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CASE REPORT

Gitelman syndrome and primary hyperparathyroidism: a rare association

Teresa Rego,[1] Fernando Fonseca,[1] Rita Cerqueira,[2] Ana Agapito[1]

[1]Department of Endocrinology, Hospital Curry Cabral, Lisboa, Portugal
[2]CGC Genetics, Molecular Diagnostics and Clinical Genomics, CGC Genetics, Porto, Portugal, Porto, Portugal

Correspondence to
Dr Ana Agapito, amagapito@chlc.min-saude.pt

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SUMMARY

Gitelman syndrome(GS) is a rare autosomal recessive salt-losing tubulopathy of young adults, characterised by hypokalaemia, hypomagnesaemia, hypocalciuria and secondary hyperaldosteronism. Hypercalcaemia due to hypocalciuria in these patients is extremely rare.

A 25-year-old healthy woman was referred to the Endocrinology clinic for evaluation of persistent hypokalaemia. She presented with fatigue, myalgias, cramps and paraesthesia. Her physical examination was normal. Laboratory workup revealed: K^+ 2.7 mEq/L (r.v.3.5–5.1), 24 hours urinary K^+ 84.7 mEq/24 hours (r.v.25–125), Mg^{2+} 0.71 mg/dL (r.v.1.6–2.6), 24 hours urinary Mg^{2+} 143.1 mg/24 hours (r.v.73–122), Ca^{2+} 12 mg/dL (r.v.8.4–10.2), aldosterone 47.1 ng/mL (r.v. 4–31) and active renin 374.7 uUI/mL (r.v.4.4–46.1). She was diagnosed with GS and was treated with spironolactone, oral K^+ and Mg^{2+} supplementation. Further investigation confirmed hypercalcaemia due to primary hyperparathyroidism owing to a single parathyroid adenoma. Following parathyroidectomy serum calcium normalised.

Current knowledge favours that hypomagnesaemia in patients with GS protects them from hypercalcaemia. In this context of multiple electrolyte imbalances, correction of hypomagnesaemia is a challenge and should be done carefully. Like in our patient, aetiology of hypercalcaemia should be promptly diagnosed and reversed.

BACKGROUND

Gitelman syndrome (GS) was first described in 1966 in a family characterised by hypokalaemia, hypomagnesaemia, hypocalciuria, metabolic alkalosis and hyper-reninemic hyperaldosteronism.[1] It is a rare autosomal recessive salt-losing tubulopathy with a prevalence estimated at approximately 1:40.000.[2] It is caused by mutations of *SLC12A3* gene that encodes the sodium chloride cotransporter (NCC) and magnesium channels in the thiazide-sensitive segment of the renal distal convoluted tubule.[3]

GS is usually diagnosed during adolescence or adulthood and the clinical spectrum is wide, ranging from asymptomatic to severe manifestations, such as episodes of paralysis, seizures or cardiac arrhythmias. Symptoms are related to electrolyte abnormalities; however, its severity does not correlate with the intensity of symptoms.[4] Moreover, the phenotype–genotype correlation is heterogeneous, since different phenotypes have been reported in family members presenting identical genetic defects.[5]

Hypocalciuria is a prominent feature in GS[1 6]; nevertheless, the total plasma calcium concentration has been reported to be normal.[1 6] Rarely, slight hypercalcaemia can occur in the course of GS due to dehydration-induced hyperproteinaemia.[6] Thereby, the presence of hypercalcaemia in the course of this disease should require further investigation.

Herein, we describe a rare case of GS associated with moderate to severe hypercalcaemia resulting in profound electrolyte imbalance. We also intend to report our apprehension in initial control of severe hypomagnesaemia in a patient with concomitant hypercalcaemia.

CASE PRESENTATION

A 25-year-old Caucasian normotensive woman was admitted to the emergency department in June 2015 due to malaise, fatigue, myalgias, cramps, left hemiface and left upper arm paraesthesias. Head CT excluded intracranial lesions and blood tests revealed a low serum K^+ of 2.9 mEq/L. She was referred to the Endocrinology clinic for evaluation of persistent hypokalaemia. She denied diarrhoea, abuse of diuretics, laxatives or 'natural supplements'. Concerning her family history, she has no siblings, her parents are non-consanguineous and healthy. Physical examination revealed depressed humour, normal body mass index (22 kg/m^2), blood pressure 110/80 mm Hg, pulse rate 82 bpm, no stigmata of hypercortisolism and no focal neurological signs.

INVESTIGATIONS

The patient's laboratory findings are shown in tables 1 and 2.

