

# Gitelman's Syndrome- A Rare Cause of Recurrent Syncope

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## Abstract

Gitelman's syndrome, or congenital hypokalemic hypomagnesemic hypocalciuria with metabolic alkalosis, is widely described as a benign or milder variant of Barter's syndrome. It presents with variable clinical symptoms including tetanic episodes, muscle cramps, muscle paralysis, tingling numbness, perioral tingling sensation, salt craving and nocturia. This milder salt wasting syndrome can rarely cause significant ventricular arrhythmias and even death. Here, we report a case of 59 year old male who presented with history of recurrent syncope. He was found to have recurrent polymorphic VT with persistent hypokalemia and hypomagnesemia. After extensive metabolic investigation, he was diagnosed as a case of Gitelman's syndrome. We report this case because of this rare malignant presentation of a seemingly benign syndrome.

## Introduction

Gitelman syndrome, is an autosomal recessive renal tubular disorder and is characterised by hypokalemic metabolic alkalosis, hypomagnesemia, hypocalciuria. It is milder than other sub- types of Barter's syndrome. Patients with GS usually present with tetanic episodes, muscle cramps, muscle paralysis, tingling numbness, perioral tingling sensation, salt craving and nocturia. Most cases of GS result from inactivating mutations to the SLC12A3 gene, which encodes the thiazide-sensitive Na-Cl cotransporter (NCC) on the apical membrane of distal convoluted tubule (DCT) cells. A minority of GS patients have mutations in the basolateral chloride channels (CLCNKB). The defect in thick ascending loop of Henle (TALH) or distal convoluted tubule (DCT) results in a failure to reabsorb chloride and sodium, that leads to excessive sodium and chloride delivery to the distal tubules, resulting in excessive salt and water loss from the body. The renin-angiotensin-aldosterone system (RAAS) is a feedback system activated with volume depletion. Although Gitelman syndrome, presents with seemingly mild symptoms, rarely it may provoke cardiac arrhythmias.

Here we describe a 59 year old male who presented with recurrent syncope. During his stay in hospital, he was found to have recurrent polymorphic VT. Investigations in this patient revealed persistent hypokalemia, metabolic alkalosis, hypocalciuria, and hypomagnesemia, a tetrad diagnostic of Gitelman's syndrome.

## Case Report

A 59 year old male was referred

from a peripheral hospital with history of recurrent syncope since last 2 years. Syncope occurred at rest with no precipitating factors. No history of associated chest pain, dyspnoea, polyuria or symptoms suggestive of seizures. He was not on any regular medications. No significant past history.

One year ago, he was admitted for similar episode at a peripheral hospital. He was treated conservatively at that time. ECG at that time was suggestive of NSVT. He was discharged with a advice to consult cardiologist. This time again he went with history of syncope and was transferred to our hospital.

On admission, the initial electrocardiogram (ECG) revealed nonsustained polymorphic ventricular tachycardia with intermittent sinus beats showing prolonged QT interval, features consistent with Torsades de Pointes. He was urgently put on temporary pacemaker support and intravenous calcium and magnesium were started.

Initial serum chemistries revealed a Potassium level of 2.6 mEq/L (normal range, 3.5 to 5.5 mEq/L) and a Magnesium level of 1.3 mEq/L (normal range, 1.2 to 2.1 mEq/L). Subsequent analysis of 24-hour urine chemistries revealed renal wasting of potassium, with a transtubular potassium gradient (TTKG) was approximately 12 (TTKG>7 indicates renal loss). The patient was also found to have persistently elevated serum bicarbonate of 28-30 mEq/L (normal, 22 to 32 mEq/L). The urinary calcium was subnormal at 1.2 m mols/24 hour (2.5-7.5 mmols). A transthoracic echocardiogram done on admission revealed an ejection fraction of 55%. The renin and aldosterone levels were within

normal on serum assays, essentially ruling out hyperaldosteronism. Given the combination of hypokalemia, hypomagnesemia, and metabolic alkalosis, the patient was given the diagnosis of acquired long QT syndrome secondary to a metabolic disorder, most likely Gitelman Syndrome. He was treated with intravenous/oral repletion of potassium and magnesium daily, the serum potassium and magnesium levels normalized after 5 days of treatment, temporary pacemaker was removed and patient was discharged with advise of regular potassium and magnesium supplements. He has been in 4 years of regular follow up with no recurrence of syncope since then.

## Discussion

Gitelman Syndrome is a disorder that causes a defect in the sodium-chloride cotransporter in the renal distal convoluted tubule, causing hypokalemia, hypomagnesemia, and metabolic alkalosis. The prevalence of Gitelman Syndrome is estimated at approximately 1 per 40,000.<sup>1,2</sup> It is an autosomal recessive disorder which may not be diagnosed until adulthood, with common complaints of cramps, fatigue, dizziness and polyuria.

It is caused by missense mutations in the SLC12A3 gene (located on chromosome 16q) that encodes the thiazide-sensitive sodium chloride co-transporter.<sup>3,4</sup> In SLC12A3, 172 distinct mutations have been described, leading to extreme phenotype variability.<sup>5</sup> Female patients with the same mutations are relatively asymptomatic compared with their male counterparts. The nature and position of the SLC12A3 mutation, combined with male gender, seem to be a determinant factor in the severity of GS.<sup>6</sup>

Diagnosis is often one of exclusion, ruling out other causes of hypokalemia and metabolic alkalosis, such as vomiting and diuretic use. However, diagnosis can also be made with the following laboratory findings:

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hypokalemia due to renal losses, metabolic alkalosis, hypomagnesemia due to renal losses, elevated urinary chloride excretion, and a decrease in urinary calcium excretion.<sup>7</sup>

The laboratory values in this patient explicitly satisfied all of the above criteria for the diagnosis of Gitelman Syndrome, except elevated urinary chloride excretion (which were not assayed for in the urine).

Hypokalemia and hypomagnesemia can prolong the QT interval and increase the susceptibility of the heart towards fatal ventricular arrhythmias. It has been demonstrated that there is a tendency for prolonged QT intervals in patients with Gitelman Syndrome, one study showing the prevalence of more than 40%.<sup>8</sup> However, cardiac arrhythmias have been described in far fewer patients. Sudden cardiac death has been reported in a few cases.<sup>9</sup>

Gitelman Syndrome was the most likely predisposing condition that lead to the episodes of recurrent syncope and ventricular arrhythmias in this

patient. Before starting patients on antiarrhythmic therapy for recurrent syncope due to arrhythmias, metabolic causes, such as hypokalemia and hypomagnesemia should be fully evaluated.

Treatment is directed at correcting potassium and magnesium depletion. It requires life-long supplementation and liberal salt intake. Potassium supplementation is with potassium chloride and potassium-sparing diuretics, including amiloride and spironolactone. However, in hypotensive patients, these drugs should be used with caution. Hypomagnesemia is corrected with magnesium chloride (magnesium sulfate or oxide are avoided to prevent diarrhea).<sup>10,11</sup>

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