

## Case Reports

# A Rare Case of Hypokalemia Induced Rhabdomyolysis Secondary to Gitelman Syndrome: An Easily Overlooked Inherited Tubulopathy

Richmond Ronald Gomes<sup>1</sup>, Diapankar Kumar Basak<sup>2</sup>, Akmat Ali<sup>3</sup>

### Abstract:

*Hypokalemia is a common clinical problem in endocrinologists' and nephrologists' practice. There are many obvious causes of hypokalemia such as diarrhea, vomiting or diuretics abuse. Other causes such as tubulopathies are rarely observed and their diagnosis is more challenging. There are many inherited and acquired tubulopathies causing hypokalemia, sometimes severe and life-threatening. We report a case of a middle aged female patient who presented with weakness of upper and lower limbs, muscle pain and oliguria. On evaluation, she had hypokalemia, hypomagnesemia, metabolic alkalosis and hypocalciuria and diagnosis of Gitelman syndrome was established. In addition, she had acute kidney injury (AKI) due to rhabdomyolysis secondary to hypokalemia. A short review on the etiology, pathogenesis and management of Gitelman syndrome is presented.*

**Key Words:** Hypokalemia, hypomagnesemia, hypocalciuria, tubulopathies, acute kidney injury (AKI), oliguria



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### Introduction:

Hypokalaemia is a frequent electrolyte disturbance, particularly in hospitalized patients. In most cases of chronic hypokalaemia, the cause is straightforward, usually resulting from unreplenished gastrointestinal or urinary losses. Gitelman syndrome (GS) is an autosomal recessive salt-losing renal tubulopathy that causes hypokalaemia and metabolic alkalosis<sup>1</sup>. It is caused by the mutation of *SLC12A3* gene. *SLC12A3* gene encodes the thiazide-sensitive transporter NCCT (sodium chloride co transporter). NCCT is located in the distal convoluted tubular cells (DCC), which are responsible for 7–10% of tubular electrolyte absorption<sup>2</sup>. The most severe laboratory abnormalities found in GS are hypokalemia and hypomagnesaemia caused by

renal K<sup>+</sup> and Mg<sup>2+</sup> wasting. Other typical changes are metabolic alkalosis, hypocalciuria and hyperreninemic hyperaldosteronism<sup>3</sup>. Mild to moderate hypophosphatemia is frequently observed<sup>4</sup>. Severe hypophosphatemia with severe hyponatremia was also reported<sup>5,6</sup>. Most asymptomatic patients remain untreated and undergo ambulatory monitoring with low frequency. Progression to renal insufficiency is extremely rare<sup>7</sup>.

### Case Report:

A 54-year-old pleasant was admitted to the Ad-din Women's Medical College and Hospital on 30<sup>th</sup> June, 2019 with the complaints of generalized weakness, fatigue for 2 months, vomiting, muscle pain and reduced urinary output for 5 days. Patient was hypertensive and was getting combination of amlodipine and olmesartan. Patient was not on diuretic therapy and no history of diuretics intake. There was no history of exacerbation of weakness by exertion or after heavy carbohydrate meal. Her younger sister had similar illness and there was no history of parental consanguinity. The patient's history revealed recurrent incidence of hypokalemia (the lowest value 2.1mmol/l) observed for

1. Associate Professor, Medicine, Ad-din Women's Medical College and Hospital, Dhaka
2. Associate Consultant, Medicine, Square Hospitals Limited
3. Associate Professor, Hepatology, Ad-din Women's Medical College and Hospital, Dhaka

**Corresponding author:** Dr. Richmond Ronald Gomes, Associate Professor, Medicine, Ad-din Women's Medical College and Hospital, Dhaka, E-mail: rrichi.dmc.k56@gmail.com

which she was admitted into local hospital without any confirmatory diagnosis.

