CASE REPORT

Management of a severe case of Gitelman syndrome with poor response to standard treatment

Leila Koudsi, Stanka Nikolova, Vinita Mishra

Department of Clinical Biochemistry, Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, UK

Correspondence to
Dr Vinita Mishra,
vinita.mishra@rlbuht.nhs.uk

Accepted 30 January 2016

SUMMARY

Gitelman syndrome is an autosomal recessive distal renal tubular disorder caused by defective sodium chloride transporters. Biochemically, it presents with hypokalaemic metabolic alkalosis, hypomagnesaemia and hypocalciuria. It is usually managed with oral potassium supplements and potassium-sparing diuretics. We report a case of a 28-year-old woman whose condition worsened during pregnancy; she became resistant to standard management after delivery of her second child. She was managed in a specialist metabolic clinic through a comprehensive approach including perseverance with oral potassium supplement, weekly intravenous potassium and magnesium infusion, correction of vitamin D level and the offering of appropriate dietary advice; this controlled the patient's symptoms and prevented repeated hospital admissions. In this case report, we illustrate a patient's presentation and diagnosis with Gitelman syndrome, discuss triggers of exacerbation, review the relevant literature in terms of differential diagnoses and provide practical advice on the management of difficult cases in a specialist clinic.

BACKGROUND

Hypokalaemia is commonly due to gastrointestinal (GI) or renal loss of potassium and can be due to redistribution resulting in cellular uptake of potassium.[1] Usually, these causes are easily identified and treated in clinical practice. Gitelman syndrome (GS), an autosomal recessive disorder, is a rare cause of chronic hypokalaemia, which is usually diagnosed in late childhood or adulthood.[2] Chronic refractory hypokalaemia is the trigger for identifying patients with GS who also present with a wide spectrum of biochemical abnormalities including metabolic alkalosis, mild hypomagnesaemia, hypocalciuria and secondary hyperaldosteronism.[3 4]

GS can be confirmed through genetic testing, which would demonstrate mutations in *SLC12A3*. This gene codes for the thiazide-sensitive sodium chloride co-transporter in the distal convoluted tubules of the kidneys; mutation leads to impairment in the distal renal tubular reabsorption of sodium in GS.[2] Subsequently, the higher level of sodium is reabsorbed into the renal collecting ducts in exchange of potassium and hydrogen, resulting in their increased urinary excretion. Hypocalciuria in GS is thought to occur due to a similar mechanism as seen with the use of thiazide diuretics, causing increased passive reabsorption of calcium into the proximal renal tubule.[4]

GS is usually managed with oral potassium and magnesium supplements, potassium-sparing diuretics[4] and, occasionally, non-steroidal anti-inflammatory drugs.[5] We report a case of a 28-year-old Caucasian woman with GS who failed standard treatment, and describe the management of this patient's resistant chronic hypokalaemia.

CASE PRESENTATION

At 20 years of age, the patient had been found to have a persistently low serum potassium level (<3.0 mmol/L) during the second trimester of her first pregnancy; this was initially attributed to poor nutrition. She was started on oral potassium supplements, but in spite of this, she presented with recurrent episodes of hypokalaemia requiring hospital admissions in the third trimester. She delivered her baby while on cardiac monitoring and had received intravenous potassium infusion during labour. Her serum potassium level returned within the reference range at 24 h postdelivery. She remained asymptomatic after her first pregnancy and did not require further potassium supplements.

During her second pregnancy at 22 years of age, the patient was again found to have hypokalaemia (<3 mmol/L) in association with mild hypomagnesaemia. She had a prolonged hospital admission throughout the last 4 months of her pregnancy, for regular monitoring of electrolytes and regular intravenous potassium replacement. Delivery was induced 6 weeks before due date as it was challenging to optimise the patient's serum electrolytes. Following delivery, the serum potassium level remained below the reference range. The patient was subsequently started on Sando-K, two tablets (12 mmol of potassium/tablet) three times a day, and magnesium glycerophosphate, one tablet (8 mmol) three times a day. Despite this, she required repeated hospital admissions (almost once a month) for symptomatic hypokalaemia with potassium levels as low as 2.1 mmol/L; she presented with muscle spasm, chest tightness, peripheral paraesthesia and lethargy. These symptoms were precipitated by stressful events such as illness and menstruation. During each hospital admission, the patient received intravenous 40 mmol KCl in 500 mL 0.9% saline, with further similar infusion to continue until serum potassium reached within the reference range. Since oral potassium supplements failed to correct her chronic hypokalaemia, she was treated with potassium-sparing diuretics, initially spironolactone and subsequently amiloride, but she could not tolerate either as they caused hypotension.

