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Case Report

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Proximal Weakness and Hypokalemia in a Pregnant Woman: The First Presentation of Gitelman Syndrome

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ABSTRACT

Gitelman syndrome is an inherited disorder of kidney function characterized by hypokalemia, hypomagnesemia, and hypocalciuria. Its first presentation during pregnancy might be a challenging diagnostic and management issue, as there is little data available in the medical literature. Here we report a 26-year-old pregnant woman who was diagnosed with Gitelman syndrome for the first time during her second trimester of pregnancy. Refractory hypokalemia in the 18th week of pregnancy was treated with eplerenone. The pregnancy outcome was favorable both for the mother and neonate.

Introduction

Gitelman Syndrome (GS) is an autosomal recessive tubulopathy characterized by hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria. It can be differentiated from Bartter syndrome based on hypocalciuria and hypomagnesemia. GS is caused by inactivating mutations in the solute carrier family 12 member 3 (SLC12A3) gene on chromosome 16 (16q13) that encodes the thiazide-sensitive NaCl co-transporter in the distal convoluted tubule [1]. The prevalence of GS is about 1:40000 in the general population, which makes it the most common inherited renal tubular disorder. About 1% of the Caucasian population are heterozygote for this muta-

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tion [2]. The clinical picture of GS includes salt craving, muscle weakness, cramps, abdominal pain, paresthesia, nocturia, and polyuria [3]. Pregnancy can aggravate hypokalemia or other symptoms of GS, and the first presentation of this syndrome can be manifested during pregnancy. Management of Gitelman syndrome in pregnancy has not been well established, and there is no specific guideline for the correction of hypokalemia and hypomagnesemia in this specific situation.

Case Reports

In January 2017, a 26 years old woman who was in the 17th week of her first pregnancy was admitted to the emergency department of Imam Khomeini Hospital Complex, Tehran, Iran. She was complaining of proximal weakness, epigastric pain, unspecific upper limb pain, and constipation. Her symptoms developed about 12 days before admission. She also reported gestational diabetes mellitus, previous history of asthma, and a positive family history of Gitelman syndrome. Her brother was clinically diagnosed with GS a few years ago. She was using insulin, folic acid, and iron supplements. Salmeterol and fluticasone propionate spray were stopped one month ago. Physical examination revealed a pulse rate of 110 beats/min with a regular rhythm, a blood pressure of 110/75 mm Hg, and a respiratory rate of 15 breaths/min. Physical examination was otherwise unremarkable. Lab tests showed serum potassium 2.2 mEq/L (normal range 3.5-5 mEq/L), serum magnesium 1.3 mg/dL (normal range 1.6-2.6 mEq/L) and corrected serum calcium 10.2 mg/dL (normal range 8.6-10.2 mg/dL). Examination of Venous Blood Gases (VBG) showed mild metabolic alkalosis. Other routine laboratory test results are presented in Table 1.

Her ECG showed flattening of T waves, presence of U waves, and prolongation of QU interval (corrected QU interval 588 ms); classical findings of hypokalemia that mandates emergency correction of potassium level. Therapy with isotonic saline, intravenous KCl, and magnesium sulfate was initiated. On the following day, the patient's ECG became normal, but her potassium level was still low (serum K+ 2.7 mEq/L). Fetal and renal ultrasounds were unremarkable (fetal heart rate of 150 beats/min). The patient's random urine potassium and creatinine concentrations were 33 mEq/L and 25 mg/dL, respectively. During hospitalization, the patient received 40 mL of intravenous 15% KCl, oral potassium chloride supplement, and 20 mL of intravenous 20% magnesium sulfate daily. Her symptoms resolved gradually; serum potassium and magnesium levels remained within the range of 2.9-4.1 mEq/L and 1.2-2.0 mg/dL, respectively. A 24-hour urine analysis showed a daily excretion of 148 mEq/24 h for potassium (25-125 mEq/24 h), 445 mEq/24 h for sodium (40-220 mEq/24h) and 136 mg/24 h for calcium (≤ 250 mg/24 h). Concerning the refractory hypokalemia and hypomagnesemia, we decided to administer a potassium-sparing diuretic. Some trials have compared the effectiveness of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Angiotensin-Converting Enzyme Inhibitors (ACEI), and Angiotensin Receptor Blockers (ARBs) in elevating serum potassium level. NSAIDs have shown promising results [4, 5]; however, due to possible Gastrointestinal (GI) complications and risk of renal insufficiency, induced hypertension, and premature closure of the ductus arteriosus, we did not consider using NSAIDs as the first-line medication. Instead, eplerenone, an aldosterone receptor antagonist and category B drug during pregnancy, was chosen [6].

