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Case Report
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Gitelman Syndrome Unmasked in the Setting of Hyperthyroidism: A Diagnostic Challenge in a Low-Resource Setting

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Abstract

Gitelman Syndrome (GS) is a rare autosomal recessive renal tubulopathy caused by inactivating mutations in the *SLC12A3* gene, characterised by hypokalemia, hypomagnesemia, hypocalciuria, and metabolic alkalosis. Hyperthyroidism - most commonly Graves' disease -independently produces hypokalemia through intracellular potassium shift mediated by upregulated Na^+-K^+-ATPase activity, a phenomenon termed Thyrotoxic Periodic Paralysis (TPP). When these two conditions coexist, the electrolyte derangements are synergistic, creating a more severe and refractory clinical picture that is prone to misdiagnosis. We report a 28-year-old male from northern India presenting with episodic muscle weakness, palpitations, and profound hypokalemia (serum potassium 2.6 mmol/L) in the context of biochemically confirmed Graves' disease (TSH<0.01 mIU/L, TRAb positive). Persistent hypokalemia, hypomagnesemia, and hypocalciuria (urine calcium:creatinine ratio 0.04) following restoration of euthyroidism raised suspicion for an underlying tubulopathy. A diagnosis of GS was established on clinical and biochemical criteria without genetic testing - a pragmatic approach in our low-resource setting. The patient responded to carbimazole, propranolol, oral potassium chloride, magnesium oxide, and low-dose spironolactone, with serum potassium improving to 3.2 mmol/L and serum magnesium to 0.68 mmol/L at three-month follow-up, with no further paralytic episodes. This case highlights the importance of recognising GS as a co-existing diagnosis when hypokalemia persists after hyperthyroidism is controlled.

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Introduction

Gitelman Syndrome (GS) is an uncommon autosomal recessive disease caused by inactivating mutations in the *SLC12A3* gene located on chromosome 16q13, resulting in distal tubular dysfunction [1]. Most cases are detected during routine examinations in adulthood due to hypokalemia and alkalosis. GS needs to be distinguished from diseases that cause hypokalemia, such as classic Bartter syndrome and hyperthyroidism, and in individual cases, simultaneous occurrence of GS and hyperthyroidism is prone to misdiagnosis [2].

With a prevalence of approximately 1-10 per 40,000, and potentially higher in Asia, GS is arguably the most frequent inherited tubulopathy [3]. The disease is caused by biallelic inactivating mutations in *SLC12A3* encoding the thiazide-sensitive sodium-chloride cotransporter (NCC) expressed in the distal convoluted tubule [4]. Hyperthyroidism - most commonly Graves' disease - is a prevalent endocrine disorder capable of independently causing hypokalemia through a distinct transcellular mechanism [5]. Thyrotoxic Periodic Paralysis (TPP) is a rare but potentially life-threatening complication of hyperthyroidism, most commonly associated with Graves' disease, usually presenting as sudden symmetrical paralysis characterised by hypokalemia and muscle weakness that can progress to quadriplegia and respiratory muscle involvement [6, 7].

When GS and hyperthyroidism coexist, both pathologies amplify each other's electrolyte derangements. GS combined with hyperthyroidism can manifest as frequent episodes of periodic paralysis, a comorbidity that has been reported predominantly in eastern Asian populations. In low-resource settings, where genetic testing for *SLC12A3* mutations is unavailable, the diagnosis rests entirely on meticulous clinical and biochemical evaluation, making understanding of this dual pathology indispensable [8].

Case Presentation

A 28-year-old male farmer presented with a six-month history of episodic lower-limb weakness,

Table 1: Key laboratory parameters at presentation and follow-up.