At 23 years of age, the patient underwent a genetic test, which confirmed GS as a heterozygous mutation in *SLC12A3*.

To cite: Koudsi L, Nikolova S, Mishra V. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2015-212375

When referred to our metabolic clinic at 25 years of age, the patient complained of chronic fatigue, which affected her physically and emotionally. She planned not to have further pregnancies. Her clinical history showed that she was a non-smoker and did not drink alcohol; she denied any history of liquorice or laxative intake, and vomiting or chronic diarrhoea, and had no symptoms of salt craving. Her medical history included recurrent urinary tract infections secondary to urinary reflux. She had no relevant family history related to hypokalaemia. On clinical examination, weight was 37.5 kg (body mass index 16), blood pressure (BP) was 80/60 mm Hg, heart rate was 77 bpm, jugular venous pressure was not elevated, heart sounds were normal with no murmurs and no peripheral oedema, chest was clear and neurological examination was unremarkable. ECG showed sinus rhythm with no hypokalaemia-related changes. She was on 12 tablets a day of Slow-K (8 mmol of potassium/tablet) and alfacalcidol 250 ng three times a week, and was no longer on magnesium supplement. Blood and urine biochemistry were checked and are detailed in table 1.

DIFFERENTIAL DIAGNOSIS

In our patient's case, a diagnosis of GS was confirmed through genetic testing but, given resistance to standard treatment, non-inherited conditions and dietary habits that could cause/exacerbate hypokalaemic metabolic alkalosis were considered and excluded, based on medical history and blood tests. These conditions are chronic GI loss, use of laxatives and/or diuretics, primary hyperaldosteronism and excessive liquorice intake, as this can mimic hyperaldosteronism.[1 6] Notably, the absence of hypertension in GS would help to distinguish it from hyperaldosteronism.[4]

The most important inherited differential diagnosis of GS is Bartter syndrome, which is a genetic disorder that affects sodium reabsorption at the level of the ascending part of the loop of Henle. It also causes hypokalaemic metabolic alkalosis; however, it is associated with normal serum magnesium level and hypercalciuria; and also with impaired ability to concentrate urine, whereas this is preserved in GS.[4 7]

Another group of conditions that should also be differentiated from GS is hypokalaemic periodic paralysis. The low serum potassium in these cases is the result of intracellular shifting rather than total body depletion. The majority of cases are familial and caused by mutations in the skeletal muscle voltage-gated calcium channel or the sodium channel genes.[8] They are autosomal-dominant conditions and mainly affect Caucasians.[9] An important sporadic form of hypokalaemic periodic analysis is thyrotoxic periodic paralysis, which mainly affects Asian men, with an incidence of approximately 2% in patients with thyrotoxicosis of any cause.[9] Our patient was euthyroid, developed lethargy as opposed to rapid onset muscle weakness and had other biochemical abnormalities suggestive of a different aetiology to periodic paralysis.