Its' affinity for androgen and progesterone receptors are respectively 0.1% and 1% compared with those of spironolactone, which makes it a better option in resistant GS [7]. Therefore, eight days after admission, eplerenone, 25-mg tablets BID, and oral magnesium oxide supplement were started. Finally, after 14 days of hospitalization, she was discharged with the following medications: Eplerenone 50 mg BID, magnesium oxide 300 mg daily, metformin 500 mg BID, oral potassium supplement, folic acid, and iron tablets. The patient's final serum potassium and magnesium values were 3.6 mEq/L and 1.9 mg/dL, respectively. She was advised to check her serum potassium level weekly and consume high potassium diet. Due to eplerenone-induced hypotension and GI intolerance of KCl tablets; it was difficult to keep her serum potassium between 3-4 mEq/L, although the rest of her gestation was without major problem.

The patient underwent a Cesarean section (C-section) at the 39th week of pregnancy. The neonate weighed 2832 g, without any congenital anomaly or electrolyte disturbances. Her medications were continued after delivery. Serum values of potassium, before, during, and after C-section, were 3.6 mEq/L, 3 mEq/L, and 4 mEq/L, respectively. She was hospitalized for 7 days after delivery and discharged with oral potassium and magnesium supplements, and 25-mg eplerenone tablets BID.

Discussion

There are several differential diagnoses for chronic hypokalemia, such as consumption of licorice, diuretics or xanthines, chronic diarrhea, chronic vomiting, medications (carbenicillin, amphotericin, ifosfamide, foscarnet,

Table 1. Laboratory results of patients' first admission to the hospital

Parameter	Patient's Value	Normal Range
Blood		
Hemoglobin (g/dL)	11.2	12-16
Red-cell count (million/mm^3)	3.78	4.2-5.8
White-cell count (x1000/mm^3)	7.5	4.1-10.1
Platelet count (x1000/mm^3)	207	150-400
Mean corpuscular volume (fL)	81	77-94
Serum sodium (mEq/L)	135	135-145
Serum potassium (mEq/L)	2.2	3.5-5
Serum magnesium (mg/dL)	1.3	1.6-2.6
Serum corrected calcium (mg/dL)	10.2	8.6-10.2
Serum phosphorus (mg/dL)	3.7	2.5-4.5
Serum chloride (mEq/L)	114	98-107
Serum urea (mg/dL)	36	15-47
Serum creatinine (mg/dL)	0.8	0.6-1.3 for female
Serum albumin (g/dL)	4	3.5-5.2
Aspartate aminotransferase (U/L)	18	<31
Alanine aminotransferase (U/L)	13	<31
Alkaline phosphatase (U/L)	122	64-306
Total bilirubin (mg/dL)	0.8	0.1-1.2
Direct bilirubin (mg/dL)	0.2	<0.3
C-reactive protein, quantitative (mg/L)	11	<8
Erythrocyte sedimentation rate (mm/h)	28	<20 for female
TSH (mIU/L)	0.5	0.3-5
T3 (ng/dL)	124	80-174
T4 (µg/dL)	7.9	4.5-12.5
Serum pH	7.47	7.35-7.45
HCO_3- (mmol/L)	31.5	22-26
pCO_2 (mm Hg)	46	35-45
INR	1.05	1-1.4
HbS antigen	Non-reactive	
Anti HCV	Non-reactive	
Urine specific gravity	1008	
Urine pH	7	
Urine nitrite	Negative	
Urine protein	Negative	
Random urine potassium (mEq/L)	33	
Random urine creatinine (mg/dL)	25	
Urine volume 24 h (mL)	3200	
Urine protein (mg/24 h)	135	<150
Urine sodium (mEq/24 h)	445	40-220
Urine potassium (mEq/24 h)	148	25-125
Urine calcium (mg/24 h)	136	<250
Urine creatinine (mg/24 h)	1256	600-1700

insulin, β2-adrenergic agonists, barium, etc.), primary and secondary hyperaldosteronism, renal tubular acidosis, familial hypokalemic periodic paralysis, thyrotoxic periodic paralysis, Cushing syndrome, congenital adrenal hyperplasia, Liddle syndrome, Bartter syndrome, and Gitelman syndrome. Hypomagnesemia per se may cause refractory hypokalemia, mandating prompt assessment, and correction.

