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Additional risk factors associated with symptomatic hydrochlorothiazide-induced hyponatremia in hypertensive patients

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Abstract

Background. Hydrochlorothiazide is a cheap and effective antihypertensive agent but may cause hyponatremia. Even though several risk factors for hydrochlorothiazide-induced hyponatremia have been reported, this study aimed to evaluate additional risk factors for hydrochlorothiazide-induced hyponatremia in hypertensive patients.

Materials and methods. The inclusion criteria were: adult patients, diagnosed with hypertension and receiving hydrochlorothiazide treatment. Eligible patients were divided into two groups: with and without hyponatremia. Those with hyponatremia were identified by using the ICD-10 code E871, while those without hyponatremia were patients who did not have any reported hyponatremia until the last visit. The ratio between hyponatremia and non-hyponatremia group was 1:2. Predictors for hyponatremia were analyzed by using logistic regression analysis.

Results. During the study period, there were 68 patients admitted due to symptomatic hyponatremia from hydrochlorothiazide. There were four independent factors in the model predictive of occurrence of symptomatic hydrochlorothiazide-induced hyponatremia in hypertensive patients: sex, body mass index, plasma glucose, and serum albumin. Male sex, body mass index, and serum albumin were negatively associated with occurrence of symptomatic hydrochlorothiazide-induced hyponatremia in hypertensive patients with adjusted OR of 0.099, 0.683, and 0.122, respectively. The plasma glucose had adjusted OR of 1.030 [95% CI of (1.009, 1.051)].

Conclusions. Factors associated with hydrochlorothiazide-induced symptomatic hyponatremia in hypertensive patients were sex, body mass index, plasma glucose level, and serum albumin level. The latter two risk factors have never been reported as risk factors for hydrochlorothiazide-induced symptomatic hyponatremia in hypertensive patients.

Key words: predictors; prevalence; plasma glucose; albumin

Introduction

Hypertension is a common disease in clinical practice. It was estimated that there were one billion hypertensive patients worldwide. Good control of blood pressure is important and can

lower cardiovascular morbidities or mortalities particularly stroke or heart failure [1]. The Eighth Joint National Committee (JNC 8) recommends using thiazide as the first-line treatment for hypertension [2]. A post hoc analysis of ALLHAT study found that chlorthalidone was superior to doxazosin in terms of heart failure and stroke prevention with relative risk of 1.80 and 1.26, respectively [3].

The advantage of thiazide is it's low cost but it may cause several side effects such as hyponatremia, or hypokalemia. These side effects may result in severe morbidities such as hospitalization to correct hyponatremia or osmotic demyelination syndrome from hyponatremia treatment. Several studies were conducted to evaluate risk factors of thiazide-induced hyponatremia in patients with hypertension [4–7]. At least three out of 10 hypertensive patients taking thiazide may develop hyponatremia in their lifetimes [4]. Risk factors for thiazide-induced hyponatremia included age, female sex, body mass index, and KCNJ1 rs2509585C/T or T/T polymorphisms with adjusted odds ratio (OR) of 1.13, 4.49, 0.80, and 5.75, respectively [6]. Even though several risk factors for hydrochlorothiazide-induced hyponatremia have been reported such as obesity or advanced age, this study aimed to evaluate additional risk factors for hydrochlorothiazide-induced hyponatremia in hypertensive patients.

Materials and methods

This study was a retrospective analytical study. It was conducted at University Hospital. The inclusion criteria were: adult patients, diagnosed with hypertension and receiving hydrochlorothiazide treatment. The study period was between 2005 and 2014. Eligible patients were all adult hypertensive patients treated at the University Hospital and were divided into two groups: with and without symptomatic hyponatremia.

Symptomatic hyponatremia was diagnosed in patients who had serum sodium less than 135 mEq/L, had at least one symptom caused by hyponatremia, and required admission. Those patients with symptomatic hyponatremia were identified by using the ICD-10 code; E871 in summary discharge form of admitted patients, while those without hyponatremia were patients who did not have any reported hyponatremia until the last visit in December 2014. The ratio

between hyponatremia and non-hyponatremia group was 1:2. The non-hyponatremia group was randomly selected from the patient list by simple random sampling method.