Parameter	Unit	Reference range	Presentation	8-week follow-up (near-euthyroid)	3-month follow-up (on full treatment)
Thyroid function					
TSH	mIU/L	0.4–4.0	<0.01	0.3	1.2
Free T4	pmol/L	12–22	38	16	14
Free T3	pmol/L	3.1–6.8	11.2	5.4	4.8
Electrolytes					
Serum potassium	mmol/L	3.5–5.0	2.6	2.8	3.2
Serum magnesium	mmol/L	0.7–1.0	0.48	0.52	0.68
Serum sodium	mmol/L	135–145	138	139	140
Serum chloride	mmol/L	98–106	94	95	98
Serum phosphate	mmol/L	0.8–1.5	0.9	1.0	1.1
Acid-base					
Venous *pH*	—	7.35–7.45	7.48	7.46	7.43
Bicarbonate	mmol/L	22–29	30	29	26
Urine studies					
Urinary potassium	mEq/L	<20 (with hypokalemia)	42	38	34
Urine Ca:Cr ratio	mg/mg	0.10–0.25	0.04	0.04	0.05
TTKG	—	<3 (with hypokalemia)	8.2	7.6	6.1
RAAS					
Serum renin activity	ng/mL/h	0.5–1.9	4.8	4.2	3.1
Serum aldosterone	ng/dL	<21	28	25	22

TTKG = Trans-Tubular Potassium Gradient; Ca:Cr = Calcium:Creatinine; RAAS = Renin–Angiotensin–Aldosterone System. Persistent hypocalciuria and renal potassium wasting at 8-week follow-up (near-euthyroid state) were the key findings prompting diagnosis of co-existent Gitelman syndrome.

fatigue, palpitations, heat intolerance, and weight loss despite a preserved appetite. Two discrete episodes of transient limb paralysis had occurred in the preceding three months, each self-resolving within hours. There were no family history of thyroid or renal disease and no prior medications.

On examination, pulse was 102/min, blood pressure 100/70 mmHg, and BMI 19.5 kg/m^2. A diffuse Grade II goitre was present with lid lag. Proximal muscle power was 4/5 bilaterally in the lower limbs with hyporeflexia. No proptosis, pedal oedema, or features of Cushing's syndrome were found. Rest of the physical examination was unremarkable.

Initial investigations (Table 1) revealed serum potassium 2.6 mmol/L, serum magnesium 0.48 mmol/L, serum sodium 138 mmol/L, serum phosphate 0.9 mmol/L, serum chloride 94 mmol/L, venous *pH* 7.48, and bicarbonate 30 mmol/L. Serum creatinine and blood glucose were normal. TSH was suppressed (<0.01 mIU/L) with elevated free T4 (38 pmol/L) and free T3 (11.2 pmol/L). TRAb was positive at 7.2 IU/L, confirming Graves' disease. Spot urine showed an inappropriately elevated urinary potassium (42 mEq/L), a baseline urine calcium: creatinine ratio of 0.04 (hypocalciuria), and an elevated trans-tubular potassium gradient (TTKG) of 8.2, confirming renal potassium wasting. Serum renin activity was elevated at 4.8 ng/mL/h (reference: 0.5-1.9 ng/mL/h supine) and serum aldosterone was 28 ng/dL (reference: <21 ng/dL supine), consistent with secondary hyperaldosteronism due to volume depletion - a recognised feature of GS - rather than a primary aldosterone excess syndrome. Formal confirmatory testing for primary hyperaldosteronism (saline suppression or fludrocortisone confirmation test) was not performed; however, the renin-aldosterone ratio and the clinical context - low-normal blood pressure, absence of hypertension, and renin-aldosterone concordance - made primary hyperaldosteronism unlikely. ECG showed sinus tachycardia with prominent U-waves. Thyroid ultrasound demonstrated a diffusely enlarged, hypervascular gland consistent with Graves' disease.

The initial working diagnosis was Graves' disease with Thyrotoxic Periodic Paralysis (TPP). Carbimazole 20 mg/day, propranolol 40 mg twice daily, and oral potassium chloride 3 g/day were commenced. Written informed consent for publication of this case was obtained from the patient.

At eight-week follow-up from initial presentation, thyroid function had improved significantly (TSH 0.3 mIU/L, FT4 16 pmol/L). However, hypokalemia (2.8 mmol/L), hypomagnesemia (0.52 mmol/L), and metabolic alkalosis (*pH* 7.46) persisted - disproportionate to the degree of residual hyperthyroidism. Repeat urine studies continued to show renal potassium wasting and hypocalciuria in the near-euthyroid state (Table 1). Blood pressure remained low-normal.

