CASE REPORT

In the presence of hypokalemia and hypomagnesemia; remember Gitelman syndrome

Güvercin B[1], Kaynar K[1], Güler Ö[2], Kalyoncu M[3]

[1]Department of Nephrology
[2]Department of Internal Medicine
[3]Department of Pediatric Nephrology
Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

Abstract

Background: Hypokalemia and hypomagnesemia caused due to renal losses with chloride-resistant metabolic alkalosis in normotensive patients should remind clinicians of the rare inherited tubulopathy, Gitelman syndrome. Its diagnosis is further strengthened by the presence of consanguinity and the absence of kaliuretic medications. A definitive diagnosis should be based on genetic testing.

Case report: We present the cases of three asymptomatic adult patients who were genetically (mutation in the *SCL12A3* gene) diagnosed with Gitelman syndrome of different severity and response to therapy in terms of hypokalemia, hypomagnesemia, and metabolic alkalosis.

Conclusion: This lifelong disease could cause life-threatening conditions due to the cardiac complications of hypokalemia in some of the affected patients. Therefore, it is necessary to be aware of the appropriate diagnosis and treatment for patients admitted to the clinic with hypokalemia, hypomagnesemia, hypocalciuria, and hyperreninemia. HIPPOKRATIA 2019, 23(4): 175-178.

Keywords: Adult, diagnosis, Gitelman syndrome

Corresponding author: Prof. Dr. Kubra Kaynar, Karadeniz Teknik Üniversitesi, Tıp Fakültesi, Nefroloji Bilim Dalı, 61080 Trabzon, Turkey, tel: +905422415879, fax: +904623252270, e-mail: kkaynar@yahoo.com

Introduction

Gitelman syndrome (GS) is an autosomal recessively transmitted inherited disorder that affects the renal tubules resulting in hypomagnesemia, hypokalemia, hypocalciuria, and metabolic alkalosis[1,2]. GS is one of the most frequently diagnosed familial tubulopathies with a prevalence of 1/40,000[3]. The majority of patients with GS were found to have the *SLC12A3* gene mutation that caused a defective thiazide-sensitive sodium-chloride cotransporter (NCC)[3]. The clinical manifestations of these genetic mutations are generally observed during adolescence or adulthood[3]. Herein, we discuss three incidentally found asymptomatic cases of hypokalemia and hypomagnesemia.

Case report

Patient one

A 48-year-old female married patient was found to have hypokalemia and hypomagnesemia during the preoperative evaluation of a ganglionic cyst. There was first-degree consanguinity between her parents. She was asymptomatic except for swelling and pain in her wrist. She had no history of medication, causing these electrolyte abnormalities. Her blood pressure was 120/80 mmHg. Results of biochemical tests were as follows: serum creatinine (Cr) level: 0.61 mg/dL, hemoglobin (Hgb): 13.6 g/dL, albumin level: 4.2 g/dL, potassium (K): 3.1 mmol/L, magnesium (Mg): 1.28 mg/dL, venous bicarbonate (HCO_3): 29.6 mmol/L, and creatinine clearance (from a 24-h urine collection): 140 mL/min. Fractional urinary excretion of Mg (FEMg) was calculated as 4.2 % using the following formula:

FEMg =100 × (UrineMg × PlasmaCr) / (0.7 × PlasmaMg × UrineCr)[4]

Urinary K level was 84 mmol/day that indicated renal potassium wasting. Plasma renin activity was high (6.81 ng/mL/h), plasma aldosterone concentration was 102.67 ng/dL, urine calcium/creatinine ratio was 0.04 mg/mg, urinary chloride level was 276 mmol/L, and fractional excretion of chloride (FECl) was 1.3 %. Ultrasonographic examination revealed normal-sized kidneys and echogenicity. Genetic analysis of the patient revealed a homozygous (biallelic) mutation of c.1180+1G>T in the *SCL12A3* gene. Finally, based on these findings, the patient was diagnosed with GS. Magnesium oxide (equivalent to Mg^{+2} ion of 1,095 mg/day) and potassium citrate (equivalent to K^+ ion of 120 mmol/day) were prescribed, and a diet rich in potassium and magnesium was recommended. After nine months, her serum K level was increased to 3.4 mmol/L, Mg level was increased to 1.5 mg/dL, and HCO_3 level was decreased to 27.9 mmol/L even though she did not take the medications regularly due to

reported side effect (diarrhea) (Table 1).

