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Atypical presentation of gitelman syndrome: A case report highlighting diagnostic challenges and management complexities

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Abstract

Gitelman Syndrome (GS) is a rare autosomal recessive disorder caused by mutations in the SLC12A3 gene, resulting in thiazide-sensitive NaCl co-transporter dysfunction. Characterized by hypokalemic metabolic alkalosis, hypomagnesaemia, and low urinary calcium excretion, GS presents common symptoms like muscle weakness, tetany, and paresthesias, yet some manifestations are under-recognized. A 48-year-old female presented with severe episodic fatigue, muscle weakness, slurring of speech, and bilateral upper limb tremors. Unusual for GS, she lacked typical symptoms like polyuria, polydipsia, nocturia, or salt craving. Initial examination showed a low blood pressure of 100/70 mmHg. Laboratory results revealed hypokalemia, hypomagnesaemia, and metabolic alkalosis. Urine analysis confirmed renal potassium wasting and altered calcium handling, suggestive of GS. Initial treatment included oral supplements of calcium, magnesium, and potassium. However, maintaining magnesium levels was challenging despite supplementation, requiring careful dosage titration based on regular monitoring. A comprehensive cardiac assessment was performed due to the risk of arrhythmias. Dietary recommendations focused on a high-sodium and high-potassium diet to manage symptoms effectively. This case highlights atypical presentations of GS, emphasizing the importance of considering it in differential diagnoses, even in the absence of typical symptoms. Effective management necessitates a personalized approach to supplementation and regular monitoring to prevent complications such as severe hypomagnesaemia. Awareness of atypical clinical presentations is crucial for timely diagnosis and management, improving long-term outcomes in patients with this rare disorder.

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Introduction

Gitelman Syndrome (GS) is a rare autosomal recessive disorder caused by mutations in the SLC12A3 gene, which results in dysfunction of the thiazide-sensitive NaCl co-transporter. This syndrome is characterized by hypokalemic metabolic alkalosis, hypomagnesemia, and low urinary calcium excretion [1]. Typically, it presents during early childhood or adolescence [2]. Common symptoms of GS presents include muscle weakness, muscle spasms, and paresthesias, salt craving, nocturea, and dizziness due to hypotension [3,4]. However, some manifestations are under-recognized. Diagnosis based on clinical features and laboratory testing. Treatment is to maintain normal serum electrolyte levels to relieve symptoms [2]. This case report highlights an atypical presentations of GS, underscoring the importance of considering it in differential diagnoses, even in the absence of typical symptoms.

Case presentation

A 48-year-old previously healthy female presented with severe episodic fatigue, muscle weakness, slurred speech, and bilateral upper limb tremors for the past three months. Initially, she experienced faintness and unusual fatigue during physical activities, which later progressed to weakness in both upper and lower limbs, primarily affecting the proximal muscle groups. Several weeks later, she developed episodic slurred speech and bilateral upper limb tremors that worsened with activity. These symptoms did not fluctuate throughout the day but progressively worsened over time. She reported no swallowing difficulties, headaches, double vision, or blurred vision. Additionally, she had no systemic manifestations such as weight loss or cold intolerance. Her urinary output was normal, and there were no gastrointestinal symptoms like prolong diarrhea or vomiting. She had no history of recent infections, and no family members had similar symptoms.

On examination, her pulse rate was 76 beats per minute, and her blood pressure was 100/70 mmHg in a supine posture. Other vital parameters were normal. There was no edema, and her jugular venous pulse was normal.

Neurological examination revealed muscle power of 4/5 in the proximal muscle groups of the bilateral lower limbs, while all other muscle groups had normal power. Tone and reflexes were normal in both upper and lower limbs, including proximal and distal muscle groups. Fasciculations were not observed, but she exhibited fine tremors in the bilateral upper limbs, which worsened during the finger-nose test. Despite her complaints of tingling sensation in the bilateral upper limbs, there was no sensory involvement. No bulbar, pharyngeal or respiratory muscle involvement noted. Her vision was normal, and there were no rashes or features of hypo- or hyperthyroidism. Chvostek and Trousseau signs were positive.

Initial diagnostic workup included blood tests such as a full blood count to assess for anemia, serum electrolytes including serum potassium, magnesium, sodium, thyroid function tests, inflammatory markers (ESR and CRP), creatine kinase level, and neuro-imaging with NCCT brain followed by MRI, which revealed no abnormalities.

Full blood count, random blood sugar, inflammatory markers, thyroid function tests, parathyroid hormone levels, liver profile, renal function tests, serum albumin levels, and neuroimaging findings was normal. Interestingly, her serum electrolyte levels were:

Serum potassium: 2.9 mmol/L.

Serum sodium: 135.5 mmol/L.

Serum magnesium: 1.1 mg/dL.

Serum ionized calcium: 1.1 mmol/L.

ABG showed a pH of 7.56.

HCO_3: 31 mmol/L.

Serum creatinine: 0.68 mg/dL.

Estimated glomerular filtration rate: 109 mL/min/1.73 m^2.

Given the normal findings except for serum electrolyte levels, we performed a urinary excretion of calcium test, suspecting renal loss of electrolytes, as there were no other potential causes for electrolyte loss like diarrhea or vomiting.

24-hour urinary calcium excretion: 2.3 mmol/day.