The first step in the evaluation of hypokalemia is the assessment of the daily urinary potassium excretion. If this level is higher than 15-20 mEq/d, extra-renal causes of hypokalemia are not the usual culprits [8]. The next step is the evaluation of the intravascular volume and blood pressure. If the patient has hypertension, further workup to assess the concentration of renin and or aldosterone should be done to differentiate the underlying cause (e.g. renal artery stenosis, congenital adrenal hyperplasia). On the other hand, if the patient is hypo/euvolemic, then the acid-base state can confine differential diagnosis, as patients with acidosis might have renal tubular acidosis, and those with alkalosis might have Bartter or Gitelman syndrome or be a diuretic abuser [9].

Gitelman syndrome usually manifests in late childhood (older than 6 years) or adolescence, and even some of the patients might be asymptomatic all their life [2]. The most common symptoms of GS include salt craving, musculoskeletal symptoms such as weakness, cramps, carpopedal spasms, paralysis, tetany, nocturia, polyuria, polydipsia, blurred vision, episodic abdominal pain, constipation and constitutional symptoms like fatigue, dizziness, and lethargy. Older patients may develop chondrocalcinosis, presented by articular pain and swelling [3].

Since sodium and chloride reabsorption is impaired in the distal tubules of affected kidneys, the flow rate in cortical collecting ducts is increased, which results in a higher excretion rate of potassium. Besides, mild secondary hyperreninemic hyperaldosteronism, in response to hypovolemia, exacerbates the hypokalemia and metabolic alkalosis. Several unproven theories are discussing the mechanism of hypocalciuria and hypomagnesemia in GS [10, 11].

Talaulikar et al. have shown that potassium requirements during pregnancy in patients with GS might increase to even six-fold than normal [12]. Despite the increment in glomerular filtration rate and activity of the renin-angiotensin-aldosterone axis, hypokalemia usually does not occur during pregnancy of healthy individuals, probably due to the overproduction of progesterone and resulted from refractoriness to angiotensin II [13]. These regulatory mechanisms became defective during pregnancy in GS patients. As a result, the clinical picture of GS exacerbates during pregnancy, as with our case, which was asymptomatic until the second trimester.

The diagnosis of Gitelman syndrome is mostly clinical. As mentioned earlier, our patient had almost all the necessary clinical criteria for the diagnosis of GS. The most important differential diagnosis is classic Bartter syndrome (cBS), which might be clinically indistinguishable from GS. However, cBS usually presents early in childhood and have more serious consequences than GS. Thyrotoxic periodic paralysis was ruled out due to the normal thyroid function tests. The patient denied any laxative, diuretic, licorice, or caffeine abuse. Persistent hypokalemia during hospitalization proved her claim and ruled out some other possible causes, including chronic vomiting and eating disorders.

The patient was using insulin since the first days of her pregnancy. While insulin can cause hypokalemia, it is usually seen with high doses, and hypokalemia is not severe. Nevertheless, insulin was discontinued, and metformin was started. Definite diagnosis of GS rests on genetic testing [5]. Despite the rapid progress of genetic testing, it is still too expensive in developing countries. Our patient did not accept genetic testing because of the cost. However, due to the classical clinical picture and positive family history of GS, the diagnosis was quite clear.

Treatment of GS is mainly based on lifelong oral potassium and or magnesium supplementation. Large doses of such medications can result in serious side effects, including the mouth and gastric ulcers, flatulence, vomiting, diarrhea, and dyspepsia, making the complete correction of electrolyte disturbance challenging [5]. For refractory cases that are symptomatic, a trial of treatment with NSAIDs, angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, or aldosterone antagonists might be helpful, as discussed earlier [5]. Hypovolemia and orthostatic hypotension are serious side effects of potassium-sparing diuretics, which necessitates close monitoring, especially during pregnancy because of increased risk of oligohydramnios. Correction of potassium and magnesium levels during pregnancy might be challenging. Several studies have shown no need for complete correction and even a low level as 3 mEq/L of potassium and 1.46 mg/dL of magnesium will result in a favorable outcome for both the mother and her fetus [5, 14].

The most common obstetric complications associated with GS are intrauterine growth restriction IUGR, oligohydramnios, and increased risk of miscarriage [15]. Fortunately, the pregnancy course of our patient was excellent, and her neonate weight was 2832 g with no sign of feminization.

Ethical Considerations

Compliance with ethical guidelines

The written informed consent was taken from the patient and also the anonymity of the patient was considered.

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Conflict of interest

The authors declared no conflict of interest.

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