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HYPONATREMIA: A RARE COMPLICATION OF GITELMANS' S SYNDROME - LITERATURE REVIEW AND CLINICAL CASE

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Abstract
Gitelman's syndrome (GS) is a variant of classical Bartter's syndrome (BS) in adults characterized by hypokalemic metabolic alkalosis, hypocalciuria (daily excretion <2.0 mg/kg body weight), hypomagnesaemia (<1.5 mg/dl), together with a normal to low blood pressure .In 1996, Simon et al. reported complete linkage between the syndrome and the thiazide-sensitive sodium chloride coporter (TSC) on chromosome 16q13 (Human Gene Mapping Workshop-approved symbol: SLCA3). Other metabolic features of GS include normonatremia, hyperuricemia, normocalcemia, increased plasma renin and aldosterone/potassium ratio, and inappropriately high renal potassium, magnesium, and chloride excretion. In this paper, we describe two affected patients who developed severe hyponatremia and hypouricemia. To the best of our knowledge, this complication has not been described previously.
Keywords: *Gitelman's syndrome, hyponatremia, hypouricemia*

Rezumat
Sindromul Gitelman (GS) este o variantă a clasicului sindrom Bartter (BS) la adulți, caracterizat prin alcaloză metabolică hipokaliemică, hipocalciurie (excreție zilnică <2,0 mg/kg greutate corporală), hipomagneziemie (<1,5 mg/dl), împreună cu tensiune arterială normală spre scăzută. În 1996, Simon et al. au raportat o legătură completă între sindrom și transportorul de clorură de sodiu sensibil la tiazide (TSC) de pe cromozomul 16q13. Alte caracteristici metabolice ale GS includ normonatremia, hiperuricemia, normocalcemia, renina plasmatică crescută, raportul aldosteron/potasiu crescut și excreția renală necorespunzător de ridicată de potasiu, magneziu și clor. În această lucrare, descriem doi pacienți care au dezvoltat hiponatremie și hipouricemie severă. Din câte știm, această complicație nu a fost descrisă anterior.
Cuvinte cheie: *sindrom Gitelman, hiponatremie, hipouricemie.*



Internal Medicine

Clinical Cases

Introduction

Bartter and Gitelman syndromes are inherited hypokalemic salt-losing (i.e., salt-wasting) tubulopathies. They are generally inherited as autosomal recessive traits due to loss-of-function mutations. Bartter or Gitelman syndrome should be suspected in any patient with unexplained hypokalemia, metabolic alkalosis, and a normal or low blood pressure. In such patients, it is crucial to exclude other more common causes of these findings, in particular diuretic and/or laxative abuse and surreptitious vomiting. In addition to careful history and examination, measurement of spot urine chloride concentrations (or fractional chloride excretion) should be collected, preferably in several different specimens, over several weeks.

The spot urine chloride is usually consistently high (>20 mEq/L) in Bartter and Gitelman syndromes. It is typically consistently low (<20 mEq/L) with vomiting, and it fluctuates between low and high with intermittent (and surreptitious or denied) diuretic use. If another explanation for the electrolyte abnormalities and clinical findings cannot be identified, then genetic testing should generally be performed to confirm the presence of mutations in one or more genes associated with Bartter syndrome or Gitelman syndrome.

It is necessary to distinguish Bartter syndrome type 3 from Gitelman syndrome. Bartter syndrome type 3 and Gitelman syndrome usually present in adolescence or early adulthood. All the other forms of Bartter syndrome present before birth, soon after birth, or in very early childhood.

Bartter syndrome type 3 and Gitelman syndrome are now usually identified and distinguished with genetic testing. Many of the biochemical and clinical features of Bartter syndrome type 3 and Gitelman syndrome overlap, and in the absence of genetic confirmation, it can be difficult to differentiate these disorders[1]. Nonetheless, certain features are characteristic of one disorder or the other.

