Case Report

Gitelman Syndrome in the Sixth Decade: An Atypical Presentation with Severe Electrolyte Abnormalities and Genetic Heterogeneity

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Abstract

Gitelman syndrome (GS) is a rare autosomal recessive salt-losing tubulopathy characterized by hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria. While typically presenting in adolescence or early adulthood, atypical presentations and delayed diagnoses into later adulthood pose significant clinical challenges. We report a case of a 60-year-old female who presented with generalized weakness, lethargy, and severe electrolyte abnormalities, including profound hyponatremia (109 mmol/L), hypokalemia (2.91 mmol/L), hypocalcemia (<6.0 mg/dL), and hypomagnesemia (0.6 mg/dL). Laboratory investigations revealed metabolic alkalosis, hypochloremia, elevated parathyroid hormone (172.90 pg/ml), and inappropriate renal potassium wasting. Urinary studies showed relative hypocalciuria in the context of severe hypocalcemia. Genetic testing revealed no pathogenic variants in the SLC12A3 gene typically associated with GS, though variants of uncertain significance were identified in SLC22A12 and VPS33B genes. Management included aggressive electrolyte replacement, spironolactone, and dietary modifications, resulting in clinical improvement despite incomplete normalization of electrolytes. This case illustrates the complex clinical spectrum of GS, highlighting the importance of considering this diagnosis in older adults with unexplained electrolyte abnormalities. The absence of confirmatory SLC12A3 mutations despite classic biochemical features supports emerging evidence of genetic heterogeneity in GS. This case emphasizes the value of clinical diagnosis when genetic confirmation is lacking and the effectiveness of targeted symptomatic management. GS should be considered in the differential diagnosis of electrolyte abnormalities across all age groups. A high index of clinical suspicion and characteristic biochemical profile can guide diagnosis and management even in the absence of confirmatory genetic findings.

Keywords: Electrolyte disorders, Gitelman syndrome, hypokalemia, hypomagnesemia, hyponatremia, metabolic alkalosis, SLC12A3, tubulopathy

Résumé

Le syndrome de Gitelman (SG) est une tubulopathie rare autosomique récessive responsable d'une perte de sel, caractérisée par une alcalose métabolique hypokaliémique, une hypomagnésémie et une hypocalciurie. Bien qu'il se manifeste généralement à l'adolescence ou au début de l'âge adulte, des présentations atypiques et des diagnostics retardés à un âge plus avancé posent des défis cliniques importants. Nous rapportons le cas d'une femme de 60 ans présentant une asthénie généralisée, une léthargie et de graves troubles électrolytiques, notamment une hyponatrémie profonde (109 mmol/L), une hypokaliémie (2,91 mmol/L), une hypocalcémie (<6,0 mg/dL) et une hypomagnésémie (0,6 mg/dL). Les examens biologiques ont révélé une alcalose métabolique, une hypochlorémie, une élévation de la parathormone (172,90 pg/mL) et une perte rénale inappropriée de potassium. Les analyses urinaires ont montré une hypocalciurie relative malgré une hypocalcémie sévère. Les tests génétiques n'ont pas mis en évidence de variant pathogène dans le gène SLC12A3, généralement associé au SG, bien que des variants de signification incertaine aient été identifiés dans les gènes SLC22A12 et VPS33B. Le traitement a consisté en

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une supplémentation électrolytique intensive, l'utilisation de spironolactone et des modifications alimentaires, entraînant une amélioration clinique malgré une normalisation incomplète des électrolytes. Ce cas illustre la complexité du spectre clinique du SG et souligne l'importance de considérer ce diagnostic chez les patients âgés présentant des troubles électrolytiques inexpliqués. L'absence de mutations confirmées du gène SLC12A3, malgré un tableau biochimique typique, soutient l'hypothèse d'une hétérogénéité génétique croissante dans le SG. Ce cas met en lumière la valeur du diagnostic clinique en l'absence de confirmation génétique et l'efficacité d'une prise en charge symptomatique ciblée. Le SG doit être inclus dans le diagnostic différentiel des troubles électrolytiques à tout âge. Un haut degré de suspicion clinique et un profil biochimique caractéristique peuvent orienter le diagnostic et le traitement, même en l'absence de confirmation génétique.