Table 1 Serum and urine biochemistry

Parameter	Value	Normal range
Serum sodium	138 mmol/L	135–145
Serum potassium	3.4 mmol/L	3.5–5.3
Serum magnesium	0.6 mmol/L	0.70–1
Serum bicarbonate	31 mmol/L	22–29
Serum urea	3 mmol/L	2.5–7.8
Serum creatinine	71 μmol/L	50–130
Serum-adjusted calcium	2.4 mmol/L	2.20–2.60
Serum phosphate	0.97 mmol/L	0.80–1.50
Serum alkaline phosphatase	77 U/L	30–130
Serum total protein	68 g/L	60–80
25-hydroxy vitamin D	45.9 nmol/L	50–100
Serum TSH	0.89 mU/L	0.30–6.0
Serum total T4	84 nmol/L	60–150
Serum PTH	7.3 pmol/L	1.1–6.9
Serum renin	3.4 ng/ml/h	0.2–2.8
Serum aldosterone	254 pmol/L	80–300
24 h urine volume	0.46 L	
24 h urine calcium	1.1 mmol/24 h	2.5–7.5
24 h urine creatinine	7.7 mmol/24 h	9–18
Urine calcium/creatinine ratio	0.3	0.3–0.7

PTH, parathyroid hormone; T4, thyroxine; TSH, thyroid-stimulating hormone.

TREATMENT

The patient was started on weekly intravenous infusions of potassium (40 mmol) and magnesium (10 mmol) in 1 L 0.9% saline over 8 h with a reduction in the dose of oral potassium to eight tablets a day of Slow-K. She was started on magnesium glycerophosphate, one tablet three times a day, but this was later changed to magnesium lactate one tablet three times a day, as she was intolerant to the former. Since her vitamin D levels suggested deficiency, she was started on cholecalciferol 20 000 IU once every 2 weeks for 4 months followed by 20 000 IU once a month. She was given dietary advice, which included high potassium intake through fruits and vegetables, adding extra table salt to her diet and having frequent small meals throughout the day. A central venous line was inserted within a month of the patient's first clinic visit, to avoid frequent peripheral venous cannulation or delays in initiating her regular infusions. To avoid further exacerbations of hypokalaemia, she decided not to have further pregnancies and preferred to have intravenous potassium and magnesium infusion a day before her menstrual period was due.

OUTCOME AND FOLLOW-UP

The patient has been on this protocol for 3 years, with a serum potassium level >3 mmol/L on most readings (always >2.5) and a serum magnesium level consistently >0.65 mmol/L. She has been enjoying a better physical performance level, has completed a degree in law and is in a stable job; moreover, she is capable of looking after her young children. The frequency of emergency admissions for symptomatic hypokalaemia has reduced to once every 3–4 months, and this is usually precipitated by emotional stress or infections.

DISCUSSION

Patients with GS usually present with chronic hypokalaemia, which is triggered by stressful events such as menstruation and pregnancy, as seen in our patient. There are two case reports of patients with GS whose requirement for electrolyte replacement went up dramatically during pregnancy; however, in contrast to our patient, this subsequently went back to its previous level after delivery.[10 11] It has been shown that plasma renin activity and aldosterone level increase during pregnancy, and this might be related to high levels of oestrogen and progesterone. However, serum and urine potassium levels are not affected, as tubular reabsorption of potassium in the kidneys adjusts appropriately to the increased filtered load.[12 13] It could be hypothesised that while those compensatory mechanisms are sufficient to maintain potassium balance during pregnancy in normal

situations, they fail to do so in GS. Of relevance, Moustakakis and Bockorny[10] conducted a review of case reports of 24 pregnancies in women with GS, and reported no good evidence of significant risk to the fetus; however, there were six cases of oligohydramnios.

Our case report shows that patients with GS would benefit from a comprehensive approach to their management, which includes not only potassium replacement but also optimisation of their diet and correction of associated biochemical abnormalities such as hypomagnesaemia. As our patient had low serum magnesium, we checked her vitamin D level, and this was found to be deficient. Hypomagnesaemia can cause vitamin D deficiency because magnesium is a cofactor in several steps of vitamin D metabolism and its conversion into its hormonal form in the body; also, it helps in binding vitamin D to its transport protein.[14] Dietary advice was given to the patient in the form of adding table salt to her diet, as low NaCl supply could exaggerate compensatory secondary hyperaldosteronism with subsequent worsening in the level of hypokalaemia.[6] Naturally, the patient was also advised to increase the intake of potassium-rich nutrition such as fruits, bananas and potatoes.

