Case Report

Gitelman's syndrome with panhypopituitarism: Reno-endocrine interplay

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ABSTRACT

Gitelman's syndrome is an inherited tubulopathy affecting thiazide-sensitive sodium chloride cotransporter, which manifests with hypokalemic alkalosis, hypomagnesemia, and hypocalciuria. Recently few cases have been described having an association of Gitelman's syndrome with pituitary abnormalities on imaging, though with normal hormonal status. We describe the first case of an adult patient having Gitelman's syndrome and hypopituitarism with abnormal pituitary imaging. She presented to us with hypotension, hypokalemia, hypomagnesemia with alkalosis, hypothyroidism, hypocortisolism, and hypogonadism. She was treated with replacement of electrolytes and hormones, to which she showed an excellent response.

Key words: Gitelman's syndrome, hypokalemia, hypomagnesemia, inherited tubulopathy, multiple pituitary hormone deficiencies

Introduction

Gitelman's syndrome (GS) is an autosomal recessive tubular disorder characterized by hypokalemic alkalosis, hypomagnesemia, and hypocalciuria.[1,2] Hypopituitarism can have varied etiologies including tumor in hypothalamo-pituitary region or its treatment, inflammatory, genetic, trauma, and hemorrhage,[3,4] and can result in a host of hormonal and electrolyte abnormalities. Both these disorders can cause significant morbidity and a combination of both can be potentially devastating. A few case reports are emerging which show a combination of inherited tubular disorders with pituitary abnormalities on imaging, but with normal hormonal profile.[5,6] We report the first case of a post-menopausal lady who had a combination of Gitelman's syndrome with multiple pituitary hormone deficiencies (MPHD) and was treated successfully by replacement of hormones and electrolytes.

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Case Report

A 57-year-old lady, a known case of hypothyroidism for 7 years on levothyroxine replacement, presented with complaints of generalized weakness, postural giddiness, and intermittent episodes of spontaneous carpopedal spasms for past 9 months and was bedridden for past 1 month. She used to consume approximately 250 ml of milk products per day and had sunlight exposure for 10 minutes per week. There was no history of diuretic use, protracted vomiting or diarrhea, polydipsia, or polyuria. She was noted to have hypotension on several occasions over the past 9 months for which she was treated with intravenous fluids. She has three children (last child birth 21 years back) and there was no history of lactation failure. She attained menopause at the age of 47 years, prior to which her periods were regular.

Clinically, she was obese (BMI 34.13 kg/m^2), and had supine hypotension (BP 70/50 mmHg), pallor, bilateral non-pitting edema, acanthosis nigricans, and skin tags. Trousseaus' and Chvosteks's signs were positive. There was no goiter, deep tendon jerks were normal, and rest of the examination was normal.

Investigations revealed anemia (Hb 10.3 gm%), hyponatremia, hypokalemia, hypomagnesemia, hypocalcemia,

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hypophosphatemia, hypochloremia, and metabolic alkalosis [Table 1]. Her serum 25-hydroxy vitamin D_3level was 11.89 ng/ml and intact parathyroid hormone (PTH) was 249 pg/ml (10.0–65.0). Urinary spot sodium (180 meq/l), potassium (13 meq/l), and chloride (161 meq/l) were high. 24-hour urinary calcium [127 mg (normal <200 mg)], phosphorus [412 mg (normal <1200 mg)], and copper [8.3 μg/d (normal <60 μg/d)] excretion were normal. Plasma renin activity 4.4 ng/ml/h (0.1–3.1) and plasma aldosterone 38.1 ng/dl (3–16) levels were high. Plasma glucose levels (OGTT), and renal and liver function tests were normal. Qualitative test for urinary amino acids, HIV and antinuclear antibody (ANA) serologies were negative. There was no microalbuminuria and urine pH was 6.1. Ultrasonography and magnetic resonance imaging (MRI) of abdomen revealed no pathology.

