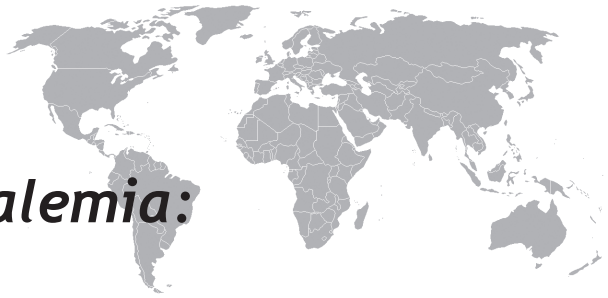

A Rare Cause of Hypokalemia: Gitelman Syndrome

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Eur J Gen Med 2011;8(2):154-6

Received: 05.01.2010

Accepted: 09.03.2010

ABSTRACT

Gitelman syndrome is a rare, inherited disorder. Hypokalemia, metabolic alkalosis, hypomagnesemia and hypocalciuria are the characteristic abnormalities of this syndrome. This syndrome can lead to growth retardation and to rarely serious complications such as paralysis and cardiac arrest. Therefore, early recognition and treatment are important. In this paper we reported a young adulthood with classic Gitelman syndrome. Electrolyte imbalances were resolved with treatment; however, further growth wasn't achieved since the epiphyses of the patients had been closed.

Key words: *Gitelman syndrome, hypokalemia, growth retardation*

Hipokalemini Nadir Bir Nedeni: Gitelman Sendromu

Gitelman sendromu nadir görülen kalıtsal bir hastalıktır. Hipokalemi, metabolik alkaloz, hipomagnezemi ve hipokalsiüri bu sendromda görülen tipik bozukluklardır. Bu sendrom ile birlikte büyüme geriliği ve nadiren de olsa paralizi ve kardiyak arrest gibi şiddetli komplikasyonlar ortaya çıkabilmektedir. Bu nedenle erken tanı ve tedavi önemlidir. Bu yazıda genç bir erişkinde görülen klasik Gitelman sendromunu sunduk. Elektrolit düzensizlikleri tedavi ile düzelmesine rağmen hastanın epifiz plaklarının kapalı olması nedeniyle daha fazla büyüme sağlanamadı.

Anahtar kelimeler: *Gitelman sendromu, hipokalemi, büyüme geriliği*

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INTRODUCTION

Gitelman syndrome (GS) is an inherited, autosomal recessive disorder which was first described by Gitelman et al. in 1966 (1). It is a rare disease, prevalence is uncertain. In a study prevalence of the disease reported as 1.2 cases per million in Sweden (2). Clinical symptoms may include fatigue, cramp, muscle weakness, carpopedal spasms, and rarely may include serious symptoms such as paralysis and sudden cardiac arrest (3-5). Growth retardation can be seen with GS, but not frequent as in Bartter syndrome (6,7). Main characteristics of the syndrome are hypokalemia, metabolic alkalosis, hypomagnesemia and hypocalciuria due to inactivating mutations in thiazide-sensitive sodium chloride cotransporter gene (NCCT) (8-10). Therefore in a case presenting with biochemical and metabolic abnormalities, especially with hypokalemia GS should be taken into consideration. We reported a case of GS with short stature, classical biochemical abnormalities, and symptoms most of which were responsive to the treatment.

CASE

A 19-year-old man was admitted to our clinic with weakness and cramps of all four limbs, and growth retardation. Six months ago he had applied to another hospital with similar complaints, and hypokalemia was detected. He was started on 16 miligram potassium per day. The patient's history was unremarkable for vomiting, diarrhea and diuretic or laxative use. On physical examination his height was 149 cm and weight was 39 kg. Standard deviation (SD) for both were below the 3 SD, arterial blood pressures were 100/60 mmHg. Cardiovascular examination was normal with sinus rhythm and no murmur. Chovstek and Trousseau signs were positive. There was no hematological abnormality. Biochemical work-up showed hypokalemia, hypomagnesemia, and hypochloremia. Serum creatinin and serum urea was 0.87mg/dL (normal range 0.2-1.2) and 16 mg/dL (normal range 10-50), respectively. Glomerular filtration rate was calculated as 71%. Daily urine potassium and magnesium excretion, and fractional excretion of magnesium were high. 24 hours calcium urine excretion was low (Table 1). The patient had metabolic alkalosis: bicarbonate and pH values were 29.4 mmol/dL and 7.46, respectively. Hormonal examination disclosed high supine plasma renin and normal plasma aldosterone levels. Thyroid function test were normal. Pituitary-adrenal and gonadal axis were intact. Cortisol level was suppressed (<1 µg/dL) with 1 mg dexamethasone suppression test. Serum PTH level was normal (Table 1). There was not any finding of gastrointestinal malabsorption: serum vitamin B12 (439.3 pg/mL; normal range 200-900), folic acid (12.2 ng/mL; normal range 3-19.9) and ferritin (167.2; normal range 13-400) levels were normal. Serum anti-gliadin and anti-endomisium antibodies were negative. On radiological examination, there was no finding of chondrocalcinosis in X-ray of the knee. Renal ultrasonography showed no nephrocalcinosis. No lesion or hyperplasia were found on adrenal gland MRI. MRI of hypothalamic-pituitary region was normal. Epiphysial plates were closed, and bone age was similar with the chronological age in the X-ray of the left hand. The final diagnosis was the GS with the evaluation of the all laboratory and clinical data. Potassium chloride (120 mEq/day i.v infusion) and magnesium (300 mg/day) were administered initially. Eventually he was treated with spironolactone 100 mg/day, magnesium 300 mg/day, potassium 16 mg/day, and indomethazine 75 mg/day per oral. Serum potassium level was 4.7 mEq/L at the fifth day of the oral treatment.