On examination, the blood pressure was 160/96 mmHg and pulse rate was 78 per minute. There was neither neurological deficit nor proximal muscle weakness. ECG showed ischemic changes. Laboratory investigations showed following results- CBC – mild microcytic hypochromic anemia with Hb% 9.5 gm/dl, MCV 74.1 fL, MCH 23.4 pg, normal TC of WBC with normal differentials, normal platelet count. Serum potassium 2.66 mEq/L (Normal range 3.5-5 mEq/L), serum sodium-114mEq (136-145 mEq)(Possibly vomiting induced), serum chloride-76 mEq/L (96-106 mEq), serum bicarbonate 31 mEq/L(24-28), serum magnesium- 0.18 mmol/L (0.66-1.0 mmol/L), serum urea-38 mg/dl, serum creatinine-2.68 mg/dl(normal 0.3 -1.4 mg/dl), blood pH-7.58 (7.35-7.45), CPK was 561 U/L(normal 24-195U/L). Corrected serum calcium was 7.63 mg/dl(normal 8.5-10.5 mg/dl).The urinary calcium was subnormal at 76 mg/24 hour (100-300 mg/day). Urine sodium is 182 mmol/24 hour (40-220 mmols), urine potassium 33 mmols/24 hour (25-125 mmols). Urine specific gravity, urinary pH (7.0) and urine osmolality (165 mOsm/kg) were normal. Thyroid function tests (FT3, FT4, TSH) and serum cortisol levels were normal. Ultrasound of the abdomen did not reveal any abnormality. Hormonal tests to exclude Conn's disease were performed, and did not reveal any abnormalities in adrenal glands. Secondary hyperaldosteronism with levels of aldosterone 289pg/ml (normal range 20–180) and renin 205mIU/ml (normal range 2.8–39.9) were typical for GS.

Based on the association of hypomagnesaemia, hypokalaemia, metabolic alkalosis, hypocalciuria and low-normal blood pressure, the diagnosis of GS was established.

Patients symptoms resolved quickly as the treatment continued. She was discharged with advice to continue oral potassium and magnesium supplements and potassium sparing diuretics. On discharge her serum sodium 139 mmol/L, serum potassium 3.89 mmol/L, corrected serum calcium 9.83 mg/dl, serum magnesium 0.89 mmol.

The patient remained symptom free and normokalemic and normomagnesemic after one month of follow up with serum potassium and magnesium. Family history revealed mild asymptomatic hypokalemia in the patient's 35-year-old sister. But further investigations to established GS were not done.

#### **Discussion:**

Tubulopathies are rare diseases. According to RenalTube database the most common primary tubulopathies are distal

renal tubular acidosis, bartter syndrome, familial hypomagnesaemia with hypercalciuria and GS<sup>8</sup>. The prevalence of GS is around 25 cases per 1 million<sup>9</sup>. More than 180 different mutations in *SLC12A3* have been described until now<sup>10</sup>. Because GS is one of the most common, probably many nephrologists and endocrinologist will be confronted with cases of GS during their careers. Our patient had typical clinical presentation of GS and responded well to therapy. The problem with GS is that overlooked hypokalemia could cause death due to cardiac arrest or respiratory muscles paralysis. The severe neuromuscular symptom such as hypokalemic paralysis occurs in up to 6% of patients (more common in Asian patients<sup>9</sup>. First symptoms of GS occur in children or young adults with normal growth and history of salt-craving behaviors (children eager to consume pickle or brine, salted cucumbers, oranges and lemons, children licking salt from potato crisps, etc.). Clinical presentation varies among patients. Some are asymptomatic but others develop life-threatening complications. Males manifest a more severe phenotype than females. The most common symptoms are muscular cramps and weakness, constipation, nocturia, polyuria, thirst, polydipsia, cardiac arrhythmias, paresthesias and increased salt appetite. Arterial hypotension is common and in many cases the most prominent symptom, however, in aging GS population hypertension can occur. The correlation between biochemical abnormalities and symptoms is not strong<sup>11</sup>.

Our patient had a long time history of persistent hypokalaemia with metabolic alkalosis and hypomagnesaemia. Vomiting and diuretic abuse, the two major diagnoses in this setting, were excluded by a negative history of diuretic use, but high urinary chloride to exclude vomiting can't be done due to lack of logistic support. The remaining differential diagnoses were the genetic disorders of Gitelman and Bartter syndromes. Bartter syndrome was improbable because it usually has an earlier onset and a more severe phenotype, urinary calcium excretion is often increased and the magnesemia is normal or mildly reduced.

Thus, our final diagnosis was GS, an autosomal recessive salt-losing renal tubulopathy. In the vast majority of cases, disease is due to inactivating mutations in the gene that encodes the renal thiazide-sensitive sodium-chloride cotransporter (NCC) present in the epithelial cells of the renal distal convoluted tubule (DCT)<sup>12</sup>. It is characterised by hypomagnesaemia, hypocalciuria and secondary hyperaldosteronism that induce hypokalaemia and metabolic alkalosis. Clinical manifestations are similar to the prolonged administration of thiazide diuretics<sup>13</sup>.

