CLINICAL STUDY OF THIAZIDE DIURETIC INDUCED HYPONATREMIA

K. Siddappa[1], Peersab M. Pinjar[2], Harsha Vardhan Reddy Y. G[3]

[1]Professor, Department of General Medicine, S. S. Institute of Medical Sciences and Research Centre, Davangere.
[2]Associate Professor, Department of General Medicine, S. S. Institute of Medical Sciences and Research Centre, Davangere.
[3]Post Graduate, Department of General Medicine, S. S. Institute of Medical Sciences and Research Centre, Davangere.

ABSTRACT

AIMS AND OBJECTIVES

The importance of Thiazide-Induced Hyponatremia (TIH) is reemerging because thiazide diuretic prescription seems to be increasing after the guidelines recommending thiazides as first-line treatment of essential hypertension have been introduced. Hyponatremia is a common complication comes across with thiazide diuretics. Aim is to determine the prevalence and vulnerability of symptoms from thiazide-induced hyponatremia.

MATERIALS AND METHOD

Study included 100 patients attending outpatient department/admitted in S. S. Hospital, Davangere fulfilling the inclusion and exclusion criteria. Patients received 6.25mg to 25mg hydrochlorothiazide with or without combination of other anti-hypertensives. Patients were followed up every day with estimation of serum electrolytes after hospitalization.

RESULTS

Female patients presented with lower serum sodium levels than male counterparts (114±8 versus 117±8 mmol/L, P=0.02), although the frequency of central nervous system manifestation was comparable between both gender groups. The most frequent symptoms were malaise and lethargy (49%), followed by dizzy spells (47%) and vomiting (35%). Degree of hyponatremia depend upon presentation predicted the development of confusion and vomiting symptoms. Serum sodium concentration <115 mmol/L was significantly associated with the development of confusion (odds ratio 2.6, 95% confidence interval 1.3 to 5.1, P=0.004). Our results show that symptoms from thiazide-induced hyponatremia primarily reflect osmotic water shift into brain cells rather than extracellular fluid volume depletion.

CONCLUSION

In our study hyponatremia is common and serious side effect of thiazide diuretics. Timely detection and intervention is very essential and improves the outcomes in patients with thiazide diuretics.

KEYWORDS

Hyponatremia, Thiazide, Diuretics.

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INTRODUCTION: Thiazide diuretics include all diuretics believed to have a primary action to inhibit NaCl reabsorption in the distal convoluted tubule and have been used in the management of hypertension for over 50 years.[1] Thiazide diuretic-induced hyponatremia is a common cause of symptomatic hyponatremic disorders.[2] To establish the diagnosis of thiazide-induced hyponatremia, we need simple biochemical investigation. Nonetheless, delayed diagnosis of this disease entity commonly occurs because of overlooking the vague presentation of thiazide-induced hyponatremia. Symptomatology of this subgroup of hyponatremic disorder deserves specific consideration because:

1. Delayed recognition of this potentially preventable disease would lead to mortality and morbidity.
2. Symptom analysis aids in understanding of the pathophysiology. To evaluate the symptoms of thiazide-induced hyponatremia, we undertook a survey to determine the frequency of such symptoms and the corresponding risk factors.

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Corresponding Author:
Dr. Harsha Vardhan Reddy Y. G,
Department of General Medicine,
S. S. Institute of Medical Sciences and Research Centre,
Davangere.
E-mail: harshavardhanyadiki@gmail.com
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METHODOLOGY:

Source of Data: Study included 100 patients attending outpatient department/admitted in S. S. Hospital, Davangere with symptoms and signs hyponatremia during the study period March 2014 to March 2015.

Methods: Detailed history, physical examination and confirmation of hyponatremia by estimation of serum electrolytes, along with complete blood count, Random

blood sugar, Renal function test, fasting lipid profile, Liver function test, serum uric acid, Thyroid stimulating hormone, urine sodium, serum osmolality, urine potassium were done. Patients were followed up every day with estimation of serum electrolytes after hospitalisation.

Inclusion Criteria:

1. Hypertensive patients on thiazides diuretic treatment.
2. Age >40 years.
3. Serum sodium <130mmol/l with symptomatic hyponatremia.

Exclusion Criteria:

1. Acute Gastroenteritis.
2. Trauma.
3. SIADH.
4. Drugs like Mannitol, Steroids.
5. Hypothyroidism.
6. Cardiac Failure.
7. Cirrhosis of Liver.
8. Chronic Kidney Disease.

Statistical Analysis: Analyses were performed by with the use of Chi-squared test or, when appropriate, Fisher's exact test. Continuous variables were analyzed with the use of Student's t test; the results are expressed in mean ± standard deviation (SD) unless otherwise specified. Odds ratios and 95% confidence intervals were calculated. A P value of below 0.05 was considered significant. All probabilities were two-tailed.