Clinical data of all patients were reviewed from medical records. Baseline and clinical characteristics of those with and without symptomatic hyponatremia were compared using descriptive statistics. When appropriate, a Wilcoxon rank sum/Student's t-test and Fisher's exact tests/chi-square test were applied to compare the differences between the two groups in terms of numbers and proportions, respectively. Univariate logistic regression analysis was applied to calculate the crude odds ratio (OR) of individual variables for occurrence of symptomatic hyponatremia. All clinically significant variables were included in subsequent multivariate logistic regression analysis. Analytical results were presented as crude OR, adjusted OR, and 95% confidence intervals. The goodness of fit of the multivariate logistic regression model was tested using the Hosmer–Lemeshow method. All data analysis was performed using STATA software (StataCorp LP, College Station, TX, USA).

Results

During the study period, there were 68 patients admitted due to symptomatic hydrochlorothiazide-induced hyponatremia. The two most common presenting symptoms were fatigue (44 patients, 65.67%) and nausea/vomiting (39 patients, 59.09%). The other presenting symptoms were drowsiness (15 patients, 22.39%), hiccup (8 patients, 119.4%), headache (8 patients, 119.4%), confusion (6 patients, 8.96%), seizure (3 patients, 4.48%), and muscle cramp (2 patients, 2.99%). The median serum sodium was 117 mEq/L. The median hospital stay was 3 days (range 2–5 days). After admission, 32 patients (47.06%) did not received hydrochlorothiazide permanently without adding any other antihypertensive drug, while 19 patients (27.94%) switched to other antihypertensive drugs, 14 patients (20.59%) temporarily stopped taking hydrochlorothiazide, 2 patients (2.94%) still received hydrochlorothiazide with the same doses, and 1 patient received lower dose of hydrochlorothiazide.

Table 1 showed clinical factors of hypertensive patients treated with hydrochlorothiazide categorized by presence of symptomatic hyponatremia. There were six factors significantly different between those with and without hyponatremia including age, sex, body mass index,

duration of hydrochlorothiazide therapy, history of diabetes mellitus, and history of coronary artery disease. Those with hyponatremia had older age (73 *vs.* 64 years), lower percentage of male (23.53% *vs.* 37.41%), and lower body mass index (22.43 *vs.* 25.32 kg/m^2), and shorter duration of hydrochlorothiazide use (12 *vs.* 36 months) than those without hyponatremia (Tab. 1).

Regarding laboratory results, hypertensive patients treated with hydrochlorothiazide with hyponatremia had 15 different laboratory values from those without hyponatremia (Tab. 2). For example, those with hyponatremia had higher plasma glucose (132 *vs.* 106 mg/dL), lower eGFR (47.81 *vs.* 70.06 mL/min/1.732), and lower serum albumin level (3.9 *vs.* 4.2 g/dL) than those without hyponatremia.

There were four independent factors in the model predictive of occurrence of symptomatic hydrochlorothiazide-induced hyponatremia in hypertensive patients. These factors were sex, body mass index, plasma glucose, and serum albumin (Tab. 3). Male sex, body mass index, and serum albumin were negatively associated with occurrence of symptomatic hydrochlorothiazide-induced hyponatremia in hypertensive patients with adjusted OR of 0.099, 0.683, and 0.122, respectively. The plasma glucose had adjusted OR of 1.030 (95% CI of (1.009, 1.051). The Hosmer-Lemeshow Chi square of the final model was 5.70 (p value 0.681).

Discussion

Among the four independent predictors for hydrochlorothiazide-induced symptomatic hyponatremia, two of them were similar to other previous reports including female sex [8, 9] and lower body mass index [5, 7, 9, 10]. Small size patients may have tremendous change in serum sodium due to less total body water [11]. The mechanism of association between female sex and diuretic-induced hyponatremia is not well understood [9].

A nested case-control study [12] found that thiazide may increase risk of new-onset diabetes by 1.54 times (95% CI of 1.41, 1.68). However, there is no previous study showing the association of having high plasma glucose as a risk factor for hydrochlorothiazide-induced symptomatic hyponatremia. Similarly, there is no previous report on albumin level on hydrochlorothiazide-induced symptomatic hyponatremia in literatures. Increasing of serum

albumin by 1 gm/dL lower risk of hydrochlorothiazide-induced symptomatic hyponatremia by 88% (Table 3). We postulate that lower albumin level may be associated with poor nutritional status and low intravascular volume causing hypervolemic hyponatremia.

