Case Report

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Managing Gitelman Syndrome: Socioeconomic Barriers and Clinical Outcomes

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Abstract: Gitelman syndrome (GS) is a rare autosomal recessive renal tubulopathy characterized by hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria due to mutations in the SLC12A3 gene. This case report presents a 54-year-old African American female with near syncope and palpitations. The patient had a history of intermittent palpitations and generalized anxiety disorder and was previously diagnosed with GS. On presentation, the patient exhibited symptoms of severe hypokalemia and hypomagnesemia, attributed to medication non-adherence. Laboratory tests confirmed critically low potassium and magnesium levels, with elevated urine sodium and chloride. Treatment was initiated with oral and intravenous potassium and magnesium, leading to the normalization of electrolyte levels. This case highlights the challenges of managing GS, particularly in patients facing socioeconomic barriers that impede medication adherence and healthcare access. Personalized patient education, combined with comprehensive healthcare resources, is essential to mitigate complications and improve long-term outcomes in such cases.

Keywords: nephrology; gitelman syndrome; socioeconomic determinants of health

1. Introduction

Gitelman syndrome (GS), first described by Gitelman et al. in 1966, is a rare inherited renal tubulopathy characterized primarily by hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria. This autosomal recessive disorder results from mutations in the SLC12A3 gene, which encodes the thiazide-sensitive sodium-chloride cotransporter (NCC) located in the distal convoluted tubule of the kidney. The prevalence of GS is estimated at 1 in 40,000 individuals, though this may be underestimated due to the condition's often mild and asymptomatic presentations [1].

GS's pathophysiology involves defective sodium and chloride reabsorption in the distal convoluted tubule, leading to renal salt wasting, volume contraction, and secondary hyperaldosteronism. This, in turn, results in the excessive renal loss of potassium and magnesium and a decrease in calcium excretion. Clinically, GS is often characterized by a spectrum of symptoms ranging from mild to severe, including fatigue, muscle weakness, cramps, and tetany, which are primarily due to hypokalemia and hypomagnesemia [1].

Diagnosis of GS relies on clinical presentation, biochemical findings, and genetic testing. The biochemical hallmark of GS includes hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria. Molecular genetic testing confirms the diagnosis by identifying mutations in the SLC12A3 gene [2]. Differentiating GS from other hypokalemic metabolic alkalosis causes, such as Bartter syndrome and diuretic abuse, ensures appropriate management and follow-up.

Management of GS primarily involves correcting the electrolyte imbalances and alleviating symptoms. This typically includes supplementation with potassium and magnesium, as well as the use of potassium-sparing diuretics and magnesium-potassium-sparing agents. Although prognosis is generally favorable, GS can significantly affect the quality of life due to chronicity and potential complications, including chronic kidney disease. [1].

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For health providers to offer quality comprehensive care, increased awareness and knowledge of the disease is necessary, as well as more strict diagnostic criteria. Often, the diagnosis of GS and other rare diseases is prolonged, as seen in our patient. Delaying the diagnosis extends the time to receive proper treatment, which ultimately can lead to worse health outcomes. Additionally, it augments unnecessary healthcare costs related to an increased number of emergency department visits that could have been better spent on therapeutics for disease management [3].

Like many other chronic diseases, managing GS typically requires 1-2 clinic visits yearly by a primary care physician, in addition to variable interim visits to specialists (e.g., nephrologists, cardiologists). Each clinic visit typically requires multiple blood and urine lab tests to monitor electrolyte levels and kidney function. Due to the limited number of randomized clinical trials investigating efficacious therapeutic management of GS, as seen with many rare diseases, the current standard management relies heavily on patient symptomatology and trending serum and urine electrolyte levels, which can be costly [3]. Thus, optimal management of GS requires strict patient follow-up and medication adherence. In patients that face socioeconomic hardships and/or have poor mental health, treating the symptoms and complications of GS is further complicated due to a variety of factors and healthcare barriers such as uninsured status, loss to follow-up, external stressors, poor health literacy, inability to afford medication, and medication nonadherence.