Measurement of urine calcium and magnesium excretion (with either a 24-hour urine collection or spot calcium/creatinine and magnesium/creatinine ratios) can help differentiate between Bartter syndrome type 3 and Gitelman syndrome. Urine calcium excretion is high-normal or elevated in Bartter syndrome type 3 but reduced with Gitelman syndrome (analogous to the effects of loop diuretics and thiazide diuretics on calcium excretion). Renal magnesium wasting and hypomagnesemia are present in Gitelman syndrome but are usually not seen with Bartter syndrome type 3. However, the range of normal values for these

measurements is wide and varies with age and body weight. In addition, the urine calcium/creatinine ratio in a given individual can vary with the urine osmolality and, for unclear reasons, with both the urine and serum concentrations of magnesium[2,3].

In healthy adults, the upper limit for 24-hour urinary calcium excretion is approximately 275 mg (6.9 mmol) in females and 300 mg (7.5 mmol) in males. The upper range for the urine calcium/creatinine ratio in healthy adults is approximately 200 mg/g of creatinine (565 mmol/mol). The lower limit of normal for calcium excretion is unclear, and adult data are scarce.

In one series of 29 adults with genetically confirmed Gitelman syndrome, a spot urine calcium/creatinine ratio of less than 44 mg/g had a sensitivity of 80 percent[1]. A spot urine calcium/creatinine ratio of less than 70 mg/g (0.2 mmol/mmol) has been proposed to define hypocalciuria in adults when Gitelman syndrome is suspected[4].

The urine electrolyte response (for example the change in spot urine chloride concentration or fractional chloride excretion) to loop or thiazide diuretics has also been utilized as a diagnostic test in the past. Patients with Barter syndrome type 3 would be expected to exhibit a blunted response to loop diuretics and an enhanced response to thiazide diuretics. Patients with Gitelman syndrome should exhibit the opposite pattern of response[5-8]. However, a brisk diuretic response to these drugs can be dangerous in hypovolemic patients. For that reason, and because genetic testing is now readily available, diuretic response tests are generally no longer utilized. The abnormal luminal membrane transporters in Gitelman syndrome (the sodium chloride cotransporter (NCC)) are shed into the urine in nanovesicles called urine exosomes. Reduced NCC activity in urine exosomes has been described in patients with Gitelman syndrome, and this may be utilized in the future as a diagnostic test[9].

Patients with unexplained hypokalemia, metabolic alkalosis, normal or low blood pressure, and persistently elevated urine chloride who have had other more common etiologies excluded have a presumed clinical diagnosis of Bartter or Gitelman syndrome. Such patients should be offered genetic testing to confirm the diagnosis[4,10].

Genetic analysis for many of the gene mutations leading to Bartter and Gitelman syndromes is commercially available. Although the practicality of genetic testing had been limited by the large size of the involved genes, the multitude of recognized mutations, an absence of "hot spots" along the gene, intrafamilial heterogeneity, and high cost, most of these barriers have been overcome. Gitelman syndrome and Bartter syndrome type 3 are autosomal recessive diseases, and it is likely that more than 1 percent of the general population are heterozygous for one of these disorders[11-14]; mutations that usually generate Gitelman syndrome are much more common than mutations generating Bartter syndrome type 3. These are recessive disorders, and heterozygotes are either normal or very subtly affected (e.g., their average blood pressure and serum potassium levels are slightly lower than a well-matched control group)[12-15]. However, 15 to 20 percent of patients with clinically overt Gitelman syndrome have only one mutation that can be identified with contemporary available genetic techniques[4]. This anomaly may be explained by the inability of the techniques to identify less common and/or occult mutations or genomic rearrangements of the of the **SLC12A3** gene.



Also, some mutations located in noncoding regulatory regions or in introns may not be identified yet may have pathogenicity. In one large cohort of such individuals, a substantial fraction of patients was found to have large genomic rearrangements in the other apparently "unaffected" allele[16]. Thus, some apparently "heterozygous" patients may represent individuals with compound biallelic mutations, including one mutation that can be identified and one that cannot with available technology. As genetic testing becomes more sophisticated, more patients with compound biallelic mutations may be identified. As an example, two thirds of patients in one study who had only one mutation identified using older methodology were found to have apparently pathogenic intron variations or previously unrecognized exon mutations using newer testing methods[17]. Alternatively, patients with Gitelman-like syndrome may have a mutation that does not involve the **SLC12A3** gene. In one study, for example, several mutations of mitochondrial DNA were identified in 13 different families with Gitelman-like syndrome[18].

