Hyponatremia - A rare complication of Gitelman's syndrome

A. Ganguli, J. H. Veis

Division of Nephrology, Georgetown University/Washington Hospital Center, Washington, DC 20010, USA

ABSTRACT

Gitelman's syndrome (GS) is a rare autosomal recessive disorder caused by mutations in thiazide-sensitive NaCl cotransporter. We report a 49-year-old, normotensive lady with prolonged hypokalemia since her 20s who was diagnosed with GS at our renal clinic. During follow-up, she was found to have mild, asymptomatic, euvolemic hyponatremia with low serum uric acid, inappropriately high urine osmolality and sodium consistent with syndrome of inappropriate antidiuretic hormone-like presentation. Despite life-long urinary sodium losses, hyponatremia has rarely been reported in GS to be due to the primary disease process. We present relevant clinical data and hypothesize on why this disease *per se* may be a risk factor for dilutional hyponatremia.

Key words: Complication, Gitelman's SYNDROME, hyponatremia

Introduction

Gitelman syndrome (GS) is a rare autosomal recessive disorder caused by mutations in the SLC12A3 gene on chromosome 16q13 encoding the thiazide-sensitive NaCl cotransporter (NCC).[1] Estimated population prevalence is 1:40,000 making it the most common inherited tubulopathy.[1] It is commonly diagnosed in the second or third decade and presents with hypokalemic metabolic alkalosis, hypocalciuria (daily calcium excretion of <2 mg/kg of body weight), hypomagnesemia, and normal blood pressure.[2] Despite lifelong phenomena of renal salt wasting, reports of hyponatremia in this disease is rare and coincident to other commonly attributable causes.[2,3]

Case Report

A 60-year-old Caucasian female patient was diagnosed with Gitelman's syndrome when she first presented to our renal clinic in 2000. She had documented a history of persistent hypokalemia and hypomagnesemia since the last 8 years associated with intermittent fatigue and muscle weakness. Past medical history was significant for severe symptomatic hypomagnesemia after an episode of viral gastroenteritis in her early 20s although no detailed work up was done then. She has 3 children none of whom have congenital defects. She is a product of nonconsanguineous marriage. Her brother was diagnosed with "Bartter's syndrome" in adolescence although details of the circumstances leading to either his diagnosis nor genetic testing were available. Her only medications were potassium chloride 20 meq p.o. BID and magnesium oxide 400 mg p.o. BID. She was an occasional drinker, ex-smoker quit 20 years prior, and denied using recreational drugs. Biochemical panel supporting a diagnosis of GS is presented in Table 1. Patient refused genetic testing. Subsequent to our first clinic evaluation, oral potassium and magnesium supplementation was increased and her electrolyte abnormalities remained in normal range till the event of interest.

The patient was lost to follow-up in the renal clinic for 4 years till she returned back in July 2008. Interval

Address for correspondence:
Dr. A. Ganguli,
Georgetown University/Washington Hospital Center, 110 Irving Street, NW, Suite 2A70, Washington, DC 20010, USA.
E-mail: ranagang77@gmail.com

Access this article online	
Quick Response Code:	**Website:** www.indianjnephrol.org
	DOI: 10.4103/0971-4065.177208

How to cite this article: Ganguli A, Veis JH. Hyponatremia - A rare complication of Gitelman's syndrome. Indian J Nephrol 2017;27:74-7.