DISCUSSION

Causes of hypokalemia can be divided to four main groups; inadequate intake (i.e anorexia nervosa, long-term hunger), gastrointestinal losses (i.e. vomiting, diarrhea), potassium shift from extracellular fluid to intracellular fluid and excess renal losses (11). At the beginning of the evaluation of hypokalemia, pseudohypokalemia, due to the extreme increase in the number of leukocytes, should be eliminated. Leukocyte number was in the normal range in our case. Vomiting, diarrhea, anorexia nervosa, and long-term hunger were not detected. Potassium shift between extra and intra cellular fluid might be related with hypokalemic periodic paralysis, barium ingestion, insulin, vitamin B12 therapy, and thyrotoxicosis. In our case there was no history of medication except potassium intake, and thyroid functions were normal. Urinary excretion of potassium was increased, arterial blood pressure was normal; therefore, we analyzed serum bicarbonate level. Furthermore we detected metabolic alkalosis. As a result we made differential diagnosis of GS and Bartter syndrome.

Bartter syndrome is present in the infancy or early childhood and is related with increased or normal uri-

***Table 1**. Hematological, biochemical and hormonal parameters of the case*

Parameters	*Patient (normal value)*
Leukocyte (x10³/µL)	*7.97 (4.3-10.3)*
Hemoglobin (g/dL)	*17.8 (14-18)*
Platelet (x10³/µL)	*314 (140-420)*
Urea (mg/dL)	*16 (10-50)*
Creatinine (mg/dL)	*0.87 (0.2-1.2)*
Sodium (mEq/L)	*138 (135-150)*
Potassium (mEq/L)	*2.4 (3.5-5.1)*
Chloride (mEq/L)	*93.4 (98-110)*
Calcium (mg/dL)	*9.7 (8.4-10.6)*
Phosphor (mg/dL)	*2.8 (2.3-4.7)*
Magnesium (mg/dL)	*1.4 (1.5-2.6)*
Daily urine calcium (mg)	*29 (100-300)*
Daily urine potassium (mmol)	*90 (40-120)*
Daily urine magnesium (mg)	*81 (10-30)*
FEMg (%)	*7.57 (<2)*
TSH (uIU/mL)	*2.39 (0.27-4.2)*
Free T3 (pg/mL)	*4.55 (1.82-4.62)*
Free T4 (ng/dL)	*1.66 (0.932-1.71)*
ACTH (pg/mL)	*34.3 (10-48)*
Cortisol (ug/dL)	*19.9 (10-23)*
Prolactin (ng/mL)	*15.4 (4.1-18.4)*
FSH (mIU/mL)	*1.21 (1.5-12.4)*
LH (mIU/mL)	*3.75 (1.7-8.6)*
Total testosterone (ng/dL)	*584 (280-1000)*
PTH (pg/mL)	*22.6 (15-65)*
Plasma renin (ng/mL/hour)	*5.5 (0.2-1.6)*
Plasma aldosterone (pg/mL)	*132 (30-160)*

FEMg: fractional excretion of magnesium

nary calcium excretion. Molecular defects are occurred in the ascending limb of loop of Henle in this disorder. Presentation age is late childhood or adult age, and urinary calcium excretion is low in GS (4-6). NCCT gene defects have been found in GS. This gene is located on chromosome 16 and a variety of mutations cause NaCl co-transporter function loss resulting in defective resorption of NaCl at the distal convoluted tubule (5,8). Eventually, resorption of NaCl reduces; so that NaCl concentration increases in the collecting tubule. Elevated sodium level in this lumen leads to mild plasma volume contraction. Reduction of vascular volume activates renin-angiotensin-aldosterone system, and renin activity and aldosterone levels increase. In the cortical collecting tubules, elevated aldosterone level increases reabsorption of sodium and secretion of both potassium and hydrogen ions. Finally, hypokalemia and metabolic alkalosis occur. At the same time the loss of thiazide-sensitive co-transporter function can inhibit reabsorption of Mg via on the apical Na/Mg exchanger in the distal convoluted tubule; so that Mg excretion elevates and hypomagnesemia may develop (5,9,10). Our diagnosis was GS syndrome since the presentation age was higher than Bartter syndrome and urinary calcium excretion decreased. We could not analyze gene defects because of technical incompetence. In our case there was growth retardation, this can be seen in GS. It has been showed that if GS is recognized in early age, growth retardation can be improved with indomethazine treatment (7). However, we diagnosed our case in the late age, and epiphysial plates were closed. Growth progression was not our expectation with the treatment. Therefore, we did not apply growth hormone stimulation tests at that time.

In the conclusion, GS should be taken into consideration in a hypokalemic patient. Early recognition of this syndrome might provide normal growth development and prevent possible serious complications such as paralyses and sudden cardiac arrest.

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