Patient two

A 27-year-old female married asymptomatic patient was noticed to have hypokalemia and hypomagnesemia during a routine follow-up for goiter four years earlier. Her parents were first cousins. She had no history of medicine usage such as diuretics and amphotericin B. Her blood pressure was 90/60 mmHg. Results of her biochemical tests were as follows: serum creatinine level: 0.54 mg/dL, Hgb: 14.4 g/dL, albumin level: 4.8 g/dL, K: 3.2 mmol/L, Mg: 1.26 mg/dL, venous HCO_3: 31.2 mmol/L, urine calcium/creatinine ratio: 0.06 mg/mg, urinary chloride: 227 mmol/L, FECl: 1.3 % and creatinine clearance (from a 24-h urine collection): 109 mL/min. Her FEMg was 10 %[4]. Urinary K level was 51.2 mmol/day indicating renal K wasting. A diagnosis of GS was confirmed based on the genetic analysis of the patient [homozygous (biallelic) mutation of c.938C>T in the *SCL12A3* gene]. Magnesium oxide (equivalent to Mg^{+2} ion of 1,460 mg/day) and potassium citrate (equivalent to K^+ ion of 160 mmol/day) were prescribed to the patient. Oral supplements were not sufficient when she became five months pregnant, and therefore amiloride (10 mg/day) was added. On her last visit, her serum K level was 3.4 mmol/L, and the Mg level was 1.3 mg/dL (Table 1).

Patient three

A 33-year-old asymptomatic female patient was recommended to undergo GS screening because of being the younger sister of patient two. She was found to have hypokalemia (2.7 mmol/L) and hypomagnesemia (1.13 mg/dL). Her blood pressure was normal (102/70 mmHg). Her biochemical test results were as follows: serum creatinine level: 0.55 mg/dL, Hgb: 15 g/dL, albumin level: 4.2 g/dL, venous HCO_3: 27.7 mmol/L, urine calcium/creatinine ratio 0.05 mg/mg, and creatinine clearance (from a 24-h urine collection): 160 mL/min. FEMg level was calculated as 14.3 %[4]. Urinary K level was 117.6 mmol/day. Genetic analysis revealed GS [homozygous (biallelic) mutation of c.938C>T in the *SCL12A3* gene]. She was also prescribed magnesium oxide (equivalent to Mg^{+2} ion of 1,095 mg/day) and potassium citrate (equivalent to K^+ ion of 160 mmol/day) were prescribed, but she denied her disease and refused treatment.

Discussion

The normal renal response to hypokalemia, which is defined as a serum K level of ≤3.5 meq/L, is the decrement of urinary K to levels ≤25-30 mmol/day or a spot urine potassium/creatinine ratio ≤18 mmol/g[2,4]. In normotensive patients with metabolic alkalosis, it is important to consider urinary chloride concentration to discriminate chloride-unresponsive (urine chloride >20 mmol/L, FECl >0.5 %) diseases such as GS[2]. High FEMg levels (³4%) in patients with hypomagnesemia indicate renal magnesium wasting[4]. These patients should be evaluated for genetically transmitted tubulopathies such as GS and Bartter syndrome in the absence of a history of medications (such as amphotericin B, aminoglycosides, diuretics, cisplatin, calcineurin inhibitors, and digoxin), alcoholism, and diabetes mellitus[2,5]. Therefore, GS or Bartter syndrome should be considered when normotensive patients have chloride-resistant metabolic alkalosis, hypokalemia, and hypomagnesemia caused due to renal wasting with hyperaldosteronism caused by high plasma renin activity due to chronic volume depletion[2]. Bartter syndrome is phenotypically classified into classic and neonatal forms. Severe polyhydramnios, prematurity, growth retardation, and hearing loss have been detected in antenatal (neonatal) Bartter syndrome. Although hypomagnesemia and hypocalciuria are mostly found in patients with GS, some

Table 1: Clinical and laboratory findings of the three asymptomatic adult patients diagnosed with Gitelman syndrome.

