

# Gitelman's syndrome presenting with hypocalcaemia, basal ganglia calcification and periodic paralysis

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**ABSTRACT** Gitelman's syndrome (GS), also referred to as familial hypokalaemia-hypomagnesaemia syndrome, is an autosomal recessive renal tubular disorder characterised by hypokalaemic metabolic alkalosis, hypomagnesaemia and hypocalciuria. It is caused by a defect of the thiazide-sensitive sodium chloride co-transporter at the distal tubule. This condition was previously confused with Bartter syndrome. Documentation of hypocalciuria helps to differentiate GS from Bartter syndrome. We report a 44-year-old woman who presented with a history of seizure disorder and periodic paralysis. On investigation, she was found to have hypokalaemic metabolic alkalosis, hypomagnesaemia, hypocalciuria, hypoparathyroidism, hypocalcaemia and basal ganglia calcification, consistent with GS. The atypical features in our case, namely basal ganglia calcification and hypocalcaemia, prompted the writing of this case report.

*Keywords:* Bartter syndrome, Gitelman's syndrome, hypocalcaemia, hypomagnesaemia, periodic paralysis  
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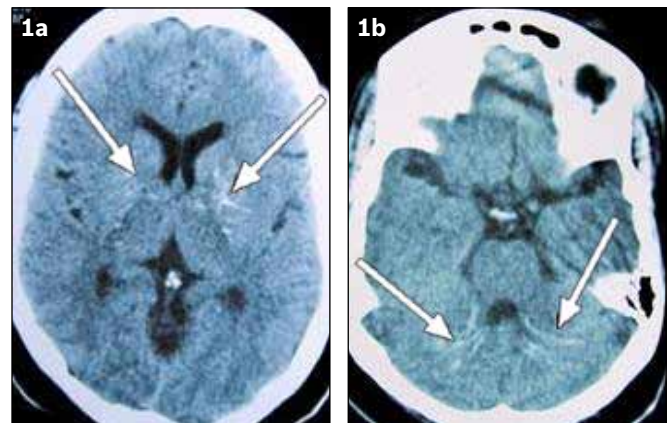
## INTRODUCTION

Gitelman's syndrome (GS), which was discovered by Gitelman, Grehm and Welt in 1966, is characterised by hypomagnesaemia, hypokalaemia, hypocalciuria and metabolic alkalosis. Patients usually present during early childhood or adolescence. The typical presentations of this condition include muscle spasms, muscle paralysis, tingling, perioral numbness, salt craving, nocturia, and hypotension. The diagnosis can be made on the basis of clinical features, laboratory investigations and renal function tests. Treatment usually aims to correct electrolyte imbalance. This case report aims to demonstrate the uncommon association of GS with basal ganglia calcification, hypocalcaemia and periodic paralysis.

## CASE REPORT

A 44-year-old Indian woman presented with a history of tingling and numbness of the whole body for the last eight years, two episodes of convulsion within the last six months, and diffuse muscle pain and multiple tetanic spasms in the form of carpopedal spasm and perioral numbness for the last two weeks. She had undergone a cataract operation in both eyes eight years ago. She was non-hypertensive and non-diabetic. There was no history of prolonged diarrhoea, vomiting, surreptitious diuretic or laxative abuse, self-medication, neck surgery or radiation, joint pain and oral ulcers. There was no history of similar illnesses in her family.

Physical examination revealed average build, normal skin turgor, no oedema and normal jugular venous pressure. The patient's blood pressure was 90/70 mmHg in a supine posture. Chvostek's and Trousseau's signs were strongly positive. Nervous system examination revealed that she was conscious and oriented; however, there was diminished power of 3/5 in both



**Fig. 1** CT images of the brain show (a) bilateral basal ganglia calcification (arrows); and (b) bilateral cerebellar calcification (arrows).

her proximal and distal muscles. She had normal jerk and sensation of all modalities. Bulbar, pharyngeal and respiratory muscles were not involved. Other systemic examinations were non-contributory. Laboratory investigations revealed normal blood count and blood biochemistry, including liver function test. Blood electrolytes revealed normal Na<sup>+</sup>, persistent very low K<sup>+</sup>, and persistently low Ca<sup>++</sup> and Mg<sup>++</sup> levels (Table I). Serum creatinine was 61.88 μmol/L and estimated creatinine clearance was 100 ml/min, while urine creatinine was 9 (normal range [NR] 8.8–14) mmol/day. There were no signs or symptoms of malnutrition, and serum albumin was 4 g/dL.

The patient's electrocardiogram (ECG) featured prolonged PR intervals, prolonged QT intervals and the presence of U-waves. Computed tomography (CT) of the brain revealed bilateral basal ganglia, internal capsule and cerebellar calcification (Figs. 1 & 2). Electroencephalogram (EEG) was normal. Radiography of the big joints and bone revealed no abnormality. Serum intact

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parathyroid hormone (iPTH) level was very low at 2.70 (NR 12.0–68.0) ng/L and serum phosphate was low at 0.64 (NR 0.81–1.4) mmol/L. Arterial blood gas revealed hypokalaemic metabolic alkalosis (pH 7.50, HCO<sub>3</sub><sup>-</sup> 28 mmol/L, PCO<sub>2</sub> 46 mmHg, PO<sub>2</sub> 94 mmHg, SaO<sub>2</sub> 98%, K<sup>+</sup> 1.09 mmol/L, ionised Ca<sup>2+</sup> 0.33 mmol/L). Urine pH was 6.5, with specific gravity 1.015. No other abnormality was detected. 24-hour urinary Ca<sup>2+</sup> was low at 0.6 (NR 1.5–5.5) mmol/day. 24-hour urinary excretion of magnesium was 6 (NR 3–5) mmol/day and serum magnesium was 0.41 mmol/L. Plasma renin activity was high-normal at 2.27 ng/ml/hr (NR 1.31–3.95 ng/ml/hr in upright posture). 8-am paired serum samples of cortisol and adrenocorticotrophic hormone (ACTH) were normal, while cortisol was 551.8 (normal 138.0–690.0) nmol/L and ACTH was 8.36 (NR 1.3–16.7) pmol/L. Thyroid profile and serum 25(OH)D<sub>3</sub> were normal.