Thyroid profile at baseline was suggestive of hypothyroidism [low T4, thyroid stimulating hormone (TSH) 9.06 μU/l], whereas it was normal at presentation. There was hypocortisolism (random plasma cortisol: 164 nmol/l and peak cortisol during insulin-induced hypoglycemia: 453.2 nmol/l), relatively normal adrenocorticotropic hormone (ACTH) 11.6 pg/ml (7.2–63.3), and low gonadotropins [luteinizing hormone (LH) 1.36 mIU/ml, follicle stimulating hormone (FSH) 4.00 mIU/ml]. Serum prolactin [5.8 ng/ml (5–25)] and serum insulin-like growth factor 1 (IGF-1) [156 ng/ml (66–310)] were low normal. Peak growth hormone level after IIH was 5.6 ng/ml. Anti-thyroid peroxide antibody levels were normal. MRI sella showed loss of posterior pituitary bright spot [Figure 1]; however, anterior pituitary was normal.

In view of the above, a diagnosis of Gitelman's syndrome with MPHD was made. She was treated with levothyroxine, hydrocortisone, and supplementation with vitamin D, sodium, potassium, magnesium, calcium, and chloride. She showed global improvement in symptoms, her carpopedal spasms resolved, blood pressure normalized, and biochemical parameters improved which are enumerated in Table 1.

Table 1: Biochemical parameters pre- and post-presentation (at 6-month follow-up)

Serum level of electrolyte	Reference range	Pre-treatment	Post-treatment
Sodium	135 – 145 mmol/l	114	138
Potassium	3.5 – 5.5 mmol/l	1.5	4.9
Magnesium	1.6 – 2.6 mg/dl	1.0	1.8
Ionized calcium	4.6 – 5.3 mg/dl	2.9	5.0
Phosphorus	2.8 – 4.2 mg/dl	1.8	3.3
Chloride	96 – 110 mmol/l	65	98
pH	7.35 – 7.45	7.84	7.61
HCO_3	22 – 30 mmol/l	33.8	32.6

Discussion

Bartter's and Gitelman's syndrome are two ends of a spectrum of inherited renal tubulopathies that are characterized by renal salt wasting, hypokalemic metabolic alkalosis, hyperreninemic-hyperaldosteronism with normal blood pressure, and hyperplasia of juxtaglomerular apparatus. Gitelman's syndrome (GS), in addition, also exhibits hypomagnesemia and hypocalciuria.[5] Bartter's syndrome is the more severe of two and presents in antenatal period or early childhood, whereas Gitelman's syndrome presents later in life and adult cases have also been described.[1,2]

Our patient presented with nonspecific features of generalized weakness that can be explained on the basis of severe dyselectrolytemia and hypopituitarism. Postural giddiness can be a manifestation of Gitelman's syndrome *per se* or that of hypotension that our patient had. Our patient had hyperreninemic-hyperaldosteronism similar to that described in the literature.[2,7] Loss of fluid and electrolytes leads to activation of renin – angiotensin – aldosterone system (RAS) resulting in hyperaldosteronism on one hand and renal release of vasodilator prostaglandins (PGE2 and prostacyclins) on the other.[2,8,9] Hence, blood pressure remains normal despite hyperaldosteronism as prostaglandin-induced vasodilatation counters the hypertensive effects of overactive RAS. Our patient had concomitant hypocortisolism which resulted in hypotension. Association of Conn's syndrome that results in hyporeninemic-hyperaldosteronism has also been recently reported with GS.[6] Our patient, however, had hyperreninemic-hyperaldosteronism and normal adrenals on MRI, hence such an association is ruled out. Hypokalemic metabolic alkalosis occurs due to hyperreninemic-hyperaldosteronism leading to increased potassium and hydrogen ion secretion in the collecting tubules. Magnesium wasting in distal convoluted tubules as a result of inhibition of its uptake in the presence of