She presented with secondary hyperaldosteronism, renal wasting resulting in hypokalaemia and hypomagnesaemia. These laboratory findings associated with her normotensive profile favoured the diagnosis of GS. She was provided with a low dose of magnesium aspartate (500 mg/day) and oral potassium chloride progressively adjusted to 600 mg 4 id with improvement of the symptoms

The severity of hypercalcaemia did not seem to be justified by hypocalciuria of GS; furthermore, hypophosphataemia did not fit in this context. Additional tests revealed Ca^{2+} 11.8 mg/dL, Pi 1.9 mg/dL, PTH107.3 pg/mL (n.r. 14.8–83.1) and 25 OH vitamin D 20.4 ng/mL (n.r. 4.8–52.8) that were consistent with hypercalcaemia due to primary hyperparathyroidism (PHPT). Abdominal CT scan excluded renal lesions, such nephrolithiasis. Urinary

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Table 1 Laboratory results (July 2015)

		Normal range
Haemoglobin	12.9 g/L	12–15
Leucocytes	11.90×10^9/L	4.5–11
Platelets	317×10^9/L	150–450
Glucose	69 mg/dL	60–100
Urea	27 mg/dL	15–40
Creatinine	0.57 mg/dL	0.57–1.11
Glomerular filtration rate (GFR)>60 mL/min		
Total proteins/albumin	74 g/L	60–83
Sodium (Na^+)	139 mEq/L	136–145
Potassium (K^+)	2.7 mEq/L	3.5–5.1
Chloride (Cl^-)	97 mEq/L	98–107
Calcium (Ca^{2+})	12 mg/dL	8.4–10.2
Phosphorus (Pi)	1.6 mg/dL	2.3–4.7
Magnesium (Mg^{2+})	0.71 mg/dL	1.6–2.6
Total cholesterol	254 mg/dL	<190
Aldosterone	47.1 ng/mL	4–31
Active renin	374.7 uUI/mL	4.4–46.1

metanephrines and pituitary function were normal. A cervical Doppler ultrasonography revealed a hypervascular, hypointense nodule with 19×9×9 mm at the inferior pole of left lobe of thyroid, between oesophagus and left carotid artery, compatible with parathyroid adenoma.

To confirm our clinical suspicion of GS, genetic study was required. The variant c.602–16G>A and the variant c.2221G>A (p.Gly741Arg), both in heterozygosity, were detected in *SLC12A3* gene (figure 1). Genetic study of the parents was requested. The father presents the variant c.602–16G>A and the mother the variant c.2221G>A (p.Gly741Arg), in *SLC12A3* gene. The genetic study of the parents concluded that the variants found are in different alleles (*trans*), which reinforce their pathogenicity.

Table 2 Laboratory results—24-hour urine (vol. 2300 mL)

		Normal range
K^+	84.7 mEq/24 hours	25–125
Mg^{2+}	143.1 mg/24 hours	73–122
Ca^{2+}	133 mg/24 hours	100–300
Pi	1.1 g/24 hours	0.4–1.3

The occurrence of PHPT in a young patient also justified DNA analysis of *HRPT2* and *MEN1* genes that were both normal in this case.

TREATMENT

An inferior left parathyroidectomy was performed and histological study confirmed the diagnosis of parathyroid adenoma.

OUTCOME AND FOLLOW-UP

Serum Ca^{2+} and PTH normalised after surgery (Ca^{2+} 9.7 mg/dL, PTH 5 pg/mL and Pi 4.8 mg/dL). Hypocalciuria emerged and in 17 months of follow-up normocalcaemia persists (table 3). She maintained mild symptomatic hypokalaemia on oral KCl 600 mg 6id, thus spironolactone 100 mg/day was prescribed. During the last 6 months, medicated with spironolactone 100 mg/day, KCl 600 mg 2id, magnesium aspartate 1229.6 mg 4id, she presented serum K^+ in the inferior limit of normal range. She maintains mild-to-moderate hypomagnesaemia which can be explained by *poor medication* adherence due to gastrointestinal intolerance (table 3). The patient keeps regular follow-up in our department with clinical and biochemical evaluation.

