An interesting case of salt-losing tubulopathy - Gitelman’s syndrome

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An interesting case of salt-losing tubulopathy - Gitelman's syndrome

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Abstract:

Background. Gitelman's Syndrome (GS) is a rare autosomal recessive renal tubular disorder affecting the distal convoluted tubule, leading to hypokalaemia, hypomagnesemia, hypercalciuria, and metabolic alkalosis. Diagnosis is often delayed due to nonspecific symptoms and overlap with other conditions, particularly in patients with comorbidities like diabetes. Early recognition through biochemical tests and genetic analysis is essential for effective management.

Case presentation. A 54-year-old female with Type 2 Diabetes Mellitus presented with generalized muscle weakness, polyuria, and metabolic alkalosis. Severe hypokalaemia (1.6 mEq/L) and hypomagnesemia (1.3 mg/dL) were identified. The thiazide challenge test revealed impaired sodium-chloride cotransporter function. Genetic testing confirmed SLC12A3 mutations, diagnosing GS. Electrolyte supplementation improved symptoms, and diabetes management was optimized.

Conclusion. This case underscores the diagnostic challenges of GS, particularly with comorbidities. The findings highlight the importance of biochemical and genetic testing in differential diagnosis and emphasize tailored long-term management to improve outcomes. Further research is needed to explore the interaction between GS and metabolic disorders.

Keywords: Gitelman's Syndrome, hypokalemia, SLC12A3, renal tubulopathy, type 2 diabetes mellitus

Abbreviations (in alphabetical order):

ABG: Arterial Blood Gas

ECG: Electrocardiogram

GS: Gitelman's Syndrome

mEq/L: Milliequivalents per Liter

mg/dL: Milligrams per Deciliter

mOSM/kg: Milliosmoles per Kilogram

NCC: Sodium-Chloride Cotransporter

SLC12A3: Solute Carrier Family 12 Member 3

T2DM: Type 2 Diabetes Mellitus

TTKG: Transtubular Potassium Gradient

BACKGROUND

Gitelman's Syndrome (GS) is a rare autosomal recessive renal tubular disorder that primarily affects the distal convoluted tubule of the kidney (1). First described by Hillel J. Gitelman in 1966, it is characterized by hypokalemia, hypomagnesemia, hypocalciuric, and metabolic alkalosis (2). The syndrome results from biallelic inactivating mutations in the SLC12A3 gene, which encodes the thiazide-sensitive sodium-chloride cotransporter (NCC). This defective transporter impairs sodium and chloride reabsorption, leading to significant renal salt wasting and compensatory mechanisms that exacerbate potassium and magnesium loss (3). Clinical manifestations are often nonspecific, including muscle weakness, fatigue, polyuria, and occasional cardiac arrhythmias, making diagnosis challenging (4). With an estimated prevalence of 1 in 40,000 to 60,000 individuals, GS is frequently misdiagnosed, especially in patients with overlapping comorbidities (5). Prompt recognition through biochemical analysis and genetic testing is vital to manage electrolyte imbalances and improve patient outcomes.

CASE PRESENTATION

A 24-year-old female, with a known history of Type 2 Diabetes Mellitus (T2DM) managed on oral hypoglycemics, presented to the clinic with complaints of generalized muscle weakness, abdominal pain, and increased urination with nocturia for one month. She also reported intermittent palpitations and worsening muscle weakness over the past two days. There was no significant family history of renal or neuromuscular disorders.

On arrival, her vitals were within normal limits: blood pressure of 130/90 mmHg, pulse rate of 78 beats per minute, respiratory rate of 18 per minute, and oxygen saturation of 99% on room air. Capillary blood glucose was 108 mg/dL. Physical examination revealed hypotonia in

both lower limbs, with muscle strength graded as 4/5 in the upper limbs and 2/5 in the lower limbs. Deep tendon reflexes, including the biceps, triceps, knee, and ankle jerks, were diminished bilaterally, while plantar reflexes were mute.

An arterial blood gas (ABG) analysis showed metabolic alkalosis, prompting further investigations for underlying causes. Laboratory tests revealed severe hypokalemia (serum potassium of 1.6 mEq/L) and elevated serum bicarbonate (35.3 mEq/L). Serum magnesium levels were also low at 1.3 mg/dL. Urine spot potassium measured 8.3 mEq/L, while serum osmolarity and urine osmolarity were 256 mOsm/kg and 110 mOsm/kg, respectively. The Transtubular Potassium Gradient (TTKG) was calculated to be 12, indicating significant renal potassium loss. A 24-hour urine analysis revealed low urinary calcium excretion (61.56 mg/day) and elevated urinary chloride levels (44 mEq/L).

Considering the possibility of a salt-losing tubulopathy, a differential diagnosis of Gitelman's Syndrome and Bartter's Syndrome was proposed. To differentiate these conditions, a thiazide challenge test was performed. The patient discontinued magnesium and potassium supplements 24 hours before the test, and a single 50 mg dose of hydrochlorothiazide (HCT) was administered orally. Blood and urine samples were collected at specified intervals to measure chloride excretion. The results indicated a blunted fractional excretion of chloride, which supported impaired activity of the thiazide-sensitive sodium-chloride cotransporter.