24-hour urinary sodium excretion: 30.57 mmol/day.

24-hour urinary potassium excretion: 63.0 mmol/day.

Based on these investigations, the patient was found to have hypokalemic, hypomagnisemic metabolic alkalosis with hypercalciurea.

A comprehensive cardiac assessment, including Electro Cardiogram, showed a prolong PR interval. An Echocardiogram was performed due to the risk of arrhythmias resulting from electrolyte imbalances. Joint radiography was normal. Ultrasonography of the abdomen, chest radiography, Electromyography (EMG) and Nerve Conduction Study (NCS) of all four limbs were normal. Based on the findings of hypokalemic hypomagnesimic metabolic alkalosis with hypocalciurea, we diagnosed Gitelman syndrome. Molecular or genetic study was not performed due to non-availability of the test.

Initial treatment included oral supplements of calcium, magnesium, and potassium:

Oral KCl: 3 tablets three times daily.

Potassium citrate extended release: 1 tablet daily.

Magnee® (magnesium oxide): 400 mg daily.

Calcium gluconate: 1 tablet daily.

However, maintaining magnesium levels was challenging despite supplementation, requiring careful dosage titration based on regular monitoring. Patient had episodes of severe hypomagnesaemia requiring hospital admissions. Magnesium levels normalized after adjusting 400 mg daily dosage to 400 mg three times daily with continuous blood levels monitoring. Dietary recommendations were done focusing on a high-sodium and high-potassium diet to manage symptoms effectively.

Currently this patient is followed-up at the clinic with regular monitoring of serum electrolyte levels.

Discussion

Gitelman Syndrome (GS) is an inherited autosomal recessive renal tubular disorder caused by inactivating mutation in the SLC12A3 gene that encodes the thiazide-sensitive sodium chloride co-transporter [5]. This condition is characterised by hypokalaemic metabolic alkalosis, hypomagnesaemia and hypocalciuria [2,3]. GS typically present in adolescent or early childhood

[2,6]. But our patient presented in mid elderly which increase the possibility of missing the diagnosis of GS if the typical age of presentation is considered. Prevalence is estimated to be in 1 in 40000, however, it is the most common in herited renal tubulopathy [7].

GS typically presents in adolescence or early childhood. It can be asymptomatic or present with common symptoms such as muscle weakness, muscle spasms, paresthesias, salt craving, nocturia, and dizziness due to hypotension [2-5].

Unusually for the diagnosis of GS, our patient lacked typical symptoms such as polyuria, polydipsia, nocturia, or salt craving [8]. Instead, the patient presented with upper limb tremors and slurred speech. Although neurological manifestations can occur in GS due to electrolyte abnormalities, these particular symptoms are atypical.

The diagnosis of GS is based on clinical features and laboratory tests, including serum electrolyte levels, Arterial Blood Gas (ABG) analysis to identify metabolic alkalosis, and urine tests to detect high levels of urinary excretion of magnesium and chloride with low excretion of calcium. Although the confirmatory test is genetic testing to identify mutations in the SLC12A3 gene, which encodes a thiazide-sensitive sodium-chloride cotransporter [7]. We diagnosed GS in our patient based on hypokalemic, hypomagnesemic metabolic alkalosis with hypocalciuria without genetic testing due to the unavailability of the test in our resource poor setting. During the diagnostic workup of GS it is important to exclude other similar conditions presenting with similar symptoms. Bartter syndrome (especially type III) is the most important genetic disorder to consider in the differential diagnosis of GS [7].

Treatment of GS mainly aim to maintain serum electrolyte levels in normal range with supplementation. Magnesium supplements should be taken in small frequent doses to avoid magnesium associated diarrhea which may worsen hypokalemia. $MgCl_2$ is preferred for magnesium supplementation as it compensates for urinary chloride loss [2,3]. We managed our patient with magnesium supplementation with Magnee® (magnesium oxide) and chloride supplementation was done together with potassium as potassium chloride tablets. This patient presented with hypomagnesaemia which was poorly responding to oral magnesium supplementation, nevertheless intravenous magnesium supplementation was not indicated given the magnesium level. Further researches are needed to check the suitability and when to decide intravenous magnesium supplementation need to be considered in patients with GS. Normal serum magnesium level is not rare in GS. Serum magnesium levels may indicate the severity of GS and need individually tailored dosages [1]. Additionally necessity of life long supplementation of electrolytes is a major patient concern.

Diagnosed patients of GS require individualized treatment with coordinated efforts of physicians, nephrologists, and cardiologists. Asymptomatic individuals can be managed without treatments with regular outpatient monitoring of electrolyte levels. Symptomatic patients are recommended to have high salt diet and may need lifelong supplementation of electrolytes [9]. The affected individuals need cardiac workup to screen high risk factors for cardiac arrhythmias [2].

Conclusion

This case highlights an atypical presentation of GS, emphasizing the importance of considering it in differential diagnoses, even in the absence of typical symptoms. Effective management necessitates a personalized approach to supplementation and regular monitoring to prevent complications such as severe hypomagnesaemia. Awareness of atypical clinical presentations is crucial for timely diagnosis and management, improving long-term outcomes in patients with this rare disorder.

Declarations

Conflict of interest: All the authors declare that there are no conflicts of interest.

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