GS is often not diagnosed until late childhood or even adulthood. Cramps, paresthesias and fatigue frequently occur. Most patients report recurrent periods of carpopedal spasms during vomiting, diarrhoea or fever. Chondrocalcinosis occurs later in life, and maybe the consequence of hypomagnesaemia<sup>14</sup>. Blood pressure is lower in the general population.

Rodriguez-Soriano et al<sup>15</sup> were the first to suggest that hypocalciuria may be useful in distinguishing the Gitelman's syndrome from classic Bartter's syndrome. It is less certain whether changes in calcium excretion provide insight into the renal tubular pathophysiology of these syndromes. The greater urinary calcium excretion in patients with classic Bartter's syndrome is consistent with impaired reabsorption in the ascending limb of loop of Henle. Alternatively the hypocalciuria of Gitelman's syndrome suggests the involvement of the distal convoluted tubule, where reduced chloride absorption is associated with augmented calcium absorption<sup>16</sup>. Our current understanding of tubular function does not easily explain the dissociation between calcium and magnesium excretion in these disorder. The thick ascending limb of loop of Henle is the major site of magnesium reabsorption, where the reabsorption thought to parallel the reabsorption of calcium. Consequently involvement of thick ascending limb would be expected to promote severe magnesium wasting, which is not usually present in classic Bartter's syndrome. Paradoxically in Gitelman's syndrome there is more consistent and severe magnesium wasting, which would not be expected from a tubular defect limited to the distal convoluted tubule. These considerations suggest the possibility of an additional tubular defect in the Gitelman's syndrome that contributes to magnesium wasting<sup>16</sup>.

The diagnosis of GS is based on the clinical symptoms and biochemical abnormalities, which include hypomagnesaemia, hypokalaemia, metabolic alkalosis and hypocalciuria. GS patients have a blunted natriuretic response to thiazide, but a prompt natriuresis after furosemide, indicating that the defect is located at the level of the distal tubule. DNA mutation analysis of the gene responsible for GS may confirm the diagnosis<sup>14</sup>. Although rarely required for diagnosis, renal biopsy reveals hyperplasia of the juxta glomerular apparatus and prominence of medullary interstitial cells, with variable degrees of interstitial fibrosis<sup>17</sup>.

In addition, our patient had AKI due to rhabdomyolysis secondary to hypokalemia, as there is no history of taking statins or myotoxic drugs and her onset of muscle pain just

happened one week before admission. Thus, hypokalemia is considered as the main reason for rhabdomyolysis in this case. During muscle contraction, potassium will be released from the intracellular to extracellular space. This is to mediate vasodilation and promote blood flow to contracting muscle. In state of hypokalemia, this stimulus is lost, the blood flow of myocytes decreases significantly and arterioles may constrict, leading to muscular ischemia and the subsequent cascade of myocyte destruction<sup>18</sup>. Afterwards, the depression of glycolytic enzyme function and stimulation of lipid activity result in the accumulation of free fatty acids (FFA) within muscle cells. High concentrations of FFA will prompt pump dysfunction (Na/K-ATPase, Ca<sup>2+</sup>-ATPase pump), increase permeability of the cell membrane and thus raise the intracellular calcium concentration. The increased intracellular calcium level soon sensitizes the downstream pathways, activates calcium-dependent proteases and phospholipases, and then destroys myofibrillar, cytoskeletal and membrane proteins, leading to muscle necrosis and intracellular sCK and MYO released into blood circulation<sup>19,20</sup>.

Concerning treatment, supplementation with magnesium is indicated, along with high sodium and potassium diet. If symptomatic hypokalemia is not corrected, it can be the associated drugs that antagonize aldosterone activity or block the sodium channel ENaC in the collecting duct. An option is the combination of amiloride, spironolactone or eplerenone with potassium chloride. In the absence of sodium wasting, more modest amounts of potassium supplementation with or without potassium sparing diuretics may be required<sup>21</sup>. Our patient responded well to oral potassium, calcium and magnesium supplement along with potassium sparing diuretics

#### **Conclusion:**

GS syndrome is one of the rare causes of hypokalemia, and it seems a challenge for physicians. We show in this paper that if one remembers about a very simple approach to hypokalemia and is aware of diuretics action and their similarity to inherited tubulopathies, the diagnosis could be quite straightforward. GS should be differentiated from other tubulopathies (inherited as well as acquired), and other causes of hypokalemia (e.g. Conn's disease). Familial history can reveal asymptomatic patients with GS. Suitable treatment protects patients from potentially dangerous complications.

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