric variables, Spearman-Rho test was used. We calculated 6-month mean medical costs, and used analysis of variance (ANOVA) to test for group differences. Generalized linear models were used to calculate unadjusted and adjusted effects of hypernatremia on 6-month costs. Type one error was determined to be 0.05. SPSS 16 and MedCalc 11.5 statistics programs were used.

Results

The mean age was 76.9±7.3 years (ranging from 65 to 97). Descriptive statistics of both groups are shown in Table 1. Total CO_2 levels, urine volume on admission, and serum osmolarity were not different in both groups (p>0.05). Overall observed prevalence of CAH was 2.0% (n=102, 102/4960). The prevalence of CAH in group 1 was 1.0% (38/3651) and group 2 was 4.8% (64/1309) (p<0.001).

Presentation reasons

The most common reasons of admission were oral intake impairment 76.4% (n=78), nausea and vomiting 13.7% (n=14), and diarrhea 9.8% (n=10). Oral intake impairment as the reason of application was statistically significantly higher as compared to other reasons (p<0.05). Between 2 groups, no difference was detected in terms of the admission reasons (p>0.005)

Co-morbidities

The most common co-morbidities for both groups are shown in Table 2, with Alzheimer's disease statistically significantly higher than the others (p<0.05). When groups 1 and 2 were compared, results were similar (p>0.05), showing 80.4% (n=82) of the subjects were hypotensive, 3.9% (n=4) were normotensive, and 15.7% (n=16) were hypertensive.

Table 2. The most seen accompanying disorders in patients with hypernatremia.

Co-morbidities	n (%)
Alzheimer disease	47 (31.4)
Alzheimer disease + Hypertension	15 (14.7)
Diabetes mellitus + Hypertension	12 (11.8)
Cerebrovascular event	9 (8.8)
Heart failure	9 (8.8)

Table 3. Most common clinical causes of community-acquired hypernatremia.

Accompanying disease	n (%)
Oral intake impairment+ ACE-inhibitor use	47 (31.4)
Oral intake impairment + ARB use	15 (14.7)
Vomiting	12 (11.8)

ACE – angiotensin converting enzyme; ARB – angiotensin II receptor blocker.

Factors responsible for CAH

The common clinical factors responsible for CAH are shown in Table 3. Totally, 62 patients were on RAS blocker medications. Mean duration of RAS blocker treatment in groups 1 patients was 91.0±25.2/d and in group 2 patients was 88.1±15.1/d before developing hypernatremia ($p>0.05$). Interestingly, oral intake impairment along with the consumption of RAS blockers (angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers) seemed to be significantly higher as compared to other reasons ($p<0.05$). When groups 1 and 2 were compared with each other, the possible causes of CAH were found in similar ratios and no statistical difference was detected ($p>0.05$).

Scores

The Katz scores at the time of application in groups 1 and 2 were 2.4±1.9 and 1.1±1.0, respectively ($p<0.001$). Mean MMSE score in group 1 was 21.1±8.1 and 12.5±7.5 in group 2 ($p<0.001$)

There was a negative correlation between scores (Katz and MMSE scores) and duration of hospitalization ($p<0.05$; for Katz and MMSE scores, $r=-0.39$ and -0.41, respectively) as well as with costs ($p<0.05$, for Katz and MMSE scores $r=-0.33$ and -0.37, respectively.) On the other hand, no relationship was detected between the scores and other parameters such as intensive care and mechanic ventilation needs, complications and mortality rates.

General complications

In 36.3% (n=37) of subjects there were no complications. The most common complications of the hypernatremic subjects were community-acquired pneumonia (n=4), community-acquired uncomplicated urinary tract infection (n=4), nosocomial pneumonia (n=14), nosocomial urinary tract infection (n=12), gastrointestinal hemorrhage (n=5), acute coronary syndrome (n=5), hyponatremia (n=5), and stroke (n=4). There was no significant statistical difference between the groups in terms of the complication types and prevalence ratios ($p>0.05$). No sex difference was found for complication type and prevalence.

Intensive care and/or mechanical ventilation need

There were significantly more subjects needing intensive care (n=67) than subjects not needing intensive care (n=35) ($p<0.05$). All of the subjects requiring intensive care needed mechanical ventilation. Mortality was 75% (n=50) among those needing intensive care and 25% (n=9) of the remaining ones died ($p<0.05$). The ex ratio of the patients with mechanical ventilator need was 83% (n=55) and 23% (n=8) for the subjects not requiring intensive care. The healing ratio of the subjects not showing mechanical ventilator need was higher ($p<0.001$). When groups 1 and 2 were compared with each other, intensive care and/or mechanical ventilator needs and complication ratios were similar and there was no statistical difference.