Mots-clés: Troubles électrolytiques, syndrome de Gitelman, hypokaliémie, hypomagnésémie, hyponatrémie, alcalose métabolique, SLC12A3, tubulopathie

Introduction

Gitelman syndrome (GS) is a rare autosomal recessive salt-losing tubulopathy characterized by hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria.[1] First described by Gitelman *et al*. in 1966, this disorder results primarily from mutations in the SLC12A3 gene, which encodes the thiazide-sensitive sodium-chloride cotransporter (NCC) in the distal convoluted tubule.[2,3] With an estimated prevalence of 1–10 per 40,000 individuals, GS is considered the most common inherited tubulopathy, though it remains underdiagnosed due to its heterogeneous clinical presentation.[4]

Unlike the phenotypically similar Bartter syndrome, GS typically manifests during adolescence or early adulthood, with a wide spectrum of clinical manifestations ranging from asymptomatic biochemical abnormalities to severe neuromuscular complications.[5] The cardinal biochemical features include hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria, mimicking the effects of chronic thiazide diuretic administration.[6] While many patients experience mild symptoms such as fatigue, muscle weakness, and salt craving, atypical presentations, including tetany, paralysis, and cardiac arrhythmias, have been reported, particularly during periods of intercurrent illness or electrolyte depletion.[7,8]

The diagnosis of GS presents a clinical challenge due to its rarity and nonspecific symptomatology, often leading to significant delays in recognition and appropriate management.[9] This case report describes an unusual presentation of GS, highlighting the diagnostic complexities and therapeutic considerations in managing this rare inherited tubulopathy.

Case Report

A 60-year-old female, presented to Dr. D. Y. Patil Medical College, Hospital and Research Centre with complaints of generalized weakness, lethargy, and hyponatremia. The patient reported a vague history of muscle cramps and fatigue that had been progressively worsening over several months. She had visited multiple healthcare facilities previously but was unable to get a definitive diagnosis.

On admission, the patient's vital signs were stable. Physical examination revealed moderate dehydration with dry mucous membranes. Neurological examination showed mild muscle weakness in all four limbs but no focal neurological deficits. Cardiovascular, respiratory, and abdominal examinations were within normal limits. There was no significant family history of renal disorders or similar electrolyte abnormalities.

Initial laboratory investigations revealed severe electrolyte abnormalities. The patient had marked hypokalemia with a serum potassium level of 2.91 mmol/L (normal range: 3.5–5.0 mmol/L) and profound hyponatremia with a serum sodium of 109 mmol/L (normal range: 135–145 mmol/L). In addition, she had severe hypocalcemia with a serum calcium <6.0 mg/dL (normal range: 8.6–10.2 mg/dL) and hypomagnesemia with a serum magnesium of 0.6 mg/dL (normal range: 1.7–2.4 mg/dL). Ionized calcium was 0.93 mmol/L (normal range: 1.12–1.32 mmol/L).

Further investigation revealed metabolic alkalosis with hypochloremia. The patient had elevated intact parathyroid hormone (iPTH) levels at 172.90 pg/ml (normal range: 15–65 pg/ml), likely secondary to chronic hypocalcemia and hypomagnesemia. Urinary studies showed spot urine potassium of 19.40 mmol/L (normal: up to 10 mmol/L), indicating inappropriate renal potassium wasting despite hypokalemia. Spot urine sodium was 84 mmol/L, suggesting renal sodium loss. The 24-h urinary calcium excretion was 102.60 mg/24 h (normal: up to 300 mg/24 h), which is inappropriately normal in the context of severe hypocalcemia, suggestive of hypocalciuria.

Renal function tests showed normal blood urea nitrogen and serum creatinine levels. Serum phosphorus was 2.10 mg/dL. Urine osmolality was 196.3 mOsmol/kg (normal: 300–900 mOsmol/kg) with serum osmolality of 224.3 mOsmol/kg (normal: 275–300 mOsmol/kg), indicating impaired urinary concentrating ability.

Radiological investigations included a computed tomography scan of the brain, which showed no significant abnormalities. Ultrasonography of the abdomen revealed normal-sized kidneys with no calculi or mass lesions. Echocardiography showed normal cardiac chambers with no valvular abnormalities. Electrocardiogram showed changes consistent with hypokalemia and hypocalcemia.

Based on the clinical presentation of hypokalemia, hypomagnesemia, metabolic alkalosis, and relative hypocalciuria, a diagnosis of GS was suspected. Whole exome sequencing was performed to confirm the diagnosis; however, no pathogenic variants were identified in the SLC12A3 gene,

which is typically associated with GS. Two variants of uncertain significance were found: A heterozygous missense variant in SLC22A12 (c.1400C>T p. Thr467Met) and a heterozygous missense variant in VPS33B (c.896G>A p. Gly299Asp), both with autosomal recessive inheritance patterns.

Despite the absence of definitive genetic confirmation, the patient was diagnosed with GS based on her clinical presentation and characteristic biochemical findings, with the understanding that the condition can sometimes be caused by mutations in genes other than SLC12A3 or by mutations not detectable by current genetic testing methods.