Age is another risk factor for hydrochlorothiazide-induced symptomatic hyponatremia previously reported [9–11]. In this present study, age is not an independent factor for hydrochlorothiazide-induced symptomatic hyponatremia by multivariate logistic regression which controls for confounding factors. The median age of study population with hyponatremia in this study was 73 years which may similar to a previous study conducted in the elderly hypertensive patients [13]. The average age of participants in the previous study from the US was 74 years [13]. The adjusted OR (95% CI) of thiazide-induced symptomatic hyponatremia was 1.47 (0.98, 2.19) which was comparable with the present study.

There are some limitations in this study. First, the study population in this study included only hypertensive patients with symptomatic hydrochlorothiazide-induced hyponatremia. Those with mild hyponatremia who did not required hospitalization were not included. The genetic factor previously reported to be associated with thiazide-induced hyponatremia, KCNJ1 rs2509585C/T or T/T polymorphisms, were not studied. Finally, due to retrospective study design, some factors were missing such as history and quantity of alcohol or smoking.

Conclusions

Factors associated with hydrochlorothiazide-induced symptomatic hyponatremia in hypertensive patients were sex, body mass index, plasma glucose level, and serum albumin level. The latter two risk factors have never been reported as risk factors for hydrochlorothiazide-induced symptomatic hyponatremia in hypertensive patients.

Compliance with ethical standards and funding

The authors declare no conflict of interests and did not receive any funding for this project.

Conflict of interests

None to be declared by authors.

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Author contributions

As in the author statement.

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Table 1. Clinical features of hypertensive patients treated with hydrochlorothiazide categorized by presence of symptomatic hyponatremia (hypoNa)

Factors	**No hypoNa (n = 139)**	**HypoNa (n = 68)**	**p value**
Basic characteristics			
Age (years)	64 (55-69)	73 (65-79)	< 0.001
Male sex	52 (37.41)	16 (23.53)	0.046
BMI [kg/mm^2]	25.32 (23.32-28.13)	22.43 (21.08–25.51)	< 0.001
Alcohol drinking	12 (22.22)	6 (17.65)	0.787
Current smoker	14 (25.45)	8 (22.22)	0.725
Co-antihypertensive drugs			
None	23 (17.29)	18 (26.47)	0.127
Calcium channel blocker	60 (45.11)	22 (32.84)	0.096

Beta-blocker	33 (24.81)	20 (29.85)	0.446
Alpha-blocker	5 (3.79)	4 (5.97)	0.488
ACEI	41 (30.83)	22 (32.84)	0.773
ARB	24 (18.05)	7 (10.45)	0.161
Vasodilator	3 (2.26)	5 (7.46)	0.121
Duration of hydrochlorothiazide use	36 (13-67)	12 (3-52)	< 0.001
Doses of hydrochlorothiazide [mg]			0.550
12.5	22 (15.83)	7 (10.77)	
25	104 (74.82)	53 (81.54)	
50	13 (9.35)	5 (7.69)	
Co-morbid diseases			
Diabetes mellitus	55 (39.57)	38 (55.88)	0.027
Dyslipidemia	54 (38.85)	18 (26.47)	0.079
Stroke	12 (8.63)	6 (8.82)	0.964
Coronary artery disease	8 (5.76)	10 (14.71)	0.032
Cirrhosis	3 (2.16)	4 (5.88)	0.221
COPD	1 (0.72)	3 (4.41)	0.105
Asthma	9 (6.47)	2 (2.94)	0.346
Gout	7 (5.04)	7 (10.29)	0.157
OSA	4 (2.88)	2 (2.94)	0.999

BPH	4 (2.88)	3 (4.41)	0.686
VHD	4 (2.88)	4 (5.88)	0.443
Old tuberculosis	4 (2.88)	2 (2.94)	0.999
Cancer	13 (9.35)	3 (4.41)	0.274

Note: Data presented as numbers (percentage) or median (1^{st} to 3^{rd} quartile range); BMI — body mass index; ACEI — angiotensin-converting enzyme innhinitor; ARB — angiotensin II receptor blocker; COPD — chronic obstructive pulmonary disease; OSA — obstructive sleep apnea; VHD —valvular heart disease

Table 2. Laboratory results of hypertensive patients treated with hydrochlorothiazide categorized by presence of symptomatic hyponatremia (hypoNa)