Treatment

Serum Na^+ level correction speed and relation with clinical complications independent of age were evaluated and following results were gathered: In patients where Na^+ levels were normalized within 0 to 24, 24 to 48, 48 to 72 and more than 72 hours, 55.2% (n=16), 47.7% (n=21), 33.3% (n=6), and 45.5% (n=5) respectively, did not show any complications. However, encephalopathy ratios were 8.8%, 6.9%, 7.2%, and 45.5%, respectively, for the same correction durations. However, number of patients was insufficient for statistical analysis. In patients with normalization durations of Na^+ within 24 to 48 and 48 to 72 hours, fewer complications were observed. Similar ratios and results were gathered in group 1 and 2 ($p>0.05$).

Length of hospital stay

While mean length of hospital stay of all patients cured from hypernatremia was 10.8±4.9 days, mean length of hospital stay of subjects who died either from hypernatremia or other reasons was found to be 15.1±10.2, which is statistically significant ($p<0.05$).

When the serum Na^+ level at the time of admission was compared with length of hospital stay, we found that as the Na^+ level increased, the length of hospital stay increased as well, but this was not statistically significant ($r=0.177$, $p=0.102$). In addition, there was a negative correlation between the hospital stay and the scores of both Katz and MMSE ($r=-0.39$, $p<0.05$, and $r=-0.41$, $p<0.05$).

Clinical outcome and mortality

Mortality occurred in 30.5% (n=18) of group 1 and 69.5% (n=41) of group 2, an overall of 57.8% (n=59) of the subjects died ($p<0.005$). Mild hypernatremia (145–160 mEq/L) was detected in 31 (81.5%) subjects in group 1 and 41

(64%) subjects in group 2 ($p<0.05$). Severe hypernatremia was detected in 7 (18.5%) and 23 (36%) patients in group 1 and group 2, respectively ($p<0.001$). The mortality ratios in group 1 for the patients with mild and severe hypernatremia were 41.9% (n=13) and 71.4% (n=5), respectively; whereas they were 56.1% (n=23) and 78.2% (n=18), respectively, in group 2.

In group 1, 6 patients (6%) were hypernatremic at time of death, compared to 21 patients (35.5%) in group 2 ($p<0.001$). There were some contributing factors to mortality, including: multiorgan failure syndrome in 11 patients, ventilator-associated pneumonia in 11 patients, sudden cardiac death in 4 patients, urosepsis and septic shock in 4 patients, non-sustained ventricular tachycardia in 3 patients, sustained increases in ventricular rate in atrial fibrillation in 2 patients, severe upper gastrointestinal hemorrhage in 2 patients, sustained delirium in 2 patients, and acute myocardial infarction in 1 patient. Most of the deaths cannot be directly attributed to the hypernatremia itself. Based on careful review of the medical records, we believe that hypernatremia partially contributed to mortality in only 19 patients (32.2%).

The mortality rates for the patients whose Na^+ levels were corrected within 0 to 24, 24 to 48, 48 to 72, and more than 72 hours were found to be 55.2%, 33.3%, 45.5%, and 47.7%, respectively. The mortality rates were higher in patients in which Na^+ levels were normalized within 24 and more than 72 hours, as compared to other treatment durations ($p<0.05$), for both groups.

Forty-three patients recovered from CAH; 6 of them had speech defect, and 2 had hemiparesis due to stroke.

Cost analysis

We used generalized linear models to calculate unadjusted and adjusted effects of hypernatremia on 6-month costs. The mean cost of a hypernatremic subject was 2251.6±1085.5 United States Dollars (USD). Mean costs for group 1 and group 2 were 2141.1±1387.1 and 2407.1±734.5, respectively ($p<0.05$). Although it seemed that there was a positive correlation between the baseline levels of Na^+ and costs, it had no statistical meaning ($r=0.099$, $p=0.320$). We found that hypernatremia was an independent predictor for 6-month cost regardless of age, sex, and co-morbid conditions.

Discussion

Although there is abundant data on hospital-acquired hypernatremia (in pediatric and adult subjects during their hospital stay), the clinical characteristics, outcomes and economic burdens of CAH are not well known [9]. On the other hand, only a few studies are available regarding the causes, accompanying clinical problems, need for intensive care, duration of normalization of Na^+ level, costs and clinical results of hypernatremia in elderly (>65y) and very elderly (>74y) subjects. With this retrospective demographic study, we have shown that the most common cause of CAH in patients above age 65 is dehydration due to reduced oral intake and concomitant treatment with RAS blockers. We found that the subjects very often developed respiratory problems requiring ventilation, with high mortality rates. The very elderly group needed more care and assistance at the time of admission as compared to the elderly group. The mental and motor status was worse and the mortality rate was higher, as well. Alzheimer's was the most common accompanying disease for both groups.