2. Case Presentation

A 54-year-old African American female presented to our emergency department due to near syncope and palpitations. The patient was sitting at her home desk when she abruptly felt her heart racing, lightheadedness, and a “hollow” and tight feeling in her chest. She endorsed associated chills, dyspnea, shakiness, cramping, and tingling in both hands. Initially, she thought her symptoms were due to low blood sugar levels as she had not eaten breakfast. However, when the symptoms worsened upon standing and persisted after attempting to eat, she called the paramedics. The patient endorsed a history of intermittent palpitation episodes since adolescence but stated she had never experienced an episode of that severity. She denied loss of consciousness, fever, nausea, vomiting, diarrhea, and chest pain. Additionally, she endorsed mild bilateral lower extremity swelling, for which she stated she saw a cardiologist the month prior, who had her wear a Holter monitor. The patient had not followed up on her Holter monitor testing results.

After further review, the patient endorsed a history of generalized anxiety disorder for which she took Buspar daily and a chronic history of hypokalemia and hypomagnesemia. She stated she was diagnosed with GS in 2017 after following up with an outpatient nephrologist for electrolyte abnormalities found during a prior unrelated emergency department visit. Since then, the patient has been taking oral potassium, magnesium, and amiloride daily but admits to frequent medication non-adherence. Pertinent to the current ED visit, the patient stated she had not taken her medications that week after her grandson misplaced her medication bottles. The patient denied a history of or current diuretic and/or laxative abuse, obsession with body image, self-induced vomiting, and hypertension. The patient endorsed drinking socially and denied tobacco or illicit drug use. She used to work in-office full-time in sales at a cellphone company but recently began working part-time from home due to becoming “easily fatigued and tired,” which she related to having GS.

A thorough chart review of her previous nephrology appointments demonstrated a clinical diagnosis of GS in 2017 based on her symptoms and extensive laboratory testing, which revealed hypokalemia, hypomagnesemia, and metabolic alkalosis in the setting of normotension and no medication use, along with a positive family history of GS in her granddaughter. The patient was encouraged to undergo genetic testing at that time but ultimately did not receive testing.

Her vital signs demonstrated mildly elevated systolic and diastolic pressures and bradycardia. All other vital signs were within normal limits. Physical examination revealed a well-nourished and anxious but cooperative woman. The patient was alert and oriented to person, place, and time. No thyromegaly was appreciated. Chest examination revealed bradycardia and a normal rhythm. The lungs were clear to auscultation bilaterally. There was trace pedal edema bilaterally. No focal neurological deficits were appreciated. Muscle strength was 5/5 throughout.

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Relevant serum and urinary laboratory results at admission are provided in Table 1 and Table 2. Notably, the patient was found to have critically low potassium (2.2 meq/L), low magnesium (1.2 mg/dL), and elevated creatinine (1.08 mg/dL) from her previous baseline level of 0.73 mg/dL. Pertinent negative findings include normal calcium levels and a negative 8-panel urine drug screen. The patient had elevated spot urine sodium and chloride levels, which have been associated with renal tubular disorders, as well as various other etiologies [4]. Furthermore, the patient had a urine sodium/urine chloride ratio (1.21) slightly greater than 1. A urine sodium/urine chloride ratio of approximately one has been shown to correlate with renal tubular disorders and, therefore, can help differentiate various etiologies of chronic hypokalemia (e.g., diuretic use, gastrointestinal losses, renal tubular disorders, laxative use, etc.) [4].

Table 1. Relevant biochemical tests performed at admission.

Scheme .	Values Presented	Reference Range
Glucose (mg/dL)	123	70 - 99
Potassium (meq/L)	2.2	3.6 - 5.0
Magnesium (mg/dL)	1.2	1.6 - 2.6
Creatinine (mg/dL)	1.08	0.55 - 1.02
Blood Urea Nitrogen (mg/dL)	17	7 - 18
Calcium (mg/dL)	8.8	8.5 - 10.1
Albumin (g/dL)	3.1	3.4 - 5
Phosphorous (mg/dL)	3.8	2.7 - 4.5
White Blood Cell Count (K/uL)	5.6	4.5 - 11
Hemoglobin (g/dL)	12.8	12 - 16
Hematocrit (%)	37.8	36.0 - 47.0
Troponin I, HS (ng/L)	36	< 59
Thyroid Stimulating Hormone (uIU/mL)	1.59	0.36 - 3.74

Table 2. Relevant urine tests at admission.

