

Case Report

A Case of Gitelman's Syndrome Presenting with Hypocalcemia

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ABSTRACT

Gitelman's syndrome (GS) is an autosomal recessive disorder caused by a defect of the thiazide-sensitive Na-Cl cotransporter (TSC) at the distal tubule, characterized by hypomagnesemia, hypokalemic alkalosis and hypocalciuria. This condition was previously confused with Bartter's syndrome (BS). The documentation of

hypocalciuria helps to differentiate this syndrome from BS. We report a 35-year-old female patient presented to our hospital with a history of muscle weakness and carpal spasm. She showed hypokalemia, hypocalcemia, hypomagnesemia and hypocalciuria. She was treated with electrolyte supplements.

KEY WORDS: autosomal recessive disorder, hypocalcemia, renal disorder

INTRODUCTION

Gitelman's Syndrome (GS) is an inheritable renal disorder characterized by hypomagnesemia, hypokalemia and hypocalciuria. Patients usually present at an older age and have mild clinical picture and normal or slightly decreased concentrating ability. GS is caused by a defect in NaCl transport in the distal convoluted tubule^[1-4]. The diagnosis of GS can be made on the basis of clinical features, laboratory data and renal function test. The treatment is usually to correct electrolyte imbalance^[4]. The objective of this study is to report the first case of GS in Kuwait which presented with symptoms and signs caused by hypocalcemia.

CASE REPORT

A 35-year-old female patient presented with a two week history of malaise, diffuse muscle pains and weakness, leg cramps, diarrhea, vomiting, polyuria and carpal spasm. These symptoms were recurrent over the last four years. She denied any form of self-medication, surreptitious diuretic and laxative abuse, persistent vomiting and diarrhea and there was no history of chest problems. Past history as well as family history were unremarkable.

Physical examination revealed a lady of an average built. She was clinically euvoletic with normal skin turgor and no peripheral edema. Her blood pressure was 100/ 65 with no evidence of postural hypotension. She had clinical evidence of distal muscle weakness. The rest of the examination

was within normal limits.

Biochemical investigations revealed hypokalemia (s.K 2.9 mmol/l, normal values 3.6-5.1), hypocalcaemia (corrected s.Ca 1.9 mmol/l, 2.1-2.6), hypomagnesemia (s.Mg 0.3 mmol/l, 0.74-1.2), hypochloremic metabolic alkalosis (s.Cl 87 mmol/l, 94-115), pH 7.48 (7.35-7.45), HCO₃ 31 mmol/l (22-26). PO₄ 1.02 mmol/l (0.87-1.45), Alk phos 58 iu/l (42-98), serum albumin 39g/l (35-48), Hb 123 g/l (120-150), WBC 6.9 (4.0-12.0), platelet count 260 (150-400), creatinine 67mmol/l (53-97), BUN 2.9mmol/l (2.5-7.2), ALT 16 iu/l (10-60), AST19 iu/l (10-42), T. bil 9 umol/l (3-35) .

Urinalysis was normal with a pH of 6.8 and specific gravity of 1.013. Urine calcium/creatinine ratio was low 0.045 (0.08-0.57). 24 hour urine collection showed hypocalciuria (U.Ca 0.9 mmol/l, 1.5-5.5), hypermagnesuria (U. Mg 5.5 mmol/day, 3.0- 5.0) and hyperkaluria (U. K 148.6 mmol/day, 25-125). The plasma renin was increased at 83 mU/l (7.0-76.0) with secondary hyperaldosteronism (s. Aldosterone 964 pmol/l, 111 - 862). Other investigations showed normal levels of PTH (3.7 pmol/l, 0.7-5.6) , 25 OH Vit D (52.1 nmol/l, 23-113) and no glucosuria.

Renal Ultrasound study was normal. Molecular genetic studies and urinary prostaglandins were not performed. The presence of hypokalemia, hypomagnesemia, hypochloremic metabolic alkalosis, hypocalciuria and hyperaldosteronism makes Gitelman's syndrome the most likely

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Table 1: Characteristics of Bartter's syndrome and Gitelman's syndrome (modified from Devendra and Rowe)^[6]

	Bartter's syndrome	Gitelman's syndrome
Age of presentation	Prenatal, during infancy or early childhood	Late childhood or at adulthood
Clinical features	Lethargy, failure to thrive, polyuria, polydypsia, vomiting, constipation, salt craving, dehydration, nephrocalcinosis, chondrocalcinosis	Weakness, abdominal pain, constipation, vomiting and tetany
Localization of defect	Ascending limb of Henle	Distal tubule
Biochemical differences	Serum magnesium may be decreased Urinary excretion of calcium increased or normal	Serum magnesium decreased Urinary calcium excretion reduced
Molecular differences	Na-K-2Cl transporter or apical K channel or basilateral Cl channel in thick ascending limb of Henle	Na-Cl cotransporter in the distal tubule
Furosemide test	No or little response	Shows a response
Thiazide test	Shows a response	No or little response

diagnosis. Hypocalcemia may have been secondary to hypomagnesemia. Despite the low corrected Ca, PTH level was normal as persistent hypomagnesemia impairs the synthesis and secretion of PTH^[1].