Medical therapy, which generally must be lifelong, is aimed at correcting or minimizing electrolyte abnormalities and extracellular volume depletion. Most patients will need a combination of treatments.

Sodium and potassium supplements (first line) - Patients with Bartter syndrome type 3 or Gitelman syndrome require oral supplementation with generous doses of sodium chloride, potassium chloride, and when magnesium levels are reduced, magnesium salts. Electrolyte supplementation is a first-line therapy. The typical required doses are sodium chloride tablets, 1 to 3 g two to four times daily; potassium chloride tablets, 20 to 40 mEq two to four times daily and, if magnesium supplementation is needed, 15 to 125 mmol/day.

Potassium-sparing diuretics (second line) - Patients who have an inadequate response to oral sodium chloride, potassium chloride, and if needed, magnesium salt supplementation, we suggest adding an agent that inhibits distal sodium-potassium exchange such as spironolactone, or amiloride, rather than other secondary options such as nonsteroidal anti-inflammatory drugs (NSAIDs) or angiotensin-converting enzyme (ACE) inhibitors. Spironolactone may be started at 100 mg daily and is often titrated, as needed, to doses of 300 mg daily. Eplerenone may be started at 50 mg daily and can be titrated to levels of 150 mg daily. Amiloride can be started at 10 mg daily and then titrated up to 20 to 30 mg daily.

Third-line options - In patients who have an inadequate response to the combination of

electrolyte supplementation and a potassium-sparing diuretic, options for additional therapy include NSAIDs and ACE inhibitors. The choice should be individualized. NSAIDs have significant gastrointestinal side effects and can reduce kidney function and even precipitate severe kidney injury. ACE inhibitors reduce blood pressure, and this can be problematic for these patients who already have low or low-normal blood pressure.

Clinical case 1

In 2004, a 27-year-old man diagnosed with a psychoaffective disorder and benzodiazepine addiction complained of muscle weakness, tremor, and muscular cramps. Routine biochemical analysis showed a serum potassium of 2.42 mmol/l and a serum magnesium of 1.42 mg/dl, together with hyperaldosteronism (31 ng/dl, normal 2–20 ng/dl) and high plasma renin activity (22 ng/ml/h, normal 0.3–3.0 ng/ml/h). Twenty-four-hour urinary collection showed a high fractional excretion (FE) of chloride (1.6%, normal 0.6–0.8%), hypocalciuria (7.2 mg/24 h), inappropriate kaliuresis (FE K^+=26%) and renal magnesium-wasting despite hypomagnesaemia (FE Mg^{2+}=8.1%, normal 3–5%). Arterial blood gas analysis showed a pH of 7.50 and a plasma HCO^-_3 of 30 mmol/l. These findings together with his psychiatric history oriented to surreptitious diuretic ingestion, and he was considered as a covert diuretic abuser during recent years. In 1996, his genomic DNA was screened for mutations at Yale University, and two base pair substitutions in the SLC12A3 gene compatible with GS were revealed. A treatment with amiloride, potassium and magnesium supplements were instituted.
In 2009, he was readmitted to the hospital with a 5-day history of headache, vomiting, progressive confusion, and restlessness. His observers noted that he had been drinking excessive amounts of fluids and smoking 2–3 packs of cigarettes daily. On admission, he was disoriented with psychotic features. Arterial blood pressure was 135/70 mmHg. Focal neurologic deficits were absent; his extremities were free from oedema, and the rest of the physical examination was also unremarkable. Blood and urine analysis revealed a serum sodium of 119 mmol/l, serum osmolality of 237 mOsm/kg, serum uric acid concentration of 2.28 mg/dl, serum magnesium of 1.31 mg/dl, potassium of 2.18 mmol/l, together with inappropriately high urine osmolality (243 mOsm/kg) and urinary sodium concentration (54 mmol/l). The patient was placed on fluid restriction (1 l daily), peroral electrolyte supplementations were reinstituted and he was started on fluphenazine decanoate injections and peroral haloperidol. Despite this therapeutic regimen, body weight was not reduced, the urinary osmolality remained inappropriately high (300 mOsm/kg) and hyponatremia (range 120–124 mmol/l) persisted during the first 3 days after admission. The anti-psychotic therapy became maximally effective 7 days after admission and was followed by free-water diuresis (124 mOsm/kg), cessation of excessive drinking, a 4-kg body weight reduction and normalization of serum sodium to 137 mmol/l and serum uric acid to 4.96 mg/dl.

