Case Report

Severe hyponatraemia and hypouricaemia in Gitelman’s syndrome

Hans Schepkens¹, Joris Stubbe², Heidi Hoeben¹, Raymond Vanholder¹ and Norbert Lameire¹

¹Department of Internal Medicine, Renal Division and ²Division of Gastroenterology, University Hospital Gent, Belgium

Keywords: Gitelman’s syndrome; hypomagnesaemia; hyponatraemia; hypouricaemia; syndrome of inappropriate ADH release (SIADH); thiazides

Introduction

Gitelman’s syndrome (GS) is a variant of classical Bartter’s syndrome (BS) in adults characterized by hypokalaemic metabolic alkalosis, hypocalciuria (daily excretion < 2.0 mg/kg body weight), hypomagnesaemia (< 1.5 mg/dl), together with a normal to low blood pressure [1]. In 1996, Simon et al. [2] 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 normonatraemia, hyperuricaemia, normocalcaemia, increased plasma renin and aldosterone/potassium ratio, and inappropriately high renal potassium, magnesium and chloride excretion [3,4]. In this paper, we describe two affected patients who developed severe hyponatraemia and hypouricaemia. To the best of our knowledge, this complication has not been described previously.

Case 1

In 1984, 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 Mg²⁺ = 8.1%, normal 3–5%). Arterial blood gas analysis showed a pH of 7.50 and a plasma HCO₃⁻ 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 was instituted.

In 1999, 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 serum sodium concentration (137 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.
Case 2

A 50-year-old male was evaluated at the age of 18 for persistent hypokalaemia (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 diarrhoea, 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 1998, 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 PO₄ = 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 H₂O. 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 postural hypotension. Laboratory evaluation showed inappropriately high urine osmolality and phosphate excretion (FE PO₄ = 48%, normal 10–18%). An attempt for endoscopic stenting was unsuccessful and a cholecysto-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 PO₄ = 16%). At that time, the patient was clinically euvoalaemic and a random ADH determination revealed an appropriately suppressed value of 0.8 pg/ml for a plasma osmolality of 277 mOsm/kg H₂O.

Discussion

Hyponatraemia is a well-recognized complication of diuretics whereby thiazides are most frequently implicated. Thiazide diuretics may predispose to hyponatraemia through several mechanisms including renal sodium wasting, hypovolaemia-induced vasopressin (ADH) release, increased thirst and water intake, hypomagnesaemia and intracellular potassium depletion, and lack of interference with renal concentrating mechanisms [5]. 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) E2 but potentiated by indomethacin [6]. 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 [2]. Urinary diluting capacity is disturbed in GS, but concentrating mechanisms are intact since, in contrast to BS, the generation of a hypertonic medullary interstitium is well preserved and the action of ADH is not antagonized by urinary PG E2 [7]. It therefore seems paradoxical that hyponatraemia is frequent in BS but rare in GS [3]. 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 hyponatraemia in BS.

Both patients developed hyponatraemia, hypouricaemia, inappropriately high urine osmolality and urinary sodium concentration, which are the hallmarks of the syndrome of inappropriate ADH release (SIADH). Fichman et al. [8] observed that the majority of patients with thiazide-induced hyponatraemia 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 hyponatraemia [9]. An analogous alteration of uric acid excretion that resembles SIADH has been described in the polydipsia-hyponatraemia syndrome [10]. Furthermore, several case reports documented that thiazides may trigger and aggravate hyponatraemia in compulsive water drinkers [11]. 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 hyponatraemia and hypouricaemia. It is of note that the urinary diluting mechanisms (243 mOsm/kg H₂O) were more compromised than expected in GS (85 mOsm/kg H₂O) 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 hyponatraemia. The administration of 3 l isotonic saline improved the hyponatraemia and must be considered as a reliable indicator of hypovolaemic hyponatraemia. In addition, the appropriate suppression of ADH (0.8 pg/ml) after adequate volume repletion and the persistent hypouricaemia after the correction of hyponatraemia, are both incompatible with SIADH. Maesaka et al. [12] 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, hyponatraemia and hypouricaemia, volume depletion and inappropriately high urine osmolality and urine sodium concentrations. These authors also suggested that the persistence of hypouricaemia and high fractional excretion of uric acid (>10%) after correction of hyponatraemia 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 [13]. Volume depletion, hyponatraemia, hypouricaemia, increased renal urate excretion, and phosphaturia have all been described as the consequence of severe hyperbilirubinemia and cholaemia per se [13,14]. 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 develop serious hyponatraemia and hypouricaemia. Whereas the majority of patients with GS do not develop significant hyponatraemia, 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.

References


Received for publication: 2.12.00
Accepted in revised form: 11.5.01