Factors	**No hypoNa (n = 139)**	**HypoNa (n = 68)**	**p value**
Hematocrit (%)	37.6 (33.8–41.0)	32.2 (28.6–37.3)	< 0.001
White blood cells [x $10^3/mm^3$]	7800 (6500–9270)	7150 (6150–8700)	0.109
Platelet [x $10^6/mm^3$]	261 (226–314)	280 (216–336)	0.524
Glucose [mg/dL]	106 (93–130)	132 (109–180)	< 0.001
BUN [mg/dL]	13.85 (10.00–18.45)	15.90 (11.10–23.80)	0.025
Cr [mg/dL]	0.9 (.07–1.1)	1.0 (0.8–1.3)	0.112
eGFR [mL/min/1.73^2]	70.06 (53.74–92.87)	47.81 (31.68–69.33)	< 0.001
Uric acid [mg/dL]	6.0 (4.9–7.1)	4.5 (3.7–5.6)	< 0.001
Sodium [mEq/L]	140 (137–141)	117 (114–121)	< 0.001

Potassium [mEq/L]	4.0 (3.7–4.4)	3.8 (3.2–4.3)	0.001
HCO_3 [mEq/L]	25.2 (23.2–27.1)	24.5 (22.4–26.3)	0.158
Chloride [mEq/L]	100 (97–103)	80 (75–86)	< 0.001
Calcium [mg/dL]	9.1 (8.6–9.4)	8.8 (8.3–9.2)	0.105
Phosphate [mg/dL]	3.6 (3.1–3.9)	3.3 (2.6–3.6)	0.028
Cholesterol [md/dL]	178 (153–210)	181 (146–214)	0.559
Albumin [g/dL]	4.2 (3.7–4.4)	3.9 (3.5–4.2)	0.012
Globulin [g/dL]	3.1 (2.7–3.6)	3.2 (2.9–3.5)	0.606
Total bilirubin [mg/dL]	0.5 (0.4–0.7)	0.7 (0.4–1.2)	0.016
Direct bilirubin [mg/dL]	0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.566
ALT [U/L]	21 (15–26)	23 (17–40)	0.070
AST [U/L]	22 (18–30)	31 (24–49)	< 0.001
Alkaline phosphatase [U/L]	75 (62–94)	82 (71–100)	0.172
Magnesium [mg/dL]	2.0 (1.9–2.2)	1.8 (1.5–1.9)	< 0.001
Triglyceride [mg/dL]	133 (104–178)	110 (75–177)	0.554
HDL–C [mg/dL]	53 (43–61)	47 (41–59)	0.223
LDL–C [mg/dL]	113 (95–141)	86 (72–156)	0.207
Urine sp.gr.	1.014 (1.009–1.018)	1.010 (1.005–1.011)	< 0.001
Urine pH	6.0 (5.5–6.5)	7.0 (6.5–7.0)	< 0.001

Note: Data presented as median (1^{st} to 3^{rd} quartile range); BUN — blood urea nitrogen; Cr — creatinine; eGFR — estimated glomerular filtration rate; HCO_3 — bicarbonate; ALT — alanine aminotransferase; AST — aspartate aminotransferase; UACR — urine albumin-creatinine ratio; HDL — high density lipoprotein; LDL — low density lipoprotein

Table 3. Factors associated with symptomatic hyponatremia in hypertensive patients treated with hydrochlorothiazide (HCTZ)

Factors	**Unadjusted odds ratio (95% CI)**	**Adjusted odds ratio (95% CI)**
Age (years)	1.062 (1.031, 1.093)	1.026 (0.954, 1.105)
Male sex	0.515 (0.267, 0.993)	0.099 (0.013, 0.764)
BMI	0.834 (0.761, 0.914)	0.683 (0.542, 0.860)
Duration of HCTZ	0.986 (0.977, 0.995)	0.975 (0.951, 1.001)
Dose of HCTZ	1.162 (0.625, 2.160)	6.981 (0.876, 55.617)
Plasma glucose	1.015 (1.006, 1.024)	1.030 (1.009, 1.051)
GFR	0.978 (0.967, 0.989)	0.998 (0.970, 1.027)
Serum albumin	0.558 (0.333, 0.936)	0.122 (0.027, 0.532)

CI — confidence interval; BMI — body mass index; GFR — glomerular filtration rate