Genetic testing was subsequently conducted to confirm the diagnosis. A mutation in the SLC12A3 gene, responsible for encoding the NCC in the distal convoluted tubule, was identified, conclusively diagnosing Gitelman's Syndrome.

During hospitalization, the patient was managed with intravenous potassium chloride and magnesium sulphate to correct the severe electrolyte imbalances. Oral supplementation was initiated to maintain stability. Her diabetes management was optimized to reduce the risk of further complications. The patient's symptoms, including muscle weakness and fatigue, improved significantly following electrolyte correction.

DISCUSSION

This case report presents a complex interplay between Type 2 Diabetes Mellitus (T2DM) and Gitelman's Syndrome (GS), highlighting the challenges of diagnosing rare disorders with overlapping clinical features. The 54-year-old female patient exhibited hallmark biochemical abnormalities of GS, including severe hypokalaemia, hypomagnesemia, and metabolic alkalosis, confirmed through genetic testing identifying SLC12A3 mutations. The

use of the thiazide challenge test provided critical diagnostic insights, demonstrating reduced fractional chloride clearance.

The findings align with prior studies, such as Colussi et al. (2007), where the thiazide challenge test was validated as a diagnostic tool for GS, with a blunted fractional chloride clearance of <2.3% (6). Similarly, Bettinelli et al. (1992) emphasized hypercalciuria as a distinguishing feature of GS compared to Bartter syndrome, a finding observed in this case as well (7). Vargas-Poussou et al. (2011) further contextualized these findings by highlighting the genetic heterogeneity of SLC12A3 mutations, which accounts for the variable phenotypic expressions, as noted in this patient (8).

A broader comparison with other case reports reveals the variability in GS presentations. For instance, Rocha et al. (2023) reported severe hypokalemia leading to arrhythmias (9), while Bakir et al. (2021) noted diagnostic delays due to resource limitations (10). Huang et al. (2023) described GS in a patient with diabetes, emphasizing the need for tailored management strategies in comorbid scenarios (11). This overlap of symptoms with diabetic complications, such as neuropathy and renal insufficiency, mirrors the challenges in differentiating GS in this case.

Further, Hsu et al. (2009) described the limited phenotypic impact of heterozygous SLC12A3 mutations, contrasting with the severe manifestations seen in compound heterozygous cases like the one described here (12). Takeuchi et al. (2015) and Riveira-Munoz et al. (2007) expanded on the role of mutations causing exon skipping or producing nonfunctional NCC proteins, findings that deepen the understanding of GS pathophysiology in this patient (13, 14). Jiang et al. (2024) introduced finerenone as a novel therapeutic option for GS patients, which might inform alternative management strategies in similar cases (15).

These comparisons underscore the importance of integrating clinical, biochemical, and genetic analyses for an accurate GS diagnosis. While similarities with prior cases support the generalizability of findings, the unique clinical context of diabetes in this patient raises new questions about the interplay between GS and metabolic disorders. This suggests a hypothesis that diabetes may exacerbate electrolyte wasting or amplify GS symptoms, warranting further research.

This case also informs practice by demonstrating the utility of cost-effective diagnostic tools like the thiazide challenge test, especially in resource-limited settings. It reinforces the value of genetic testing to confirm ambiguous cases, aligning with the recommendations of Vargas-Poussou et al. (2011) (8). Long-term management strategies, such as regular

monitoring, electrolyte supplementation, and dietary modifications, are crucial to improving outcomes and quality of life.

CONCLUSION

This report highlights the diagnostic and management complexities of Gitelman's Syndrome in a diabetic patient. Key findings, such as the diagnostic utility of the thiazide challenge test, the role of genetic testing, and the unique challenges posed by comorbid conditions, contribute to the understanding of GS in complex clinical contexts. These findings have broader implications for clinical practice, calling for multidisciplinary approaches and targeted research. Future directions should explore the genetic and phenotypic spectrum of GS across diverse populations, assess the impact of comorbidities, and develop cost-effective diagnostic guidelines. Clinicians and researchers are urged to prioritize early recognition, holistic management, and further exploration of rare tubulopathies like GS to optimize care.

Authors' contribution:

Shrinidhi B. is the first and corresponding author and was primarily responsible for drafting and structuring the manuscript. Prem Balaji Lankapothu contributed to data collection, clinical interpretation, and critical revision of the manuscript. Magesh Kumar S. supervised the study, provided expert guidance, and reviewed the manuscript for intellectual content. All authors have read and approved the final version of the manuscript.

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Tables and Figures:

Table 1: Clinical Investigation Results for Gitelman's Syndrome Diagnosis	
Investigation	**Results**
ECG	Sinus rhythm with VPCs & U-waves
ABG	Metabolic Alkalosis with Severe Hypokalaemia
Serum Potassium	1.6mEq/L
Serum Bicarbonate	35.3mEq/L
Serum Magnesium	1.3mg/dl
Urine spot potassium	8.3mEq/L
Serum Osmolarity	256mOSM/kg
Urine Osmolarity	110mOSM/kg
TTKG	12
24hr Urine Calcium	61.56mg/dl,
Urine Chloride	44mEq / l.

Figure 1: Serum potassium levels at various time points.