Clinical case 2

A 50-year-old male was evaluated at the age of 18 for persistent hypokalemia (range 2.2-2.6 mmol/l) and hypomagnesaemia (range 1.0-1.25 mg/dl), accompanied by episodes of muscular weakness and cramps in the calves



provoked by physical exertion. There was no history of diarrhea, vomiting, polyuria, or polydipsia. His somatic growth was normal, and his blood pressure was 115/70 mmHg. Despite marked hypocalciuria (15 mg/24 h), he was diagnosed as having classical BS and a treatment with potassium chloride, magnesium lactate, spironolactone, and indomethacin was instituted.

In 2008, he was admitted to the emergency room with a 2-month history of weight loss, abdominal discomfort, progressive jaundice, vomiting, postural dizziness, and unsteady gait. He appeared severely dehydrated with dry mucous membranes and sunken eyeballs. The blood pressure was 95/60 mmHg but decreased to 70/50 mmHg when standing upright. Physical examination revealed scleral icterus, a palpable gallbladder, muscular weakness but no neurologic deficits. Laboratory evaluation showed a serum sodium concentration of 116 mmol/l, serum potassium of 1.95 mmol/l, serum magnesium of 1.32 mg/dl, serum uric acid of 0.68 mg/dl, and serum phosphate level of 2.1 mg/dl. The total serum bilirubin level was 21 mg/dl whereas the rest of the liver function tests were compatible with biliary obstruction. Urinalysis showed inappropriately high urine osmolality (621 mOsm/kg) and high renal sodium (150 mmol/l) and phosphate excretion (FE PO_4=48%, normal 10–18%). He was treated with 4 l isotonic saline over the first 24 h which resulted in an increase of serum sodium to 124 mmol/l and a rise of central venous pressure from −1 to +3 cm H_2O. Abdominal ultrasound and CT scanning showed an unresectable carcinoma in the head of the pancreas. The diagnosis of SIADH was considered and fluid restriction was instituted. On this regimen, he lost 4.1 kg in 7 days and deteriorated clinically with reoccurrence of lethargy and orthostatism. The serum sodium finally corrected to 137 mmol/l, but serum uric acid remained low (1.1 mg/dl). An attempt for endoscopic stenting was unsuccessful and a cholecystic-jejunostomy was performed as a palliative measure. The serum bilirubin level decreased progressively, uric acid values rose to 3.9 mg/dl, and phosphate excretion returned to the normal range (640 mg/24 h, FE PO_4=16%). At that time, the patient was clinically euvolemic and a random ADH determination revealed an appropriately suppressed value of 0.8 pg./ml for a plasma osmolality of 277 mOsm/kg H_2O.

Discussion

Hyponatremia is a well-recognized complication of diuretics whereby thiazides are most frequently implicated. Thiazide diuretics may predispose to hyponatremia through several mechanisms including renal

sodium wasting, hypovolemia-induced vasopressin (ADH) release, increased thirst and water intake, hypomagnesaemia and intracellular potassium depletion, and lack of interference with renal concentrating mechanisms[21]. In addition, the direct stimulation of water reabsorption in the distal nephron has been shown. This effect appears to act independently from the inhibition of TSC and is blocked by the addition of prostaglandin (PG) E_2 but potentiated by indomethacin[22]. Thiazides evoke a net decrease of urine flow with lowering of urine volumes and play an important role in the treatment of diabetes insipidus. The phenotype of GS is identical to the chronic use of thiazides, whereas classical BS is mimicked by the intake of loop diuretics[19].