Parameter	Patient one	Patient two	Patient three
Age (years)	48	27	33
Gender	female	female	female
Complaint	none	none	none
Family history	absent	present	present
Consanguinity between parents	present	present	present
Blood pressure (mmHg)	120/80	90/60	102/70
Serum potassium level (mmol/L)	3.1 / 3.4	3.2 / 3.4	2.7 / -
Serum Mg level (mg/dL)	1.28 / 1.5	1.26 / 1.3	1.13 / -
Serum HCO3 level (mmol/L)	29.6 / 27.9	31.2 / -	27.7 / -
Pregnancy outcomes	Two healthy children	Expecting first baby	Single, zero gravidity
Urine chloride level (mmol/L) / FECl (%)	276 / 1.3	227 / 1.3	-
Urine potassium level (mmol/day)	84	51.2	117.6
Urinary calcium:creatinine ratio (mg/mg)	0.04	0.06	0.05
FEMg (%)	4.2	10	14.3
Diagnosis based on	*SLC12A3* gene mutation	*SLC12A3* gene mutation	*SLC12A3* gene mutation

Reported Serum potassium, magnesium, and serum bicarbonate levels are at diagnosis / last visit, Mg: magnesium, HCO3: bicarbonate, FECl: Fractional urinary excretion of chloride, FEMg: Fractional urinary excretion of magnesium.

forms of Bartter syndrome may also have similar manifestations. The discrimination of these salt-losing inherited tubulopathies depends on the genetic analysis (Table 2)[6,7]. Hence, biallelic inactivating *SLC12A3* mutations should be identified for confirming clinically suspected cases of GS[2]. Oral potassium and magnesium supplementations are the cornerstones of treatment in GS aiming the target blood levels of 3 meq/L for potassium and 1.46 mg/dL for magnesium[2]. For resistant cases, potassium-sparing diuretics such as amiloride, spironolactone, and eplerenone could be added to therapy.

Herein, we have described three cases of patients diagnosed with GS in their second and fourth decades of life (Table 1). The average age at GS diagnosis has been reported to be 31 years (range: 0.3-80 years)[8]. Although the mode of inheritance of GS is autosomal recessive, the female gender's predominance is documented at a ratio of 63 %[8]. Similarly, all our cases were females. The serum K level at presentation differed from one patient to another. In the literature, 34 % of cases were reported to have very low serum K levels (<2.5 mmol/L), whereas 47 % of cases had serum K levels of 2.5-3 mmol/L. Consistent with these different serum K levels, two of our cases had K >3.0 mmol/L, and the other patient had a serum K level of 2.7 mmol/L. In a recent study, 16 % of reported patients with GS had normal serum Mg levels (1.7-2.4 mg/dL), 5 % had high serum Mg levels, and 57 % had low Mg levels[8]. All of our patients had low Mg levels. With potassium supplements, all our patients achieved the target potassium level of 3 mmol/L. However, due to the side effects of magnesium-containing supplements such as diarrhea, the patients could not tolerate these drugs. Hence, only one of our patients achieved the target magnesium level of 1.46 mg/dL because of intolerance to medication.

The outcome of pregnancy in patients with GS during gestation and labor is generally favorable under close control of electrolyte replacement[2]. As the rate of decrease in serum potassium levels is more important than the absolute level of serum potassium, patients with GS do not have serious cardiac arrhythmias such as long QT interval, bradycardia, atrioventricular block, ventricular fibrillation, and rhabdomyolysis unless severe hypokalemia exists[9,10]. One of our patients had a healthy gestational period and labor. None of our patients had any cardiac complications.

