A rare cause of rhabdomyolysis: Gitelman syndrome

Yaşar Yildirim, Ali Veysel Kara, Zulfikar Yilmaz, Erdal Bodakci, Vehbi Demircan, Ali Kemal Kadiroglu, Mehmet Emin Yilmaz

ABSTRACT

Introduction: Gitelman syndrome is a rare and autosomal recessive disorder characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, hypocalciuria and hypertension. A careful history, physical examination and determination of urine chloride concentration are important for diagnosis. In this case report, we discuss a patient with hypokalemia and rhabdomyolysis which is diagnosed as Gitelman syndrome.

Case Report: A patient with sudden loss of sensation in the arms and legs and difficulty in the moving admitted to the emergency service. She had intermittent weakness in the extremities and chronic fatigue complaints over the last ten years. In her laboratory examination, serum potassium level, serum creatinine level and creatine kinase level were found 1.4 mEq/L, 1.58 mg/dl and >4260, respectively. The patient was transferred to our clinic due to hypokalemia etiology. She was diagnosed as Gitelman syndrome after a detailed medical history, physical examination and laboratory evaluation. Central venous catheter was opened and vigorous potassium chloride replacement was made. Patient's symptoms and muscle enzymes were improved with potassium replacement. Oral potassium citrate, spironolactone, magnesium citrate was started in addition to intravenous potassium chloride after the patient was diagnosed as Gitelman syndrome. After that, clinical and laboratory findings of the patient were improved progressively and patient was discharged with normal laboratory findings.

Conclusion: As a result; Gitelman syndrome should be thought in the differential diagnosis of hypokalemic rhabdomyolysis although it is a rare disease.

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CASE REPORT

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laboratory evaluation. Central venous catheter was opened and vigorous potassium chloride replacement was made. Patient's symptoms and muscle enzymes were improved with potassium replacement. Oral potassium citrate, spironolactone, magnesium citrate was started in addition to intravenous potassium chloride after the patient was diagnosed as Gitelman syndrome. After that, clinical and laboratory findings of the patient were improved progressively and patient was discharged with normal laboratory findings. **Conclusion:** As a result; Gitelman syndrome should be thought in the differential diagnosis of hypokalemic rhabdomyolysis although it is a rare disease.

Keywords: Gitelman syndrome, Hypokalemia, Rhabdomyolysis, Sensation loss, Weakness

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INTRODUCTION

Gitelman syndrome is a rare and autosomal recessive disorder characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, hypocalciuria and hypertension [1, 2]. The prevalence of Gitelman syndrome was 1 in 40,000. It is one of the most frequent inherited renal tubular disorders [3]. Genetic mutations that responsible for disease affect the NaCl co-transporter in the distal tubule [4, 5]. Clinical manifestations such

as cramps of the arms and legs which are observed in nearly all patients and may be due to hypokalemia and hypomagnesemia, polyuria due to salt and water loss, fatigue due to renal salt wasting can be develop in the most of patients [1, 2]. Growth retardation may be seen rarely [6]. Other causes of hypokalemia and metabolic alkalosis especially vomiting and diuretic usage must be excluded before the diagnosis of Gitelman syndrome. A careful history, physical examination and determination of urine chloride concentration are important for diagnosis. Genetic testing is important for diagnosis but not widely used. In this case report, we discuss a patient with hypokalemia and rhabdomyolysis which is diagnosed as Gitelman syndrome.

CASE REPORT

A patient with sudden loss of sensation in the arms and legs and difficulty in the moving admitted to the emergency service. He had intermittent weakness in the extremities and chronic fatigue complaints over the last ten years. In her laboratory examination, serum potassium level, serum creatinine level and creatine kinase level were found 1.4 mmol/L (3.5–5.5 mmol/L), 1.58 mg/dl (0.5–1.4 mg/dl) and >4260 U/l (40–165 U/l), respectively. She was hospitalized and intravenous and oral potassium replacement was made during 2 days. However, there was no increase in potassium levels. She was transferred to our clinic due to hypokalemia etiology. At the time of admission; she had no nausea, vomiting and diarrhea. There was no diuretic and laxative usage in the patient medical history. Physical examination, electrocardiography (normal QT interval), echocardiography and X-ray lung graphy of the patient revealed no abnormal finding. On abdominal ultrasonography; bilateral kidney size were at the upper limit and renal parenchymal echo were grade 1. Laboratory findings of the patient are given in Table 1. Central venous catheter was opened and vigorous potassium chloride replacement was made (50 mEq in 1000 ml normal saline, 3000 ml/day). There was no usage of drugs which can cause transcellular shift such as insulin, and β_2 adrenergic agonists, and thyroid functions were normal. We detected urine potassium level to differentiate renal and extrarenal losses. Urine potassium were detected 30 mmol/l and 35 mmol/l (normally <15 mmol/l) in repeated tests. Transtubular potassium gradient (TTPG) was 8 (>4 are significant). So, we thought increased distal potassium secretion. Causes which complicated with hypertension such as Cushing syndrome, Liddle syndrome, licorice ingestion, renal artery stenosis were ruled out due to patient was normotensive and she had central venous pressure of 4 cm H₂O. Renal tubular acidosis was also ruled out due to metabolic alkalosis. Urine chloride level was 88 mmol/l. So, there were four main causes to explain hypokalemic metabolic alkalosis and elevated urine chloride level. These were thiazide