She was treated with magnesium and potassium supplements and potassium sparing diuretic. Serum potassium and magnesium levels were partially corrected to 3.0-3.2 mmol/l and 0.48 mmol/l respectively. Serum Ca was corrected to 2.03 mmol/l. However, the urinary excretion of the potassium and magnesium were still higher than normal. As the patient was planning to get pregnant, potassium sparing diuretic was stopped and she continued on magnesium and potassium supplements. The patient's symptoms were partially improved.

DISCUSSION

To best of our knowledge this is the first reported case of GS in Kuwait. Although GS is unlikely to present with hypocalcemia, our case is not the only case with such a finding. In 2005 there were two reported cases of GS associated with hypocalcemia^[2,3].

Gitelman's syndrome is an inherited renal disorder characterized by hypomagnesemia, hypokalemia and hypocalciuria. The diagnosis is usually made on the basis of clinical and biochemical findings. Patients are frequently asymptomatic or may present with transient episodes of weakness, abdominal pain, constipation, vomiting, fever and tetany. Disease-free intervals may be prolonged resulting in delay in diagnosis until adulthood^[4].

The outstanding biochemical findings in GS are hypomagnesemia and hypocalciuria. Hypokalemia and mild to moderate metabolic alkalosis are usually present but their presence is not necessary to establish the diagnosis. Urinary calcium in affected patients is usually below 2.0 mg/kg body weight per day and the urine calcium/creatinine is less than 0.1^[5].

This condition was previously confused with Bartter's syndrome (BS). Some of the features that

help to differentiate the two conditions are shown in Table 1 (modified from Devendra and Rowe)^[6].

The documentation of hypocalciuria, hyperkaliuria and hypermagnesuria helps to differentiate this syndrome from BS which is associated with nephrocalcinosis^[7] and chondrocalcinosis^[8]. The pathophysiology of GS has been clearly outlined by Bhandari^[9]. There is Na-Cl wasting and hypovolemia which stimulates the renin-angiotensin-aldosterone system and causes an increase in apical Na⁺ reabsorption and stimulation of the basolateral Na⁺/K⁺-ATPase. The increased aldosterone levels also stimulate cortical and medullary collecting ducts H⁺/ATPase pumps leading to an increased apical H⁺ ion secretion. K⁺ and H⁺ ion excretion increases as K⁺ enters from the basolateral membrane via the Na⁺/K⁺-ATPase pumps resulting in hypokalemic metabolic alkalosis. The resultant low intracellular Na⁺ increases distal convoluted tubule Ca⁺ reabsorption via basolateral Na⁺/Ca⁺⁺ exchangers causing hypocalciuria. Mg⁺⁺ loss via apical Mg⁺⁺/Na⁺⁺ exchangers increases due to the net negative transepithelial potential. Hypermagnesuria may be caused also by associated hypokalemia^[10], metabolic alkalosis^[11] or low renal Mg threshold^[12]. Hypomagnesemia and hypocalciuria may also occur following the administration of thiazide diuretics which inhibit the distal luminal Na-Cl cotransporter. The combination of hypokalemia and hypocalciuria is also a feature of cis-platinum toxicity^[13]. Patients also show an increase in potassium concentration in the sweat^[14].

Hypomagnesemia results in failure of repletion of cellular potassium stores due to urinary losses. The resulting hypokalemia is refractory to treatment with potassium salts alone and its correction requires the prior or simultaneous correction of Mg deficiency^[15]. The poor absorption of magnesium and its high urinary excretion in patients with GS may explain why some patients do not respond to magnesium supplement^[16]. Normalization of serum magnesium may be difficult to achieve since

high doses of magnesium may cause diarrhea. All magnesium salts have been used but $MgCl_2$ is preferred because it compensates for urinary Cl loss^[12]. Each milliliter of the 5% solution contains 0.5 mEq (6 mg) of Mg^{++} . The total dose is individualized and given at 6 to 8 hour intervals. Potassium and prostaglandin inhibitors are usually not needed, although some patients may require potassium salts and/or anti-aldosterone medications such as amiloride or spironolactone to correct and maintain the serum potassium level^[17].

CONCLUSION

In conclusion, hypocalcemia could be considered as a feature of GS. In the absence of surreptitious diuretic intake, laxative abuse and persistent vomiting and diarrhea, the presence of hypomagnesemia, hypokalemic alkalosis, hypokalemia, hypocalcemia and hypocalciuria should raise the possibility of GS.

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