Age-related declines in organ function and appetite, illness and disability, and increased fluid requirements predispose older adults to dehydration and hypertonicity. In a cohort study, Thunhorst et al found that compared to young rats, old rats drink less water in response to several thirst-inducing stimuli [10]. In addition, they showed that the amount of liquid taken in the old group was less than in the young group. Both middle-aged and old rats were less able than young rats to repair their water deficits after sodium loading, attributable almost entirely to their reduced drinking responses compared with young rats [10]. Another mechanism that leads to hypernatremia is that although the anti-diuretic hormone level is increased, urine concentrating ability in the elderly is impaired [11]. On the other hand, Latcha et al found that hypoangiotensinemia impairs the secretion of arginine vasopressin, which increases the predisposition to hypernatremia [12]. The seriousness of Alzheimer's disease accompanying hypernatremia may be another factor that hinders patients from drinking sufficiently and regularly. Furthermore, antihypertensive agents that blockade the RAS cause hypoangiotensinemia and therefore participate in this process.

Kettritz et al. reported that the mortality rate is increased approximately 7-fold in elderly hypernatremic subjects as compared to young people [5]. Alshayeb et al showed that when Na^+ level is increased to a value more than 160 mEq/L, the mortality rate increases to 75% [13]; their study included 131 elderly hypernatremic subjects with mean Na^+ level of 159±3mEq/L and mean age of 82.2. Warren et al, in a multicentric study, found 6-fold more hypernatremia in patients aged 85 to 99, as compared to subjects ages 65 to 70 [14]. Our study revealed that hypernatremic patients older than 75 had significantly higher mortality rates compared to subjects ages 65 to 75. Daggett et al., in their retrospective study in which patients with serum sodium level >155 nmol/l were assessed as severe hypernatremic, reported that mortality rates increase parallel to the increase in serum Na^+ levels [15]. In our study, on the other hand, for both groups we found that the mortality rates were higher in patients with severe hypernatremia as compared to patients with mild hypernatremia.

The factors determining the course of treatment are the rapidity of development and the severity of hypernatremia, along with being symptomatic or not. The target in acute symptomatic hypernatremia is to reduce the serum Na^+ level 1.0 mEq/L/hour. Horn et al. reported that normalization of Na^+ level in hypernatremic subjects should be done as soon as possible if any of complications have occurred [16]. However, they suggested that in the opposite situation this correction would be better if done slowly [16]. While some authors indicate that patients recover best from encephalopathy if normalization of Na^+ level is done within 72 hours [17], others say that mental functions can be permanently impaired if normalization takes more than 96 hours [12,18]. Samuels et al., on the other hand, reported that permanent mental impairment and death could

occur if the normalization is achieved before day 1 [19]. In this sense they have suggested that achieving normalization within 3 to 4 days would decrease the mortality rates to the minimum level. In our study, mental problems and increased mortality rates were most commonly seen when serum Na^+ level normalized within the first 24 hours or after 72 hours. Our study's results in terms of treatment durations were similar to the results of some other studies regarding the normalization speed in hypernatremic subjects.

A variety of authors have reported possible risk factors for the development of hypernatremia, such as being older than 65, being female, having mental status impairment, infections, and some medical treatments, especially in subjects needing care [20]. In our study, hypernatremia was detected more in men than women. Darmon et al. recruited 1245 patients, detecting hypernatremia in 228 subjects, and finding bacterial infections to be the most common cause of hypernatremia in patients with mean age above 65 years [21]. In our study the most common etiological factors for hypernatremia were oral intake impairment and use of RAS blockers. Angiotensin II is the direct stimulator of thirstiness [22]. Treatment with RAS blockers in elderly subjects increases the deterioration of the sensation of thirstiness, which is in fact already being damaged. Moreover, RAS blockers decrease the reabsorption of water from the tubules [23]. Our study shows that the treatment of RAS blockers facilitates the development of hypernatremia in elderly people.

Warren et al. found in their multicentric study that hypernatremic elder subjects had a very heavy cost burden. They stated that 6.7% of the 10 million hospitalized elderly subjects were hospitalized due to hypernatremia caused by dehydration. In addition they found that each patient had a mean cost of 2.942 USD/year, leading to a yearly total cost of $446 million USD [14]. In our study, we found that a patient who is hospitalized due to CAH incurs a mean cost of $2251.2±1085.0 USD. Detailed examination reveals that for the elderly and very elderly groups the costs were 2141.7±1387.2 and 2407.1±734.5 USD, respectively. This seems to be clear evidence that the costs increase as the ages of the subjects increase, and this might be associated with the increase in the co-morbidities as the patients aged.

Conclusions

The main features of elderly and very elderly patients with CAH are that Alzheimer's is the most common accompanying disease. Moreover, they have impaired and inadequate oral intake, are very often treated with RAS blockers, and most are hypotensive at time of admission. Another important feature is that the very elderly subjects with CAH have greater needs for intensive care and mechanical ventilation. Clinically, an important question is how these results could aid in preventing and treating hypernatremia in the elderly and very elderly. In our opinion, prevention of hypernatremia requires close monitoring of daily hydration with convenient salines, and careful prescription of medications such as RAS blockers.

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