Urine Laboratory Parameters	Values Presented	Reference Range
Chloride Urine Random	99 mmol/L	None
Sodium Urine Random	120 mmol/L	None
Creatinine Urine Random	49.70 mg/dL	< 20 mg/dL

A 12-lead EKG showed a normal rate of 62 bpm, sinus rhythm, a slightly prolonged PR interval of 216 ms, a QRS duration of 106 ms, a QT/QTc interval of 424ms/430ms, and P-R-T axes of 52, -34, 17degrees, respectively. Therefore, the patient's EKG findings demonstrate a first-degree AV block and an incomplete left bundle branch block with nonspecific T wave abnormality. The first-degree AV block may correlate with the patient's hypokalemia; however, no other characteristic findings of hypokalemia were noted. The chest x-ray was normal, revealing no acute cardiopulmonary processes.

The patient was observed on telemetry for 24 hours and seen by internal medicine, nephrology, cardiology, and case management. The patient was given oral and intravenous potassium and intravenous magnesium with correction to normal electrolyte values before discharge. During her hospital stay, the patient underwent a transthoracic echocardiogram (TTE) as ordered by the attending cardiologist to rule out a structural etiology for her near syncopal episode. The TTE showed

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a left ventricle of normal size, a normal ejection fraction of 50-55%, and a grade 1 LV diastolic dysfunction, making a structural etiology less likely. Additionally, the results of the patient's recent Holter monitor testing were obtained by the attending cardiologist and did not reveal any arrhythmias or abnormalities. Lastly, case management met with the patient to review healthcare access.

At discharge, the patient was instructed to resume her home medications of amiloride 20 mg PO daily, potassium chloride 40 meq PO twice daily, and magnesium oxide 400 mg PO twice daily. The patient was reminded of medication compliance and to follow up outpatient with nephrology and cardiology.

3. Discussion

Patients with lower socioeconomic status may have limited access to healthcare resources crucial for managing GS effectively. Delayed diagnosis or inadequate treatment can exacerbate complications associated with the syndrome. Patients with GS often require a diet rich in potassium and magnesium. Lower socioeconomic status can limit access to a balanced diet, exacerbating symptoms like hypokalemia and hypomagnesemia [5]. The cost of medications and supplements (such as potassium and magnesium) may be prohibitive for lower-income individuals, leading to poor adherence to treatment regimens. Lower levels of education and health literacy, often correlated with socioeconomic status, can also affect patients' ability to understand and manage their condition, potentially leading to poor health outcomes [6]. Furthermore, economic hardships can increase stress levels, which may negatively impact overall health and exacerbate chronic conditions like GS. Individuals with lower socioeconomic status may be more exposed to environmental stressors affecting health, such as poor living conditions or high-stress environments, which can further complicate their condition.

The significant physical, emotional, and financial burden of living with a rare disease should not be overlooked. According to the 2021 Impact of Rare Diseases on Patients and Healthcare Systems study, the cost of those living with a rare disease is estimated to be 3-5 times higher than those without rare diseases [7]. Additionally, this study analyzed Eversana's yearly cost data, concluding that the estimated annual direct medical costs of individuals living with rare diseases may reach $ 400 billion dollars. This nearly equates to the yearly direct medical costs of those with heart failure, Alzheimer's disease, and cancer.

The differentiation of GS from other similar disorders like Bartter syndrome is crucial but challenging. Both conditions involve alterations in renal tubular function, but they differ in their clinical manifestations and management strategies. The hypokalemia and hypomagnesemia typical of GS, as seen in our patient, require a nuanced understanding of renal physiology and a careful approach to the biochemical profile, which often involves not only routine serum assays but also detailed urine electrolyte analyses. The patient's history of non-compliance with medication, possibly influenced by socioeconomic factors, emphasizes the importance of personalized patient education and follow-up strategies.

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