Table 1: Initial blood work on diagnosis of Gitelman's syndrome

Results	Interpretations
Hemoglobin (g/dl) 11.2, hematocrit (%) 33.6, WBC (×10³/μL) 9.8, platelets (×10³/μL) 325	Normal blood counts

Serum chemistry-conventional units (× conversion for SI units)
  Na - 136 mEq/L, K - 3.3 mEq/L, Cl - 99 mEq/L, HCO₃-32 mEq/L, BUN - 16 mg/dl
  (×0.35 mmol/L), creatinine - 0.71 mg/dl (×88.4 μmol/L), Mg - 1.5 mg/dl (×0.411 mEq/L),
  Ca - 8.78 mg/dl (×0.25 mEq/L), serum osmolality - 282 mOsm/kg
	Hypokalemia, hypomagnesemia, normal renal and liver functions, metabolic alkalosis

Urine analysis Specific gravity=1.010, pH=7.0, nitrite/leukocyte esterase/glucose/proteins=negative	Normal urine analysis

Urine chemistry (mEq/L)
  Na - 127, K - 95, Cl - 121, urine osmolality - 505 mOsm/kg
  TTKG - 16.8
  Diuretic screen negative
	Elevated TTKG, renal K and Cl wasting, not due to diuretics

24 h urine protein 93 mg, Ca 43 mg	Minimal proteinuria, hypocalciuria (definition <2 mg/kg/day or <100 mg for our patient)
Supine AM PRA 9.9 mcg/L/h (normal 0.3-3 mcg/L/h)	Elevated PRA
Supine AM aldosterone 260 ng/dl (normal 20-20 ng/ml)	Elevated aldosterone levels
Plasma renin activity to aldosterone ratio 2.62	Secondary hyperaldosteronism

PRA: Plasma renin activity, TTKG: Transtubular potassium gradient, WBC: White blood cell, BUN: Blood urea nitrogen, AM: Morning/Anti-Meridian

history was notable for a brief period of hospitalization in January 2008 from lumbar vertebral compression fracture due to a fall. As per records, preoperative biochemistry panel showed a serum Na of 128 mEq/L (last recorded value was normal in 2007). During the hospital stay, serum sodium dipped further postoperatively to a nadir of 122 mEq/L while on saline infusions and nonsteroidal anti-inflammatory drugs (NSAIDs) and improved spontaneously to 130 mEq/L at the time of discharge. She had no symptoms of hyponatremia, and no renal opinion was sought in-patient. Notably, a patient admitted to be drinking large amounts of water (approximately 4–6 L/a day) to "keep the system clean" since the last 1 year or so. She denied any increasing thirst or compulsive drinking, changes in memory, mood or thought process, using psychoactive substances, antidepressants, opiods, or NSAIDs preoperatively.

On examination, supine pulse and blood pressure were 74/min and 94/58 while readings after 2 min of standing were 80/min and 88/58 with no orthostatic symptoms. In addition, physical examination showed no jugular venous distension, clinical euvolemia and normal chest, cardiac, neurological, and psychiatric evaluation. Repeat biochemical evaluation from our clinic, which are shown in Table 2, in the context of euvolemic hyponatremia and normal thyroid and adrenal function suggested a diagnosis of a syndrome of inappropriate antidiuretic hormone (SIADH) like state. No obvious cause of antidiuretic hormone (ADH) hypersecretion could be discerned in her clinical picture prior to the vertebral fracture. A whole body computed tomogrpahy scan was also done to rule out pulmonary or intracranial lesions as potential sources of ADH hypersecretion and was negative. She was started on fluid restriction to 1.5 L a day. Within 1-month, serum sodium went up to 134 and subsequently she became normonatremic [Figure 1].

Table 2: Biochemistry panel at the time of evaluation of hyponatremia

Test (conventional units)	Value (conversion factor for SI units)	Normal range (range in SI units)
Serum sodium (mmol/L)	127	135-147
Serum potassium (mmol/L)	4.0	3.3-5.5
BUN (mmol/L)	12.9 mg/dl (×0.35 mmol/L)	6-20 (2.1-7.1)
Serum creatinine (mg/dl)	0.61 mg/dl (×88.4 mmol/L)	0.52-1.04 (62-115)
Serum magnesium (mg/dl)	1.4 mg/dl (×0.411 mmol/L)	1.6-2.3 (0.65-1.07)
Serum osmolality (mOsm/kg)	277 (same)	277-305
Thyroid stimulating hormone (mIU/L)	1.73 (same)	0.4-4.5
AM cortisol (μg/dl)	9.52 (×27.59 nmol/L)	9-20 (138-635)
Urine osmolality (mOsm/kg)	581	50-1400
Urine sodium (mmol/L)	30	Variable
Serum uric acid (mg/dl)	2.3 mg/dl (×59.48 μmol/L)	2.5-6.2 (150-370)