Table 1: Laboratory values of the patient at admission

Parameters	Patient (normal value)
Creatinine (mg/dl)	1.58 (0.5–1.4)
Urea (mg/dl)	64 (10–45)
Sodium (mEq/l)	139 (136–145)
Potassium (mmol/l)	1.8 (3.5–5.1)
Magnesium (mg/dl)	1.1 (1.5–2.6)
Calcium (mg/dl)	8.4 (8.4–10.2)
Daily urine calcium (mg)	34 (100–300)
Creatine kinase (U/l)	>4267 (40–165)
Lactate dehydrogenase (U/l)	896 (125–243)
Supine plasma renin (ng/mL/h)	195.6 (0.2–1.6)
Supine plasma aldosterone (pg/ml)	132.55 (30–160)
TSH (uUI/ml)	4.1 (0.27–4.2)
ACTH (pg/ml)	38 (10–48)
PTH (pg/ml)	83 (15–65)
25-OH-Vit D (ug/l)	20.69 (10–60)

and loop diuretic usage, Bartter syndrome and Gitelman syndrome. We ruled out Bartter syndrome because there were hypomagnesemia, hypocalciuria and urine calcium creatinine ratio <0.1. Hypomagnesemia, hypocalciuria, hypokalemia, metabolic alkalosis and high plasma renin activity (195.6 ng/ml/hour) was detected and patient was diagnosed as Gitelman syndrome. Patient's symptoms and muscle enzymes were improved with potassium replacement (120 mEq/day intravenous infusion in 3000 ml/day saline). Oral potassium citrate, spironolactone, magnesium citrate was started in addition to intravenous potassium chloride after the patient was diagnosed as Gitelman syndrome. After that, clinical and laboratory findings of the patient were improved progressively and patient was discharged with normal laboratory findings.

DISCUSSION

Firstly described by Gitelman et al. in three adult patient who had intermittent episodes of muscle weakness and tetany with hypokalemia, hypomagnesemia and hypocalciuria. Gitelman syndrome is now a well-known inherited disorder of renal tubules. The primary pathology in this syndrome is in the renal tubular transport mechanism which caused by mutations in the gene coding for the thiazide-sensitive Na-Cl transporter in the distal tubule [7, 8]. Therefore, physical examination and laboratory findings in this syndrome such as

volume contraction, reduced blood pressure, increased renin activity, hypokalemia, hypomagnesemia and hypocalciuria are consistent with the persistent thiazide diuretic action and exclusion of diuretic usage and other conditions which cause hypokalemia and metabolic alkalosis with a normal or low blood pressure are very important for differential diagnosis. Bartter syndrome is the most important genetic disorder to consider in the differential diagnosis of Gitelman syndrome. Twenty-four hour urine calcium creatinine ratio is useful diagnostic marker to differentiate these two syndromes. Bettinelli et al. showed Bartter and Gitelman syndrome are easily distinguished on the basis of urinary calcium [9]. In Gitelman syndrome there is hypocalciuria, a low ratio of calcium to creatinine in 24 hour urine collection. Primary aldosteronism, which is another cause of hypokalemia and metabolic alkalosis, is usually not in the differential diagnosis since affected patients tend to be hypertensive and have a low plasma renin activity in contrast to elevated values in Bartter and Gitelman syndromes and with vomiting or diuretic use.

In contrast to Bartter syndrome, which is usually diagnosed in infancy or early childhood, Gitelman usually does not affect growth and typically presents in late childhood to adulthood although presentation in infancy has been described [10]. It commonly presents with cramps of the arms and legs, fatigue, ranging from mild to severe, seizures, polyuria and nocturia, chondrocalcinosis, growth retardation if presents younger, and surprisingly hypertension later in life which may be due to prolonged exposure to elevated renin and aldosterone levels [11]. Prolonged Qtc and arrhythmias with resultant palpitations and/or syncope has been estimated to occur in half of affected patients [12]. The prognosis of Gitelman syndrome is generally good, but a few patients with severe hypokalemia especially joined with severe hypomagnesemia and alkalosis may be at risk of developing life-threatening cardiac arrhythmias. Therefore, a detailed cardiac assessment is very important to identify patients at risk of malignant arrhythmias.

The tubular defects in Gitelman syndrome cannot be corrected. As a result, treatment, which must be life-long, is aimed at minimizing the effects of the secondary increases in renin, and aldosterone production and at correcting the volume deficit and electrolyte abnormalities. Potassium replacement, correction of hypomagnesemia, potassium sparing diuretics such as amiloride, triamterene and spironolactone can be used. Angiotensin converting enzyme inhibitors can also be used for hypokalemia control [12]. Correction of hypokalemia may need large amount of potassium especially in the form of potassium chloride due to better absorption (up to 500 mEq/d) [13]. Potassium-sparing diuretics amiloride (5–10 mg/day) and spironolactone (200–300 mg/day) can be used but in hypotensive patients, these drugs should be used cautiously [14]. Hypomagnesemia can contribute the urinary potassium loss. High doses, which are often difficult to tolerate (e.g.,

diarrhea with magnesium), are required to achieve a substantial elevation in serum potassium or magnesium. Non-steroidal anti-inflammatory drugs are not generally useful in Gitelman syndrome due to normal prostaglandin levels unlike Bartter syndrome.

In the light of above knowledge, patient was diagnosed as Gitelman syndrome. She had acute kidney injury due to hypokalemic rhabdomyolysis. All needed treatments were made as mentioned above and patient was discharged with improved symptoms and normal kidney functions

CONCLUSION

Gitelman syndrome should be thought in the differential diagnosis of hypokalemic rhabdomyolysis although it is a rare disease.

Author Contributions

Yasar Yildirim – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Ali Veysel Kara – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Zulfikar Yilmaz – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Erdal Bodakei – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Vehbi Demircan – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Ali Kemal Kadiroglu – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Mehmet Emin Yilmaz – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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