Therefore, GS is mostly a benign, hypokalemic, hypomagnesemic genetic disease[8]. A wide variation exists in its clinical spectrum, ranging from incidental diagnosis to severe symptoms[2]. Caution is needed to prevent the deleterious complications of hypokalemia and hypomagnesemia. The definitive diagnosis should be based on genetic testing with suspicion when renal potassium and magnesium wasting and chloride-resistant metabolic alkalosis with hypocalciuria are present. Based on our cases, we intend to emphasize and remind the approach for patients with renal hypokalemia, which ends up with a diagnosis of GS (Figure 1)[2,4,11]. For populations where consanguineous marriages are common, it is necessary to focus on GS as the majority of cases are asymptomatic with respect to hypokalemia.

Conflict of interest

Authors declare no conflict of interest.

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Table 2: Genetic and clinical features of Bartter syndrome subtypes and Gitelman syndrome.

Feature	Bartter syndrome		Gitelman syndrome
	Neonatal	Classic	
Age at onset	Neonatal period	Infancy/childhood	Childhood/adulthood
Gene affected	*SLC12A1* *KCNJ1* *BSND* *CLCNKA* *CLCNKB* *MAGED2*	*CLCNKB*	*SLC12A3*
Maternal hydramnios	Common	Rare	Absent
Polyuria/polydipsia	Marked	Present	Rare
Growth retardation	Present	Present	Absent
Urinary calcium	Very high	Normal or high	Low
Serum magnesium	Normal	Occasionally low	low

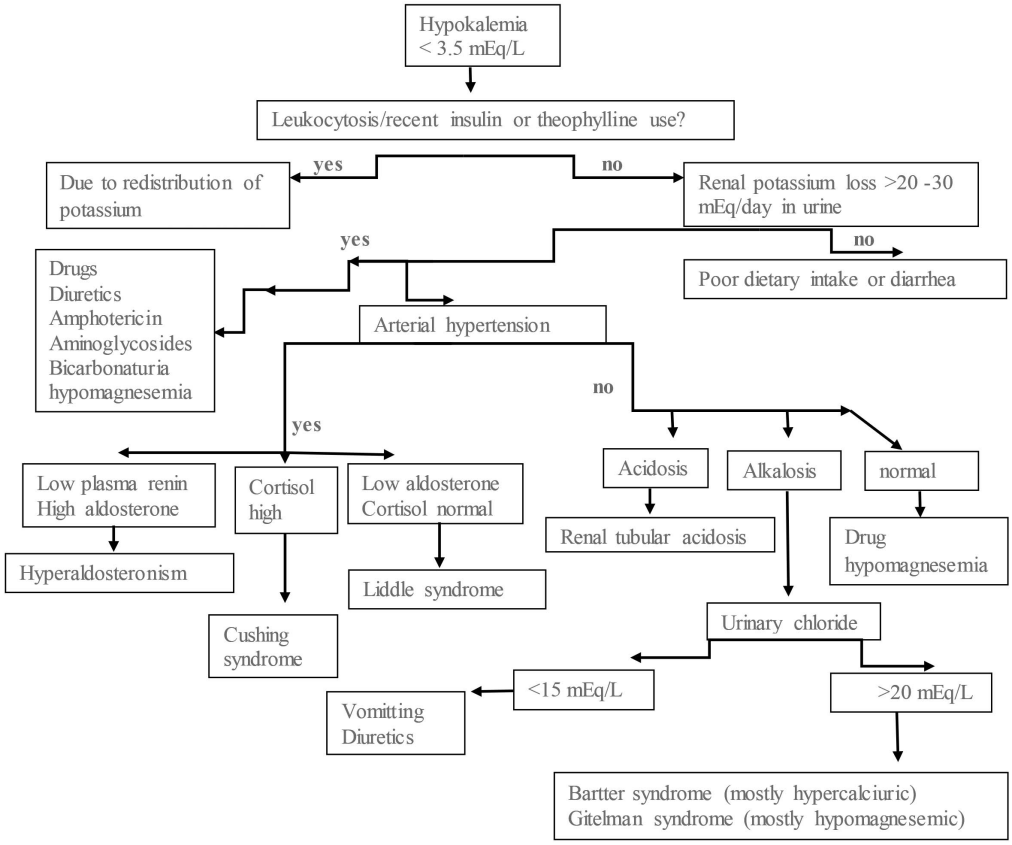

Figure 1: The diagnostic approach for investigating the etiology of hypokalemia.

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