The presence of both hypocalciuria and hypomagnesemia is highly predictive for the clinical diagnosis of GS. Together with persistent renal potassium wasting and low blood pressure - and in the absence of features of primary hyperaldosteronism (no hypertension, elevated renin consistent with secondary rather than primary aldosterone excess) - a diagnosis of co-existent Gitelman syndrome was established on clinical-biochemical grounds. The key differentials considered and excluded are summarised in Table 2. Classic Bartter syndrome (Type III) was considered unlikely given the presence of hypocalciuria (Bartter syndrome typically produces normocalciuria or hypercalciuria), normal blood pressure, absence

Table 2: Differential diagnosis of hypokalemic alkalosis with renal potassium wasting: comparison of key distinguishing features with this patient's clinical and biochemical profile.

Feature	Gitelman syndrome	Classic Bartter syndrome (Type III)	Primary hyperaldosteronism	This patient
Serum potassium	Low	Low	Low	Low (2.6 mmol/L)
Serum magnesium	Low	Normal/Low	Normal	Low (0.48 mmol/L)
Urine calcium	Low (hypocalciuria)	Normal/High	Normal	Low - Ca:Cr 0.04 (hypocalciuria)
Blood pressure	Low-normal	Low-normal	High	Low-normal (100/70 mmHg)
Serum renin	Elevated (secondary)	Elevated (secondary)	Suppressed	Elevated - 4.8 ng/mL/h (secondary)
Serum aldosterone	Elevated (secondary)	Elevated (secondary)	Elevated (primary)	Elevated - 28 ng/dL (secondary, renin-driven)
Age at presentation	Adulthood (often incidental)	Infancy/childhood (polyuria, failure to thrive)	Adulthood	28 years (adulthood)
Gene	*SLC12A3*	*CLCNKB (Type III)*	-	Not tested (resource-limited setting)
Overall match	Consistent	Inconsistent (hypocalciuria, adult onset, no polyuria)	Inconsistent (low BP, elevated renin)	Consistent with Gitelman Syndrome

of polyuria or polydipsia, and adult age of symptomatic onset. Pseudo-Gitelman phenotypes due to chronic laxative or diuretic use were excluded by history and the absence of any prior medications. A urine diuretic screen was not performed owing to resource constraints; however, covert diuretic use was considered unlikely given the consistent biochemical pattern across multiple visits and the persistence of hypocalciuria and hypomagnesemia in the near-euthyroid state - a pattern not explained by diuretic use alone. Primary hyperaldosteronism was excluded by the low-normal blood pressure, absence of hypertension, and the pattern of secondary aldosterone elevation commensurate with elevated renin. Genetic testing for *SLC12A3* mutations was not performed owing to resource constraints, consistent with the pragmatic diagnostic approach advocated in similar low-income settings.

The patient was commenced on oral magnesium oxide 500 mg twice daily as a cautious starting dose given the borderline low blood pressure, with the plan to uptitrate to 500 mg three times daily as tolerated. Spironolactone 50 mg/day was added as a cautious initial dose, again mindful of the low-normal blood pressure; uptitration to higher doses (up to 200-300 mg/day, as guided by KDIGO consensus) was deferred pending haemodynamic response [9]. At three-month follow-up, serum potassium had risen to 3.2 mmol/L, magnesium to 0.68 mmol/L, and no further paralytic episodes occurred. Residual mild electrolyte deficits were accepted as the expected biochemical floor in GS, where complete normalization is often unachievable. The patient will be reviewed at six-monthly intervals with monitoring of serum electrolytes, renal function, and blood pressure, with uptitration of magnesium supplementation and spironolactone guided by haemodynamic tolerance. Genetic referral will be pursued if resources permit, to confirm the diagnosis and facilitate family screening.