Urinary diluting capacity is disturbed in GS, but concentrating mechanisms are intact since, in contrast to BS, the generation of a hypertonic medullary interstitial is well preserved and the action of ADH is not antagonized by urinary PG E_2[23]. It therefore seems paradoxical that hyponatremia is frequent in BS but rare in GS[20]. However, salt loss and volume depletion are more pronounced in BS, reflecting the larger amounts of sodium chloride absorbed in the ascending loop of Henle under normal conditions. In addition, mutant alleles result in persistent and severe salt-wasting which may explain the predominant effects of sodium depletion and the higher likelihood for hyponatremia in BS.

Both patients developed hyponatremia, hypouricemia, inappropriately high urine osmolality and urinary sodium concentration, which are the hallmarks of the syndrome of inappropriate ADH release (SIADH). Fichman *et al.*[24] observed that most patients with thiazide-induced hyponatremia exhibit classical features of SIADH by presenting with low serum uric acid levels. Fluid restriction normalizes serum sodium and corrects the initially increased fractional uric acid clearance, which suggests that an impairment of free water excretion leading to volume expansion is a primary event in most cases of thiazide-induced hyponatremia[25]. An analogous alteration of uric acid excretion that resembles SIADH has been described in the polydipsia-hyponatremia syndrome[26]. Furthermore, several case reports documented that thiazides may trigger and aggravate hyponatremia in compulsive water drinkers[27]. In case 1, the combination of polydipsia and impaired urinary diluting capacity caused by GS was responsible for initial water retention, volume expansion, weight gain and SIADH-like biochemical features. Water restriction resulted in weight reduction and the parallel correction of hyponatremia and hypouricemia. It is of note that the urinary diluting mechanisms (243 mOsm/kg H_2O) were more compromised than expected in GS (85 mOsm/kg H_2O) since ADH secretion at admission was inappropriately high (3.9 pg./ml, normal 1.0–8.0 pg./ml). In this context, the possibility that heavy cigarette smoking and/or acute psychosis *per se* acted as potent stimuli for ADH release must be considered.

The clinical picture was obviously different in case 2. This patient was admitted with severe volume depletion and the diminished plasma volume stimulated ADH release (13.6 pg./ml) by overriding the suppressive effects of hyponatremia. The administration of 3 l isotonic saline improved the hyponatremia and must be considered as a reliable indicator of hypovolemic hyponatremia. In addition, the appropriate suppression of ADH (0.8 pg./ml) after adequate volume repletion and persistent hypouricemia after the correction of hyponatremia, are both



incompatible with SIADH. Maesaka *et al*.[28] described a similar sequence in the cerebral salt-wasting syndrome (CSW) and demonstrated the existence of a natriuretic factor which accounts for a fixed defect of sodium and urate reabsorption in the proximal tubule, hyponatremia and hypouricemia, volume depletion and inappropriately high urine osmolality and urine sodium concentrations. These authors also suggested that the persistence of hyperuricemia and high fractional excretion of uric acid (>10%) after correction of hyponatremia could provide an important clinical clue to differentiate patients with CSW from those with SIADH.

Retained bile acids can reduce fluid reabsorption in the proximal tubule[29]. Volume depletion, hyponatremia, hyperuricemia, increased renal urate excretion, and phosphaturia have all been described as the consequence of severe hyperbilirubinemia and cholaemia *per se*[29,30]. We speculate that biliary obstruction was the most likely mechanism for the temporarily increased renal sodium and urate wasting, dehydration and high similarity with the CSW. This hypothesis is further supported by the concomitant changes in renal phosphate excretion suggesting a proximal tubulopathy, and the correction of renal solute excretion to baseline when bilirubin levels decreased after surgical treatment.

In conclusion, analogous to what is observed during a treatment with thiazides, patients with GS seem to be susceptible to developing serious hyponatremia and hypouricemia. Whereas most patients with GS do not develop significant hyponatremia, probably because they achieve a balance between water intake and free water excretion under normal circumstances, the propensity is theoretically present if fluid intake and/or ADH activity become extreme.

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