RESULTS: In our study, 100 patients were diagnosed with thiazide-induced hyponatremia, 70% of the cases were females who presented with lower serum sodium levels than male counterparts (114±8 versus 117±8mmol/L, P=0.02). The mean age and body mass index of these patients were 76±9 years and 22.4±3.7 kg/m^2, respectively. Mean serum sodium concentration measured 116 mmol/L (range 98 to128 mmol/L).

There was no significant difference in demographic and clinical characteristics between the two gender groups (Table 1).

	Female Group (n=70)	Male Group (n=30)	P Value
Age (years)	77±8	76±9	0.06
Body mass index	22.4±3.9	22.6±3.0	0.69
Duration of institutionalization	5±4	3±5	0.32
Duration of thiazide diuretics use (no of days)	118(25-757)	66(9-309)	0.36

Table 1: Baseline Characteristics of Male and Female Subjects

*Plus-minus values are Mean±SD unless otherwise indicated;

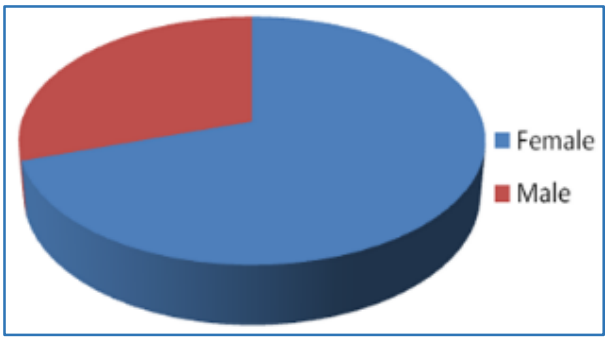

Fig. 1

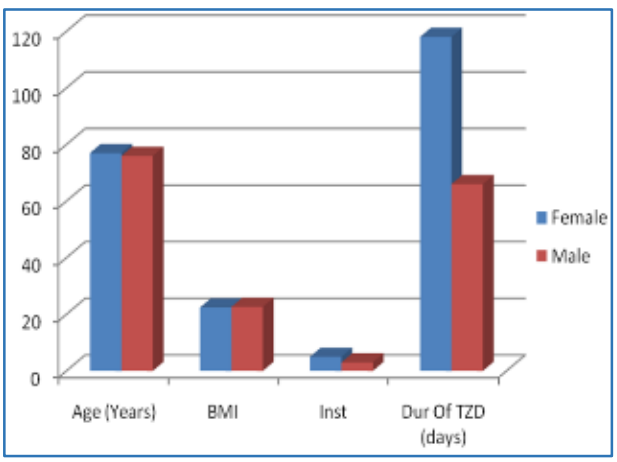

Fig. 2

SYMPTOMS AND SIGNS:

Symptoms	Number
Malaise/lethargy	49
Dizzy spells	47
Vomiting	35
Confusion/obtundation	17
Falls	17
Headache	06
Vertigo	06
Seizures	2
Non cardiogenic pulmonary oedema	0
Coma	0

Table 2: Symptoms of Thiazide-Induced Hyponatremia

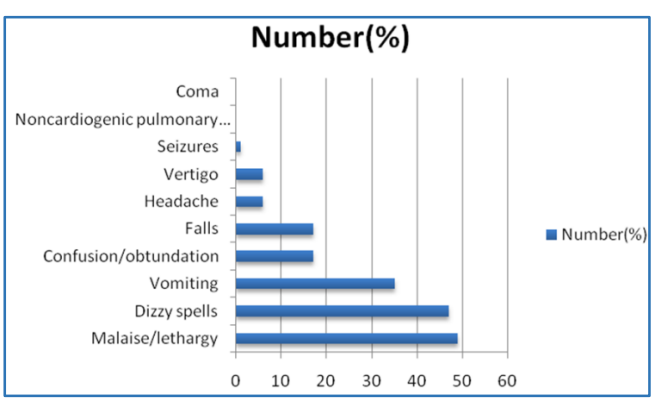

Fig. 3

The most frequent symptoms were malaise and lethargy, as encountered in almost half of the cases. Forty-seven percent of the cases in our series reported dizzy spells. Other important symptoms included vomiting (35%) and mental confusion or obtundation (17%). Seventeen percent of patients presented with falls prior to the diagnosis of thiazide-induced hyponatremia. In particular, degree of hyponatremia upon presentation predicted the development of confusion and vomiting symptoms. For instance, mean serum sodium concentration among confused patients was significantly lower than subjects without mental disturbance (111±8 versus 117±8mmol/L, P<0.001). By univariate analysis, serum sodium concentration <115 mmol/L was significantly associated with the development of confusion (odds ratio 2.6, 95% confidence interval 1.3 to 5.1, P=0.004) and vomiting (odds ratio 1.8, 95% confidence interval 1.1 to 3.1, P=0.02). Serum potassium levels and duration of thiazide diuretics, on the other hand, had no discernible correlation with these symptoms, including presence of vomiting. In terms of individual susceptibility to develop symptoms with hyponatremia, patient age did not predict the occurrence of falls with hyponatremia (P=0.73). There was comparable frequency of central nervous system manifestation in male and female patients (details not shown), despite a lower serum sodium level in the latter group as described above. Two cases developed seizures, and three required intensive care unit admission. However, none of the other cases had noncardiogenic pulmonary oedema or coma. All patients improved after discontinuation of thiazide but 14 of them had recurrence of hyponatremia after resuming thiazide diuretics. One additional patient subsequently exhibited clinical and radiologic manifestation of osmotic demyelination syndrome or central pontine myelinolysis. No mortality occurred in our cohort. Median hospitalization duration was five days.