Finally, our patient had a very low BP, at 80/60 mm Hg, when she presented to the clinic, and therefore potassium-sparing diuretics were not tried, especially as this could not be previously tolerated by her. GS is associated with low-normal BP levels and this has been suggested to be secondary to upregulation of the nitric oxide and angiotensin 1–7 systems, with subsequent reduction in vascular reactivity and decreased peripheral resistance.[15 16] Of relevance, these factors may limit the physiological response to situations that are associated with increased myocardial demand, such as pregnancy.[10]

Learning points

- Gitelman syndrome (GS) is a rare disease but should be remembered in the differential diagnosis for chronic hypokalaemia together with other inherited disorders such as Bartter syndrome.
- Women with GS should be monitored more closely during pregnancy and after delivery.
- Patients with GS should be managed in a specialist clinic, as dietary and other metabolic factors also need to be taken into consideration.
- Regular intravenous potassium infusions may prevent or reduce the frequency of acute hospital admissions in severe cases of GS.

Contributors LK collected clinical data and wrote up the manuscript after a review of the relevant literature. SN collected clinical data and reviewed the final manuscript. VM is the senior author who supervised the writing up of this manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Rhee EP, Scott JA, Dighe AS. Case records of the Massachusetts General Hospital. Case 4-2012. A 37-year-old man with muscle pain, weakness, and weight loss. *N Engl J Med* 2012;366:553–60.
2 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.
3 Gitelman HJ, Graham JB, Welt LG. A new familial disorder characterized by hypokalemia and hypomagnesemia. *Trans Assoc Am Physicians* 1966;79:221–35.
4 Knoers NV, Levtchenko EN. Gitelman syndrome. *Orphanet J Rare Dis* 2008;3:22.
5 Larkins N, Waliis M, McGillivray B, *et al*. A severe phenotype of Gitelman syndrome with increased prostaglandin excretion and favourable response to indomethacin. *Clin Kidney* 2014;7:306–60.
6 Knobel U, Modarres G, Schneemann M, *et al*. Gitelman's syndrome with persistent hypokalemia- don't forget licorice, alcohol, lemon juice, iced tea and salt depletion: a case report. *J Med Case Rep* 2011;5:312.
7 Deschênes G, Fila M. Primary molecular disorders and secondary biological adaptations in Bartter syndrome. *Int J Nephrol* 2011;2011:396209.
8 Kim JB. Channelopathies. *Korean J Pediatr* 2014;57:1–18.
9 Lam L, Nair RJ, Tingle L. Thyrotoxic periodic paralysis. *Proc (Bayl Univ Med Cent)* 2006;19:126–9.
10 Moustakakis MN, Bockorny M. Gitelman syndrome and pregnancy. *Clin Kidney J* 2012;5:552–5.
11 McCarthy FP, Magee CN, Plant WD, *et al*. Gitelman's syndrome in pregnancy: case report and review of the literature. *Nephrol Dial Transplant* 2010;25:1338–40.
12 Brown MA, Sinosich MJ, Saunders DM, *et al*. Potassium regulation and progesterone-aldosterone interrelationships in human pregnancy: a prospective study. *Am J Obstet Gynecol* 1986;155:349–53.
13 Sealey JE, Itskovitz-Eldor J, Rubattu S, *et al*. Estradiol- and progesterone-related increases in the renin-aldosterone system: studies during ovarian stimulation and early pregnancy. *J Clin Endocrinol Metab* 1994;79:258–64.
14 Zittermann A. Magnesium deficit—overlooked cause of low vitamin D status? *BMC Med* 2013;11:229.
15 Calò L, Davis PA, Milani M, *et al*. Increased endothelial nitric oxide synthase mRNA level in Bartter's and Gitelman's syndrome. Relationship to vascular reactivity. *Clin Nephrol* 1999;51:12–17.
16 Calò LA, Schiavo S, Davis PA, *et al*. ACE2 and angiotensin 1–7 are increased in a human model of cardiovascular hyporeactivity: pathophysiological implications. *J Nephrol* 2010;23:472–7.