Unusual association of diseases/symptoms

CASE REPORT

Gitelman syndrome and primary hyperparathyroidism: a rare association

Teresa Rego,1 Fernando Fonseca,1 Rita Cerqueira,2 Ana Agapito1

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), Mg²⁺ 0.71 mg/dL (r.v.1.6–2.6), 24 hours urinary Mg²⁺ 143.1 mg/24 hours (r.v.73–122), Ca²⁺ 12 mg/dL (r.v.8.4–10.2), aldosterone 47.1 ng/mL (r.v.4–31) and active renin 374.7 uU/mL (r.v.4.4–46.1). She was diagnosed with GS and was treated with spironolactone, oral K⁺ and Mg²⁺ 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 GS1 6; nevertheless, the total plasma calcium concentration has been reported to be normal.1 6 Rarely, slightly hypercalcaemia can occur in the course of GS due to dehydration-induced hyperproteininaemia.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 paraesthesia. 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/m²), 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 Ca²⁺ 11.8 mg/dL, Pi 1.9 mg/dL, 25 OH vitamin D 20.4 ng/mL (r.v. 14.8–83.1) and 25 OH vitamin D 20.4 ng/mL (r.v. 4.8–52.8) that were consistent with hypercalcaemia due to primary hyperparathyroidism (PHPT). Abdominal CT scan excluded renal lesions, such nephrolithiasis. Urinary

1Department of Endocrinology, Hospital Curry Cabral, Lisboa, Portugal
2CGC Genetics, Molecular Diagnostics and Clinical Genomics, CGC Genetics, Porto, Portugal
3Porto, Portugal

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

Accepted 29 April 2018


BMJ Case Reports: first published as 10.1136/bcr-2017-223663 on 5 June 2018. Downloaded from http://casereports.bmj.com/ on 17 September 2023 by guest. Protected by copyright.
Unusual association of diseases/symptoms

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.

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⁺⁺ and PTH normalised after surgery (Ca⁺⁺ 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

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Laboratory results (July 2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>12.9 g/L</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>11.90×10⁹/µL</td>
</tr>
<tr>
<td>Platelets</td>
<td>317×10⁹/µL</td>
</tr>
<tr>
<td>Glucose</td>
<td>69 mg/dL</td>
</tr>
<tr>
<td>Urea</td>
<td>27 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.57 mg/dL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Laboratory results—24-hour urine (vol. 2300 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K⁺</td>
<td>84.7 mEq/24 hours</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>143.1 mg/24 hours</td>
</tr>
<tr>
<td>Ca⁺⁺</td>
<td>133 mg/24 hours</td>
</tr>
<tr>
<td>Pi</td>
<td>1.1 g/24 hours</td>
</tr>
</tbody>
</table>

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.
Despite clinical and biochemical similarities between patients with GS and those on thiazide diuretic therapy, the presence of hypercalcemia in the former group is unusual. This fact can be explained by impaired calciotropic hormones due hypomagnesaemia in patients with GS. 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. Moreover in GS, normal levels of both plasma phosphate and urinary fractional phosphate excretion rule out PTH hyperfunction.

We described a rare case of a young woman with GS presenting with hypercalcemia due to PHPT. In PHPT, hypercalcemia 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.

The differential diagnosis between PHPT and familial hypercalciuric hypercalcemia 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 PHPT was sustained by concomitant hypophosphatemia, hypercalcaemia and hypercalciuria in these patients is extremely rare. This can be explained by impaired calciotropic hormones due to hypomagnesaemia observed in these patients.

The presence of hypercalcemia in the course of GS requires further evaluation in order to exclude reversible causes of hypercalcemia.

### Table 3: Laboratory tests (August 2016)

<table>
<thead>
<tr>
<th>Test</th>
<th>Value (Units)</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca²⁺</td>
<td>9.9 mg/dL</td>
<td>8.4–10.2</td>
</tr>
<tr>
<td>24 hours urine Ca²⁺</td>
<td>&lt;53 mg/24 hours</td>
<td>100–300</td>
</tr>
<tr>
<td>Pi</td>
<td>2.9 mg/dL</td>
<td>2.3–4.7</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>1.09 mg/dL</td>
<td>1.6–2.6</td>
</tr>
<tr>
<td>Parathyroid hormone (PTH)</td>
<td>14.9 pg/mL</td>
<td>14.76–83.1</td>
</tr>
<tr>
<td>25 OH vitamin D</td>
<td>35 ng/mL</td>
<td>4.8–52.8</td>
</tr>
<tr>
<td>Na⁺</td>
<td>137 mEq/L</td>
<td>136–145</td>
</tr>
<tr>
<td>K⁺</td>
<td>3.6 mEq/L</td>
<td>3.5–5.1</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>97 mEq/L</td>
<td>98–107</td>
</tr>
</tbody>
</table>

### Learning points

- **Gitelman syndrome (GS):**
  - 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 hypercalcemia in the course of GS requires further evaluation in order to exclude reversible causes of hypercalcemia.

### Contributors

All authors have substantially contributed to the conception and the design of this manuscript. TR has collected all the data, performed the required analysis and drafted the article. TR and FF are the clinicians who have observed the patient. FF, RC and AG performed a critical revision of the article. RC, MT and JP performed the genetic study. All authors approved the final version to be published.

### Funding

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

### Competing interests

None declared.

### Patient consent

Obtained.

### Provenance and peer review

Not commissioned; externally peer reviewed.

### Open Access

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/ © BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

### REFERENCES

Unusual association of diseases/symptoms