Overall, baseline creatinine clearance, as estimated by Cockcroft-Gault equation, was 47±22ml/minute. During hyponatremic episodes, mean urinary osmolality measured 392±159mOsm/kg as compared with serum osmolality of 238±18mOsm/kg, reflecting impaired diluting ability of urine. Clinical dehydration was evident in only 24% of the cases. During the onset of thiazide-induced hyponatremia, the mean serum urea: creatinine ratio was 1:14, and serum bicarbonate level being 26+5mmol/L. Mean systolic and diastolic blood pressures were 151+25 mmHg and 77±14 mmHg, respectively. The serum uric acid level was 0.31±0.16mmol/L, and serum potassium concentration was 3.3±0.8mmol/L. Thiazide-induced hyponatremia commonly caused neurologic manifestation.

DISCUSSION: Intriguingly, thiazide-induced hyponatremia patients do not fit well into usual classifications of sodium disorder because of their ambiguous volume status. As illustrated in our case series and supported by previous observation.[3,4,5] most of them appear clinically euvolemic or even with volume expansion in spite of sodium and potassium depletion. The finding of impaired diluting ability in our series comes as no surprise, because thiazide diuretics stimulate antidiuretic hormone (ADH) release, inhibit electrolyte transport at the cortical diluting sites, and increase fractional proximal water reabsorption.[4] Nonetheless, evidence for positive water balance in thiazide-induced hyponatremia has thus far remained controversial despite the presence of volume expansion (as suggested by the relatively low uric acid level and normal serum urea: creatinine ratio, for instance) in the majority of cases here. Our observation further confirmed that the manifestations are primarily central nervous system in origin, with their severity partly reflected by the absolute decrease in plasma sodium concentration. In other words, symptoms of thiazide-induced hyponatremia are closely related to osmotic water shift and hence increased intracellular volume, with the target organ being the brain and thus leading to cerebral edema.[6,7]

When the plasma sodium and osmolality falls as a result of thiazide diuretics, water starts to move into cells to achieve osmotic equilibrium. Such cellular response inside the brain is thought to cause initial swelling, which will then be counteracted by the process of extrusion of intracellular solutes in order to decrease brain osmolality to match that of plasma.[7,8] Should this adaptive process fail to achieve osmotic equilibrium between the brain and plasma, water will continue to enter the brain and neurological manifestation ensues. As demonstrated in our series, there is increased risk of neurological symptom in patients with lower blood sodium level, even though some over-lapping occurs. Similar observation from experimental animal experiments[9] and human studies[10] adds weight to our clinical finding. Such association is also biologically plausible because water influx into the brain is expected to be driven by the degree of plasma osmolality. The overlap of sodium levels, on the other hand, emphasizes how complex and multiple the pathogenesis of thiazide-induced hyponatremia symptom could be. Of note, the link between the rates of serum sodium fall and neurological symptom propensity could not be addressed in our retrospective analysis.

Previously postulated predisposition of female patients to brain damage from hyponatremia[8,11,12] could neither be confirmed nor refuted in our series because of the low event rate of seizures or coma. However, our finding of lower serum sodium concentration among female patients is speculated to be the effect of oestrogen on thiazide binding in the kidney.

Previous animal studies showed that estradiol enhanced thiazide-sensitive sodium cotransporter in the distal convoluted tubules[13] which might therefore account for the greater magnitude of serum sodium fall among female thiazide-induced hyponatremic subjects. Potential limitations of this hypothesis-generating study, nevertheless, should be noted.

First, the proposed effect of oestrogen was not further examined, in the absence of patient data in terms of menopausal status and oestrogen replacement therapy. In addition, the retrospective case series study design in the current setting without case-controls makes it difficult to infer unbiased causality.

CONCLUSION: Thiazide diuretics commonly used antihypertensive especially in elderly patients. Hyponatremia is a common complication comes across with thiazide diuretics. Hyponatremia from thiazide diuretics treatment may be easily missed if plasma electrolyte concentrations are not measured in patients with neurological manifestation, it has been shown that symptoms from thiazide-induced hyponatremia primarily reflect osmotic water shift into brain cells rather than extracellular fluid volume depletion. These days, when thiazide diuretics are advocated as the first-line antihypertensive therapy, it is important to recognize the complication of thiazide-induced hyponatremia.

Timely detection and intervention is very essential and improves the outcomes in patients with thiazide diuretics.

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