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## CLINICAL VIGNETTE

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# Gitelman's Syndrome

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### *Case Report*

A 31-year-old man came to establish care at a primary care clinic. His only complaint was ankle pain for four weeks. He had no other muscular complaints. On examination, he was afebrile, his blood pressure was 110/76, pulse 89, weight 170.8 lbs, and height 66 inches. Physical exam was normal except for tenderness at the right medial and lateral malleolus without swelling. On his initial routine laboratory studies, he was found to have hypokalemia (3.0 mmol/L) and hypomagnesemia (1.54 mg/dL). At that point, further investigation focused on the etiology of the hypokalemia. The patient denied laxative abuse, diuretic abuse, nausea, vomiting, and chronic diarrhea. He denied heat intolerance, palpitations, skin or hair changes and increased frequency of defecation. He denied taking any over the counter medications except for naproxen. He denied taking herbal medications or supplements. He reported drinking four liters of water daily. The only significant past medical history was an episode of diffuse muscle cramps of the legs, arms and fingers and difficulty breathing at age 25. At that time, he was found to have hypokalemia and was treated with potassium supplementation.

Family history was significant for his mother taking potassium supplements for a short time, his father with diabetes mellitus, and a 30-year-old sister with hypothyroidism. He also had a 21-year-old brother and two other sisters, 26 and 28 years of age who were healthy. There was no known history of renal disease in the family. His social history was significant for smoking a half a pack per day for 13 years, alcohol intake of 2 drinks per month, and he denied illicit drug use.

On physical exam there was no evidence of developmental abnormalities or growth retardation. In addition to the serum potassium

and magnesium above, laboratory studies showed chloride was slightly low at 94.0 mmol/L and CO<sub>2</sub> was elevated at 32.1 mmol/L. Creatinine was normal at 1.2mg/dL. Sodium, calcium, phosphorus, and glucose levels were normal. Additional studies showed that his plasma renin was elevated at 19.7 ng/mL/hr, but the aldosterone level was normal at 8 mg/dl. 24-hour urine collection had decreased urinary calcium excretion (<2mg/dL). Magnesium excretion was at the upper limit of normal at 119 mg/day and potassium excretion was normal at 55 mmol/day. Thyroid function tests were normal. His EKG showed normal sinus rhythm with T wave inversion in V3, but otherwise normal. His ankle x-rays were normal and without any evidence of chondrocalcinosis. A left ankle joint aspiration was performed which showed monosodium urate crystals.

The patient was started on potassium chloride and magnesium oxide and later amiloride 5mg daily was added. He developed loose stools with magnesium supplementation and became non-compliant with his treatment and follow up appointments. Subsequent labs continued to show hypokalemia and metabolic alkalosis. His magnesium level had slightly improved.

### *Discussion*

Gitelman's syndrome is a renal tubular disorder with hypokalemia, hypomagnesemia, metabolic acidosis, and hypocalciuria. It was first described by Gitelman in 1966 with patients presenting with hypokalemic alkalosis and carpopedal spasm and tetany secondary to hypomagnesemia<sup>1</sup>. It is unclear what the worldwide prevalence of Gitelman's syndrome is, however it has been estimated to be 1 per 40,000<sup>2</sup>.

Gitelman's Syndrome is inherited as an autosomal recessive trait with wide phenotypic variation ranging from mild to severe symptoms including weakness, fatigue, thirst, nocturia, and cramps<sup>1</sup>. Age of onset can vary from childhood to young adult. Although there have been many different mutations described for the TSC gene, phenotypic variation has been noted even for patients with the same genetic mutation<sup>1</sup>. There is also gender differences noted with men having more severe symptoms compared with women<sup>3</sup>.

Gitelman's Syndrome is caused by a genetic defect for the thiazide sensitive cotransporter (TSC) also known as the Na-Cl cotransporter (NCCT). This abnormality results in defective chloride reabsorption in the distal convoluted tubule of the loop of Henle<sup>4</sup>. As a consequence volume contraction occurs resulting in increases in renin, angiotensin II, and aldosterone. The increase in angiotensin II increases potassium and hydrogen ion secretion leading to hypokalemia and metabolic alkalosis. Despite increases in renin and angiotensin, blood pressure remains normal secondary to the excessive salt wasting<sup>4</sup>. Interestingly, subjects from the Framingham Heart Study were screened for variation in genes related to Gitelman's and Bartter's syndrome and found those subjects who were heterozygous carriers had lower average blood pressures and had a 60% risk reduction in developing hypertension<sup>3</sup>.

As Gitelman's syndrome is a diagnosis of exclusion, other causes of hypokalemia and metabolic alkalosis must be ruled out. Thiazide diuretics use can mimic the urine chemistries found in Gitelman's syndrome, however the fractional sodium chloride reabsorption during hypotonic saline diuresis would be normal, whereas in Gitelman's syndrome, it would be abnormal. Gastrointestinal or nutritional disorders such as anorexia nervosa would not involve renal sodium chloride wasting. The lack of hypertension would rule out other disorders with abnormal renin-aldosterone levels such as renal artery stenosis, renin-secreting tumors, and nodular adrenal hyperplasia<sup>4</sup>. Bartter's syndrome closely resembles Gitelman's syndrome, however Bartter's syndrome presents neonatally

or in early childhood and is characterized by high urinary calcium excretion.

The main treatment of Gitelman's syndrome is high dose potassium and magnesium replacement. Angiotensin-converting enzyme inhibitors have been shown to improve hypokalemia and decrease serum aldosterone levels but hypotension can limit use. Other medications such as spironolactone and amiloride have also been used to treat hypokalemia<sup>4</sup>.

As our patient presented with ankle pain, initially we suspected possible calcium pyrophosphate crystal deposition disease, as this has been associated with Gitelman's syndrome. However he was ultimately diagnosed with gout which was successfully treated with allopurinol and colchicine<sup>5</sup>. Correcting his lab abnormalities, however proved challenging because of the following reasons. His non-compliance with treatment was likely due to his development of diarrhea secondary to the magnesium replacement and his lack of symptoms. It has also been reported in the literature how difficult it is to manage Gitelman's syndrome because of the underlying tubular defect cannot be cured and therefore even with medications and replacement, the patient will continue to have renal wasting of electrolytes.

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