Discussion

The co-occurrence of GS and Graves' disease is documented in a growing body of case reports, predominantly from East Asia, though recognition is increasing globally. The mechanistic basis for this association remains debated, with hypotheses including shared autoimmune susceptibility loci, hypomagnesemia-mediated immune dysregulation, and statistical coincidence given the ~1% heterozygous *SLC12A3* carrier rate in the general population [2, 10]. Yu *et al*., (2021) highlighted that even young patients with hyperthyroidism and hypokalemia should be suspected of harbouring GS to avoid misdiagnosis [11]. Xu *et al*., (2023) reported a 14-year-old male in whom severe hypokalemia and rhabdomyolysis persisted despite antithyroid treatment, with genetic testing ultimately confirming compound heterozygous *SLC12A3* mutations - illustrating the hazard of anchoring exclusively on a thyrotoxic aetiology when an underlying tubulopathy amplifies electrolyte dysregulation [12]. Wardah *et al*., (2025) further demonstrated that TPP alone - without concurrent GS - can produce a dramatic clinical picture, underscoring that careful post-euthyroid electrolyte reassessment is essential to unmask any co-existing tubulopathy [6]. Zhang *et al*., (2024) and Qin *et al*., (2022) documented the diagnostic complexity of this dual entity across different age groups and mutation profiles [2, 10].

Against this background, the present case highlights three interrelated themes of pathophysiological and practical importance.

First, the mechanisms of hypokalemia are distinct and act in an additive fashion. In GS, loss of NCC function impairs sodium-chloride reabsorption in the distal convoluted tubule. The resulting increase in sodium delivery to the collecting duct augments urinary potassium and hydrogen excretion while promoting calcium reabsorption and magnesium wasting, with secondary RAAS activation further amplifying kaliuresis [1]. In hyperthyroidism, thyroid hormone directly stimulates the Na^+, K^+-ATPase pump and increases β-receptor number and sensitivity, driving potassium uptake into cells [13]. Decreased outward K^+ efflux through inward-rectifying Kir channels compounds this effect, trapping potassium intracellularly and creating an additive burden of hypokalemia alongside the renal wasting from GS. In coexistent disease, renal wasting and transcellular shift act in concert, producing hypokalemia more severe and refractory than either condition alone and elevating the risk of rhabdomyolysis, cardiac arrhythmia, and respiratory failure [12, 14].

Second, hypocalciuria is the pivotal diagnostic discriminator in low-resource settings. It is absent in TPP and primary hyperaldosteronism, and its persistence after achievement of euthyroidism - alongside hypomagnesemia and renal potassium wasting - constitutes a reliable clinical-biochemical basis for a probable diagnosis of GS even without genetic testing [15]. The spot urine calcium: creatinine ratio is affordable and widely available, and should be routinely requested in all patients with unexplained or refractory hypokalemia [16]. Low-normal blood pressure and a renin-aldosterone pattern consistent with secondary rather than primary excess further distinguish GS from hyperaldosteronism, as was the case in our patient.

Third, management is feasible and effective with widely available agents. Treatment focuses on replacing ions that the kidneys cannot efficiently reabsorb, with consistent intake of potassium chloride and magnesium salts such as magnesium oxide or magnesium gluconate [1]. Diarrhoea is a common side effect of oral magnesium; dividing the dose to three or four times daily is better tolerated. When supplementation alone is insufficient, potassium-sparing diuretics such as amiloride (5-10 mg/day) or spironolactone (up to 200-300 mg/day as per KDIGO consensus guidance) may be considered, with caution in patients with low blood pressure [1, 9]. In our patient, spironolactone was commenced at the conservative dose of 50 mg/day given the low-normal baseline blood pressure, consistent with the recommendation to initiate at lower doses and uptitrate cautiously. All agents used - carbimazole, propranolol, potassium chloride, magnesium oxide, and spironolactone - are included in the WHO Essential Medicines List (spironolactone on the complementary list), making this protocol fully reproducible at district-hospital level [17]. Patient education on supplementation adherence, trigger avoidance (high-carbohydrate meals, strenuous exercise, alcohol), and warning symptoms is a cost-free but essential component of long-term management.

Conclusion

GS coexisting with hyperthyroidism represents a rare but clinically important dual pathology in which the two conditions compound each other's electrolyte derangements, elevating the risk of cardiac arrhythmia, paralysis, and rhabdomyolysis. The diagnosis of GS should be actively considered whenever hypokalemia, hypomagnesemia, and hypocalciuria persist after satisfactory control of hyperthyroidism. In low-resource settings, this diagnosis can be made reliably on clinical-biochemical grounds and managed effectively with widely available, affordable medications. Clinicians practising in South Asia - a region of high Graves' disease prevalence - must maintain a high index of suspicion for this underdiagnosed dual pathology and resist premature diagnostic closure once a thyrotoxic cause is identified.