BUN: Blood urea nitrogen, AM: Morning/Anti-Meridian

Discussion

Hyponatremia is a rarely reported complication of GS despite a life-long propensity for renal salt wasting. An extensive literature search revealed only 3 cases of GS reported with coincidental hyponatremia.[2,3] Schepkens *et al*. reported 2 cases both with a long-standing diagnosis of GS preceding hyponatremia.[2] The diagnosis in the first case was psychogenic polydipsia which responded to antipsychotic medication to control compulsive free water intake and free water restriction while in the second case, patient had obstructive jaundice secondary to carcinoma of the pancreas.[2] Hyponatremia in the second case was attributed to salt-wasting nephropathy arising from tubule-toxic effects of bile salts in a biliary obstruction which resolved after biliary stenting.[2] In the second paper, Ali *et al*. reported euvolemic hyponatremia in a 17-year-old
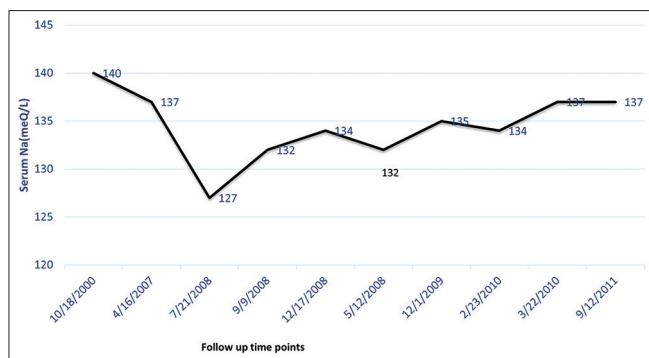
Figure 1: Trends in serum sodium of our patient over the period of clinic follow-up

boy hospitalized for pneumonia who also had normal blood pressure, hypokalemia, hypomagnesemia, and metabolic alkalosis.[3] A *de novo* diagnosis of GS was made in the acute setting. The cause of hyponatremia was attributed to SIADH although no hypouricemia was documented and follow-up clinical data specifically related to serum sodium and treatment of hyponatremia was lacking.[3]

The issue of whether the association between hyponatremia in GS is causal or not in our case will remain unsettled although we attempted to exclude all known causes. Dilutional hyponatremia as a direct consequence of a dysfunctional distal tubular NCC protein (due to SCL12A3 mutations in GS) is certainly biologically plausible given the frequent occurrence of hyponatremia from pharmacological blockade of this channel by thiazides. Striking, however, is the unpredictability of thiazide-induced hyponatremia (TIH) suggesting an idiosyncratic mechanism.[4,5] The propensity of TIH to affect elderly, females and frail individuals along with clinical euvolemia, a low blood urea nitrogen and hypouricemia resulting from increased fractional urate excretion suggest an SIADH like state.[6]

Mechanistically, an SIADH like state with NCC blockage is possible when there is an impaired renal tubular dilutional capacity due to failure to lower distal tubular Na and Cl concentration in the setting of an intact urinary concentrating mechanism.[4-8] In addition, net urinary Na loss is high leading to extracellular volume contraction which reduces GFR and promotes vasopressin release leading to further reduction in free water clearance in patients on thiazide diuretics.[8,9] Direct effects of thiazides in causing TIH such as increased thirst response or increased aquaporin-2 expression are unlikely to be operational in GS and may account for the apparent rarity of hyponatremia in this genetic disease.[5,7]