The patient was initially managed with aggressive intravenous potassium, sodium, and magnesium replacement therapy, along with careful fluid management. After stabilization of acute electrolyte abnormalities, she was started on oral potassium chloride, magnesium supplements, and a small dose of spironolactone. She was advised to maintain adequate salt intake in her diet and to avoid medications like diuretics and nonsteroidal anti-inflammatory drugs that could worsen her electrolyte imbalances.

Following treatment, the patient showed gradual improvement in her symptoms with resolution of fatigue and muscle weakness. At discharge, her electrolytes had improved significantly though still not entirely within normal ranges. She was advised to continue oral supplementation and regular follow-up to monitor her electrolyte status. Patient education regarding her rare condition was provided, emphasizing the importance of lifelong medication adherence and regular medical follow-up.

Discussion

GS represents a diagnostic challenge due to its varied clinical presentation and rarity. The case of Mrs. A. J demonstrates several typical features of GS while also highlighting some unusual aspects that merit discussion.

The patient's presentation at 60 years of age is noteworthy, as GS typically manifests during adolescence or early adulthood. Balavoine *et al*. reported that while the median age at diagnosis is 27 years, diagnosis may be delayed until the fifth or sixth decade of life in some cases, consistent with our patient's late diagnosis.[10] This underscores the importance of considering GS in differential diagnosis of unexplained electrolyte abnormalities regardless of age.

The biochemical profile in our case demonstrated severe hypokalemia (2.91 mmol/L), profound hyponatremia (109 mmol/L), and hypomagnesemia (0.6 mg/dL), consistent with classic GS. However, the severity of the hyponatremia is unusual. In a cohort study by Cruz *et al*. of 50 patients with GS, hyponatremia was not a prominent feature.[7] The severe hyponatremia in our patient may represent a more extreme manifestation or could be related to other factors, such as inappropriate ADH secretion, which has been reported in some GS cases.[11]

The elevated iPTH level of 172.90 pg/ml observed in our patient deserves special consideration. Secondary hyperparathyroidism in GS is primarily attributed to chronic hypomagnesemia, which affects parathyroid gland function and results in parathyroid hormone (PTH) resistance at the bone level.[12] Viganò *et al*. documented similar findings in their study of 27 adult GS patients, where 26% exhibited elevated PTH levels.[13]

Particularly interesting in our case is the negative genetic testing for pathogenic variants in the SLC12A3 gene. Instead, variants of uncertain significance were found in SLC22A12 and VPS33B genes. This aligns with findings by Vargas-Poussou *et al*., who demonstrated that approximately 10%–15% of clinically diagnosed GS cases lack detectable SLC12A3 mutations.[4] Recent research suggests that GS-like phenotypes can result from mutations in other genes involved in renal electrolyte handling, including CLCNKB, KCNJ10, and HNF1B.[1]

The management approach in our case followed recommendations outlined in the KDIGO Controversies Conference on GS, focusing on electrolyte correction and symptom management.[14] Unlike some reports suggesting magnesium as the cornerstone of therapy, our patient required aggressive correction of multiple electrolytes, reflecting the complex nature of her presentation. The use of spironolactone in our management strategy is supported by Blanchard *et al*., who demonstrated its efficacy in reducing potassium wasting in GS patients.[1]

The absence of cardiac arrhythmias in our patient despite severe electrolyte abnormalities is noteworthy, as GS patients can develop serious cardiac complications. Bettinelli *et al*. reported that prolonged QT interval and cardiac arrhythmias occur in approximately 50% of GS patients with severe hypokalemia.[15] Our patient's relatively preserved cardiac function may reflect compensatory mechanisms that develop in chronic electrolyte disorders.

While our patient did not have a family history of similar electrolyte abnormalities, the autosomal recessive inheritance pattern of GS means that family members might be asymptomatic carriers. Nakhoul *et al*. emphasized the importance of genetic counseling and screening of family members, particularly in reproductive-age individuals.[6]

Conclusion

This case of GS in a 60-year-old female highlights the diagnostic complexities and therapeutic challenges associated with this rare salt-losing tubulopathy. The unusual presentation with profound hyponatremia, severe hypokalemia, and secondary hyperparathyroidism, despite the absence of confirmatory genetic mutations in SLC12A3, underscores the phenotypic heterogeneity of GS and suggests the involvement of alternative genetic pathways. The case emphasizes that clinical and biochemical findings remain paramount in diagnosing GS when genetic confirmation is lacking. While

management focused on careful electrolyte replacement and potassium-sparing strategies proved effective, this case reinforces the need for lifelong treatment and monitoring. As our understanding of the genetic basis and pathophysiology of GS continues to evolve, this case contributes to the growing body of evidence supporting a more inclusive diagnostic approach based on clinical presentation rather than strict genetic criteria, ultimately improving recognition and management of this underdiagnosed condition.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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