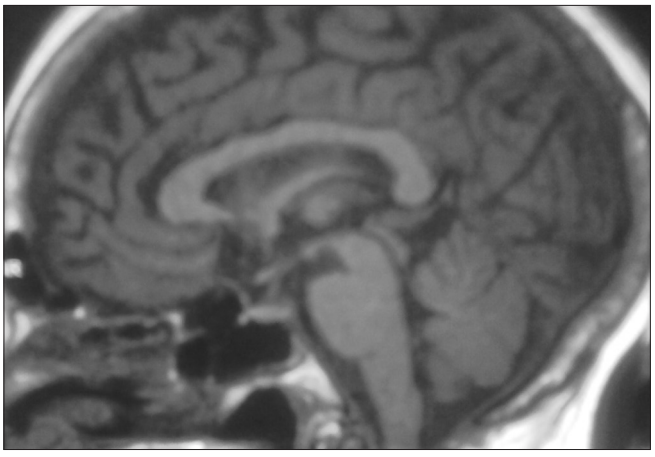

Figure 1: MRI sella (sagittal view) showing loss of posterior pituitary bright spot

hypokalemia and metabolic alkalosis leads to hypomagnesemia in Gitelman's syndrome, as was seen in our case.[1,2] Hypochloridemia with increased urinary chlorine excretion is also a feature of Bartter's syndrome and an overlap of both the conditions cannot be denied in our case. Spontaneous tetany occurred due to concomitant hypocalcemia and hypomagnesemia in our patient. Hypocalcemia in our patient is thought to have occurred due to poor oral intake of milk products; vitamin D deficiency, and possibly reduction in 1α-hydroxylase activity. An overlap with Bartter's syndrome is seen in many patients and this could also possibly have worsened hypocalcemia. Hypophosphatemia in our patient can be explained by poor oral intake, hypovitaminosis D, and secondary hyperparathyroidism.

Panhypopituitarism, on the other hand, refers to total or partial loss of pituitary hormone secretion as a result of pituitary or hypothalamic dysfunction resulting in loss of anterior pituitary hormones with or without loss of antidiuretic hormone.[3,4] Our patient had low LH, FSH levels despite having attained menopause; ACTH was relatively normal in spite of low cortisol and stimulated cortisol level was suggestive of compensated adrenal insufficiency. Her TSH value was mildly elevated despite low total T_4 that is seen in subclinical hypothyroidism, but can also occur in secondary hypothyroidism.[10] Due to the presence of above combination of hormonal profile and abnormality in pituitary on imaging, a diagnosis of pituitary failure was made.

Diuretic use and protracted vomiting or diarrhea as a possible cause of hyokalemia was were excluded by history taking. Secondary causes for tubulopathy were excluded including Fanconi's syndrome, renal tubular acidosis, systemic lupus erythematosus, Wilson's disease, and HIV.[8] In the light of above, we diagnosed our patient to be suffering from Gitelman's syndrome though she had some overlapping features of Bartter's syndrome as well. Both these syndromes are autosomal recessive disorders caused by an inactivating mutation of the thiazide-sensitive sodium–chloride cotransporter in the Loop of Henle and distal renal tubule, namely *SLC12A3 and CLCNKB* genes, encoding the chloride channel.[5] MPHD can be due to tumor or its treatment in the hypothalamo-pituitary region,[4] which was ruled out by history and imaging. Autoimmune etiology is another important factor; however, surrogate antibodies (anti-TPO and ANA) were negative in our patient to rule out autoimmune disrorder. Also, there was no history of lactation failure to suggest Sheehan's syndrome as a possible cause. Barring these, inherited causes can give rise to MPHD which could be a causative factor in our patient.

The tubular defect in Bartter's or Gitelman's syndrome cannot be corrected and lifelong magnesium and potassium supplementation is required, whereas treatment of MPHD is replacement of deficient hormones, as was done in our patient.[2] The combination of nonsteroidal anti-inflammatory drugs (NSAIDs) to reduce renal PG synthesis and a potassium-sparing diuretic to raise the plasma potassium concentration toward normal partially reverses the metabolic alkalosis and corrects the hypomagnesemia. However, in our patient, diuretics were not given as she had hypotension.

To conclude, Gitelman's syndrome is an often overlooked cause of hypokalemia and hypomagnesemia in adults. It can be associated with pituitary abnormalities on imaging or even frank hypopituitarism. Combination of both these disorders can cause profound metabolic abnormalities in a patient. Hence, a clinician should be alert to such a possibility as the outcome can be rewarding. It remains to be seen, however, whether association of Gitelman's syndrome with pituitary abnormalities with or without MPHD is just a chance association or there is a common genetic link.

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