The patient's serum Mg<sup>++</sup> and iPTH levels were retested on Day 9 after full replacement of Mg<sup>++</sup> and Ca<sup>++</sup> salts for three days. Results showed normalisation of serum iPTH level at 12.51 ng/L and serum Mg<sup>++</sup> level at 0.71 (NR 0.62–0.95) mmol/L, which excluded the diagnosis of idiopathic hypoparathyroidism. After one month, the patient's repeat 24-hour urinary calcium excretion was 1.0 (NR 1.5–5.5) mmol/day, serum calcium was 2.3 (NR 2.2–2.6) mmol/L, serum magnesium was 0.70 mmol/L and 24-hour urinary magnesium excretion was 5.2 (NR 3–5) mmol/day. Ultrasonography of the abdomen, chest radiography, electromyography (EMG) and nerve conduction study (NCS) of all four limbs were normal. Although GS was a clinical diagnosis, molecular or genetic study was not performed due to non-availability of the test.

The presence of hypokalaemic metabolic alkalosis, hypomagnesaemia, hypocalciuria, high-normal plasma renin activity indicated that GS was the most likely diagnosis. Our patient presented with hypokalaemic periodic paralysis, severe tetanic spasm that was associated with hypocalcaemia and basal ganglia, internal capsule and finally, cerebellar calcification, which is a new association. She was treated with intravenous followed by oral Mg<sup>++</sup> salt (5 mg/kg body weight), K<sup>+</sup> and Ca<sup>++</sup> salt, along with phenytoin sodium 300 mg/day and spironolactone. The patient is currently doing well and all symptoms have subsided.

## DISCUSSION

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. This condition is characterised by hypokalaemic metabolic alkalosis, hypomagnesaemia and hypocalciuria.<sup>(1)</sup> Both genders are equally affected, and GS usually presents in adolescence or early childhood, unlike in our case. Most patients with GS are either asymptomatic or complain of mild intermittent cramps, fatigue and muscle weakness. However, our patient presented with severe tetanic spasms, two episodes of convulsion and periodic paralysis. As reported by Cruz et al, approximately 6% of GS patients present with periodic paralysis.<sup>(2)</sup>

**Table 1. Levels of different biochemical parameters on Day 1, Day 3 and Day 5.**

Electrolyte	Level (mmol/L)			
	Normal range	Day 1	Day 3	Day 5
Na <sup>+</sup>	136–145	132	135	138
K <sup>+</sup>	3.5–5.0	2.01	1.5	2.15
Ca <sup>++</sup>	2.2–2.6*	0.95	1.58	1.05
Mg <sup>++</sup>	0.62–0.95	0.65	0.41	0.39
iPTH (ng/L)	12–88	-	2.70	-

\*Total calcium

Na: sodium; K: potassium; Ca: calcium; Mg: magnesium; iPTH: intact parathyroid hormone

The condition was previously confused with Bartter syndrome. However, GS is distinguished from Bartter syndrome by the presence of hypocalciuria. Severe hypomagnesaemia is not common in Bartter syndrome, although 20% of the cases are associated with mild hypomagnesaemia. Chronic abuse of diuretics, surreptitious vomiting and atypical Bartter syndrome can cause this type of clinical syndrome. These secondary factors, which were absent in our case, must be excluded before making a diagnosis of GS. Another uncommon finding in our case was basal ganglia and cerebellar calcification. The possible causal relationship between GS and calcification is unclear. Basal ganglia calcification is a well-recognised feature of chronic hypoparathyroidism due to other causes, e.g. CATCH-22 syndrome, post-thyroidectomy. Hypocalcaemia is not present in GS and is rarely associated with it, as in our case. Hypomagnesaemia results in the failure of repletion of cellular potassium stores due to urinary loss, further resulting in severe hypokalaemia, as seen in our patient. Hypoparathyroidism was secondary to severe hypomagnesaemia in our patient, as hypocalciuria and normalisation of serum iPTH level after correction of serum Mg<sup>++</sup> level was documented.

Magnesium and potassium supplementation and spironolactone are the treatment options for these individuals. All magnesium salts are used, but MgCl<sub>2</sub> is preferred because it compensates for urinary Cl<sup>-</sup> loss.<sup>(3)</sup> The total dose is individualised and administered at 6–8 hour intervals. Our patient was managed with intravenous magnesium sulphate followed by oral salt of magnesium oxide at a dose of 5 mg/kg in divided doses along with potassium, calcium and spironolactone. All GS patients are encouraged to maintain a high-sodium and high-potassium diet. In general, the long-term prognosis of GS is excellent. The atypical findings in our patient were hypocalcaemia, which is rarely associated with GS, late age at presentation, periodic paralysis and CNS calcification. To the best of our knowledge, these associations have not been previously reported in the literature.

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