Clearance studies on GS patients have demonstrated a decreased free water clearance thereby establishing a potentially favorable setting for hyponatremia in this disease even in the absence of other coexistent and unrelated causes.[10] In this backdrop, a second hit such as a voluntary increase in free water intake (first case of Schepkens *et al*.[2] and our patient), renal tubular salt wasting (second case of Schepkens *et al*.[2]) and pneumonia induced ADH hypersecretion (the case of Ali *et al*.[3]) is sufficient to trigger clinical hyponatremia. The closest differential diagnosis in our patient was reset osmostat syndrome which is usually mild (unlike our case) and does not normalize with free water restriction.[11] Other options for treatment of SIADH such as salt tablets or oral vasopressin receptor antagonist tolvaptan were not considered in our case given the mild and easily correctable nature of hyponatremia.[12-14]

To conclude, hyponatremia is a rarely reported but a clinically plausible complication of Gitelman's syndrome resulting from a complex interplay of life-long tubular salt wasting, extracellular volume depletion induced ADH hypersecretion and impaired distal tubular diluting mechanism. Closer studies in index cases of GS reported worldwide can potentially unravel a new risk factor for dilutional hyponatremia.

Financial support and sponsorship

Conflicts of interest
There are no conflicts of interest.

References

1. Knoers NV, Levtchenko EN. Gitelman syndrome. Orphanet J Rare Dis 2008;3:22.
2. Schepkens H, Stubbe J, Hoeben H, Vanholder R, Lameire N. Severe hyponatraemia and hypouricaemia in Gitelman's syndrome. Nephrol Dial Transplant 2001;16:2250-2.
3. Ali A, Masood Q, Yaqub S, Kashif W. A case of Gitelman syndrome with severe hyponatraemia and hypophosphataemia. Singapore Med J 2013;54:e18-20.
4. Hwang KS, Kim GH. Thiazide-induced hyponatremia. Electrolyte Blood Press 2010;8:51-7.
5. Friedman E, Shadel M, Halkin H, Farfel Z. Thiazide-induced hyponatremia. Reproducibility by single dose rechallenge and an analysis of pathogenesis. Ann Intern Med 1989;110:24-30.
6. Sonnenblick M, Rosin AJ. Significance of the measurement of uric acid fractional clearance in diuretic induced hyponatraemia. Postgrad Med J 1986;62:449-52.
7. César KR, Magaldi AJ. Thiazide induces water absorption in the inner medullary collecting duct of normal and Brattleboro rats. Am J Physiol 1999;277(5 Pt 2):F756-60.
8. Fuisz RE, Lauler DP, Cohen P. Diuretic-induced hyponatremia and sustained antidiuresis. Am J Med 1962;33:783-91.
9. Fichman MP, Vorherr H, Kleeman CR, Telfer N. Diuretic-induced hyponatremia. Ann Intern Med 1971;75:853-63.
10. Favre GA, Nau V, Kolb I, Vargas-Poussou R, Hannedouche T, Moulin B. Localization of tubular adaptation to renal

sodium loss in Gitelman syndrome. Clin J Am Soc Nephrol 2012;7:472-8.

11. Hoorn EJ, Swart RM, Westerink M, van den Dorpel MA, Berghout A, Bakker JJ. Hyponatremia due to reset osmostat in dementia with lewy bodies. J Am Geriatr Soc 2008;56:567-9.

12. Rohana AG, Norasyikin AW, Suehazlyn Z, Ming W, Norlela S, Norazmi MK. A case of persistent hyponatraemia due to reset osmostat. Med J Malaysia 2006;61:638-40.

13. Verbalis JG, Adler S, Schrier RW, Berl T, Zhao Q, Czerwiec FS; SALT Investigators. Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion. Eur J Endocrinol 2011;164:725-32.

14. Gross P. Clinical management of SIADH. Ther Adv Endocrinol Metab 2012;3:61-73.