References

1. Parmar MS, Muppidi V, Bashir K. Gitelman Syndrome. StatPearls. 2024.
2. Zhang Y, Yu H, Li J, Cheng L. Concurrent Gitelman Syndrome and Hyperthyroidism: Diagnostic Challenges in a 51-Year-Old Patient. Am J Case Rep. 2024; 25: e944909.
3. Hsu YJ, Yang SS, Chu NF, Sytwu HK, Cheng CJ, Lin SH. Heterozygous mutations of the sodium chloride cotransporter in Chinese children: prevalence and association with blood pressure. Nephrol Dial Transplant. 2009; 24(4): 1170-1175.
4. Simon DB, Nelson-Williams C, Bia MJ, Ellison D, Karet FE, Molina AM, et al. Gitelman's variant of Bartter's syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na-Cl cotransporter. Nat Genet. 1996; 12(1): 24-30.
5. Idham M, Prajitno JH. Management of hypokalemia in patients with thyrotoxicosis periodic paralysis in Soetomo general hospital: A case report. Ann Med Surg. 2022; 84: 104925.
6. Wardah BM, Ahmad A, Nuri MMH. Thyrotoxic Periodic Paralysis in an Asian Male With Graves' Disease. Cureus. 2025; 17(11): e96063.
7. Tun T, Htay W, Myat K. Respiratory Failure in Hyperthyroidism: Focus on Thyrotoxic Periodic Paralysis. Cureus. 2025; 17(8): e90200.
8. Zhou H, Liang X, Qing Y, Meng B, Zhou J, Huang S, et al. Complicated Gitelman syndrome and autoimmune thyroid disease: a case report with a new homozygous mutation in the SLC12A3 gene and literature review. BMC Endocr Disord. 2018; 18(1): 82.
9. Blanchard A, Bockenhauer D, Bolignano D, Calo LA, Cosyns E, Devuyst O, et al. Gitelman syndrome: consensus and guidance from a KDIGO Controversies Conference. Kidney Int. 2017; 91(1): 24-33.
10. Qin YZ, Liu YM, Wang Y, You C, Li LN, Zhou XY, et al. Novel compound heterozygous mutation of SLC12A3 in Gitelman syndrome co-existent with hyperthyroidism. World J Clin Cases. 2022; 10(21): 7483-7494.
11. Yu S, Wang C. Genetic analysis of Gitelman syndrome: co-existence with hyperthyroidism in a two-year-old boy. Endocr Metab Immune Disord Drug Targets. 2021; 21(8): 1524-1530.
12. Xu J, He J, Xu S, Wang R, Peng N, Zhang M. Gitelman syndrome with Graves' disease leading to rhabdomyolysis: a case report and literature review. BMC Nephrol. 2023; 24(1): 123.
13. Lei J, Nowbar S, Mariash CN, Ingbar DH. Thyroid hormone stimulates Na-K-ATPase activity and its plasma membrane insertion in rat alveolar epithelial cells. Am J Physiol Lung Cell Mol Physiol. 2003; 285(3): L762-L772.
14. Lin SH, Huang CL. Mechanism of thyrotoxic periodic paralysis. J Am Soc Nephrol. 2012; 23(6): 985-988.
15. Lin SH, Chu P, Cheng CJ, Chu SJ, Hung YJ, Lin YF. Early diagnosis of thyrotoxic periodic paralysis: spot urine calcium to phosphate ratio. Crit Care Med. 2006; 34(12): 2984-2989.
16. Bettinelli A, Bianchetti MG, Girardin E, Caringella A, Cecconi M, Appiani AC, et al. Use of calcium excretion values to distinguish two forms of primary renal tubular hypokalemic alkalosis: Bartter and Gitelman syndromes. J Pediatr. 1992; 120(1): 38-43.
17. World Health Organization. Essential Medicines Lists. 2023.