DISCUSSION

GS is linked to inactivating mutations in the *SLC12A3* gene resulting in loss of function of the encoded NCC in the distal convoluted tubules. The clinical and biochemical picture of patients with GS resemble those who are on thiazide diuretics, given that the affected transporter is the exact target of thiazides.[4 7]

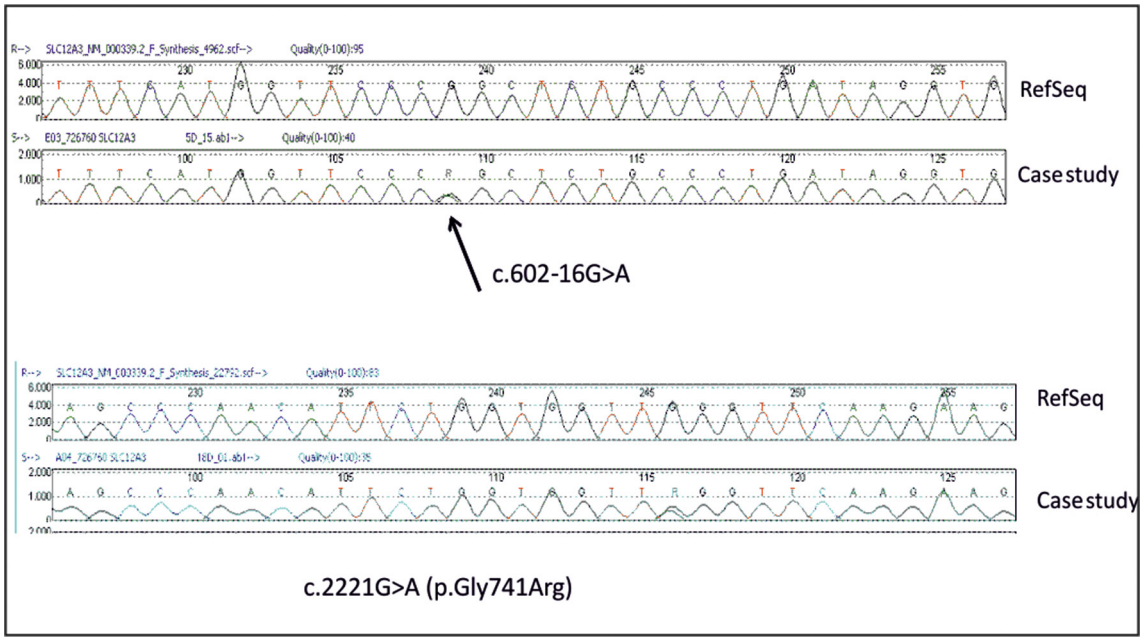

Figure 1 Chromatographe of the sequence: above: representation of variant c.602–16G>A; below: representation of variant c.2221G>A (p.Gly741Arg), both detect in *SLC12A3* gene.

Table 3 Laboratory tests (August 2016)

		Normal range
Ca^{2+}	9.9 mg/dL	8.4–10.2
24 hours urine Ca^{2+}	<53 mg/24 hours	100–300
Pi	2.9 mg/dL	2.3–4.7
Mg^{2+}	1.09 mg/dL	1.6–2.6
Parathyroid hormone (PTH)	14.9 pg/mL	14.76–83.1
25 OH vitamin D	35 ng/mL	4.8–52.8
Na^{+}	137 mEq/L	136–145
K^{+}	3.6 mEq/L	3.5–5.1
Cl^{-}	97 mEq/L	98–107

Despite clinical and biochemical similarities between patients with GS and those on thiazide diuretic therapy,[4] the presence of hypercalcaemia in the former group is unusual.[1 5] This fact can be explained by impaired calciotropic hormones due hypomagnesaemia in patients with GS.[6] Bianchetti *et al* demonstrated a blunted relationship between PTH, ionised calcium concentration and calcitriol in patients with GS providing evidence that these patients have a disturbed secretion of PTH.[6] Moreover in GS, normal levels of both plasma phosphate and urinary fractional phosphate excretion rule out PTH hyperfunction.[4 6]

We described a rare case of a young woman with GS presenting with hypercalcaemia due to PHPT. In PHPT, hypercalcaemia results from inappropriate hypersecretion of PTH from parathyroid gland(s). PTH increases tubular reabsorption of calcium in the kidney, stimulates release of skeletal calcium stores and upregulates 1α- hydroxylase resulting in increased 1,25-(OH)2D3 production and intestinal calcium absorption.[8]

The differential diagnosis between PHPT and familial hypocalciuric hypercalcaemia should be considered because the latter is a benign condition. In a patient with GS, this differentiation is difficult because of inherent hypocalciuria. In our patient, the diagnosis of PHTP was sustained by concomitant hypophosphataemia, high levels of PTH, unexpected 'normal calciuria' and the findings in neck ultrasonography. The normalisation of calcium values after parathyroidectomy also firms this hypothesis.

Genetic study of our patient detected the variant c.602–16G>A and the variant c.2221G>A (p.Gly741Arg), both in heterozygosity, in *SLC12A3* gene. The variant c.2221G>A (p.Gly741Arg) was described in other patients with GS[9 10] and is found on dbSNP and ExAC databases with a global frequency of 0.040%. It is localised in a highly conserved residue and its functional impact was already studied. Thus, it should be considered a probably pathogenic variant. The variant c.602–16G>A is described on the database of HGMD; as a disease-causing mutation,[11] it has been identified in two different families with GS, in *trans* with other pathogenic mutations. It is also described in dbSNP and ExAC databases with a frequency of 0.0016%. However, due to lack of functional studies confirming the splicing effect, this variant is considered of undetermined significance.

Genetic study of the parents revealed in the father the variant c.602–16G>A and the mother the variant c.2221G>A (p.Gly741Arg), in *SLC12A3* gene. The genetic study of the parents concluded that the variants found are in different alleles (*trans*), which reinforce their pathogenicity.

GS is a recessively inherited disease, with simple heterozygous relatives being asymptomatic. Nevertheless, there is a small percentage of affected individuals with only one mutant allele.[12] Since the expression of NCC may be influenced by epigenetic modifications and/or silent polymorphisms, this may lead to impaired function in simple heterozygous.[12] Screening of electrolyte abnormalities in parents was done and excluded a mild phenotype.

The combination of hypokalaemia, hypomagnesaemia and hypercalcaemia is uncommon but potentially lethal. To our knowledge, there is only one case reported in the literature. In our patient, initial severe hypomagnesaemia imposed carefully Mg^{2+} reposition, taking into account the risk of worsening hypercalcaemia and justified strictly electrolytic monitoring.

Molecular study added value since permits the screening of the parents and genetic counselling when pregnancy is desired.

Learning points

- Gitelman syndrome (GS) is caused by mutations in the *SLC12A3* gene.
- It is a rare autosomal recessive tubulopathy characterised by hypokalaemia, hypomagnesaemia, hypocalciuria, metabolic alkalosis and secondary hyperaldosteronism.
- Hypercalcaemia due to hypocalciuria in these patients is extremely rare. This can be explained by impaired calciotropic hormones due to hypomagnesaemia observed in these patients.
- The presence of hypercalcaemia in the course of GS requires further evaluation in order to exclude reversible causes of hypercalcaemia.

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REFERENCES

1 Gitelman HJ, Graham JB, Welt LG. A new familial disorder characterized by hypokalemia, hypomagnesemia. *Trans Assoc Am Physiol* 1966;79:221–35.
2 Knoers NV, Levtchenko EN. Gitelman syndrome. *Orphanet J Rare Dis* 2008;3:22.
3 Scheinman SJ, Guay-Woodford LM, Thakker RV, *et al*. Genetic disorders of renal electrolyte transport. *N Engl J Med* 1999;340:1177–87.
4 Graziani G, Fedeli C, Moroni L, *et al*. Gitelman syndrome: pathophysiological and clinical aspects. *QJM* 2010;103:741–8.
5 Lin SH, Cheng NL, Hsu YJ, *et al*. Intrafamilial phenotype variability in patients with Gitelman syndrome having the same mutations in their thiazide-sensitive sodium/chloride cotransporter. *Am J Kidney Dis* 2004;43:304–12.
6 Bianchetti MG, Bettinelli A, Casez JP, *et al*. Evidence for disturbed regulation of calciotropic hormone metabolism in gitelman syndrome. *J Clin Endocrinol Metab* 1995;80:224–8.
7 Wen YK. An unusual case of Gitelman's syndrome with hypercalcemia. *Ren Fail* 2012;34:241–3.
8 Fraser WD. Hyperparathyroidism. *The Lancet* 2009;374:145–58.

9 Simon DB, Nelson-Williams C, Bia MJ, *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;12:24–30.
10 De Jong JC, Van Der Vliet WA, Van Den Heuvel LP, *et al*. Functional expression of mutations in the human NaCl cotransporter: evidence for impaired routing mechanisms in Gitelman's syndrome. *J Am Soc Nephrol* 2002;13:1442–8.
11 Glaudemans B, Yntema HG, San-Cristobal P, *et al*. Novel NCC mutants and functional analysis in a new cohort of patients with Gitelman syndrome. *Eur J Hum Genet* 2012;20:263–70.
12 Xia MF, Bian H, Liu H, *et al*. Hypokalemia, hypomagnesemia, hypocalciuria, and recurrent tetany: Gitelman syndrome in a Chinese pedigree and literature review. *Clin Case Rep* 2017;5:578–86.

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