CASE REPORT

Differential diagnosis for chronic hypokalaemia

Laura Stimson,¹ Tim Reynolds²

¹Burton Hospitals NHS Foundation Trust, Burton on Trent, UK

²Clinical Chemistry, Queen's Hospital, Burton on Trent, UK

Correspondence to

Dr Laura Stimson,
laurastimson@nhs.net

Accepted 15 May 2018

SUMMARY

Doctors will often see patients with chronic hypokalaemia, frequently this is secondary to gastrointestinal losses, diuretics or renal disease. However, in this case report we review a rarer cause of chronic hypokalaemia—Gitelman syndrome (GS). GS is an uncommon genetic disorder which causes primary renal tubular hypokalaemic metabolic alkalosis with secondary hypomagnesaemia and hypocalciuria. Although rare, it is important to remember GS when considering differential diagnoses for chronic hypokalaemia. We report the case of a woman who presented to the ophthalmology department with sclerochoroidal calcification. An ophthalmologist was reviewing the medical literature, which prompted them to investigate for GS. A diagnosis was formed at that time based on the blood and urine chemistry results. However, later we were able to offer the patient genetic testing, which confirmed our provisional diagnosis.

BACKGROUND

Gitelman syndrome (GS) is a rare genetic disorder inherited as an autosomal recessive trait. It is caused by a genetic mutation affecting the function of the thiazide-sensitive sodium-chloride cotransporter located in the distal convoluted tubule of the kidney.¹ It is characterised by hypomagnesaemia, hypokalaemia and hypocalciuria. The prevalence is estimated at approximately 1 in 40 000.²

CASE PRESENTATION

Our patient was under the ophthalmology department for bilateral fundal abnormalities which had suddenly developed around the age of 49 years. These had been picked up on a routine eye test. She did not have any visual disturbance as a result of these. In 2004 the ophthalmology department found a publication on GS and performed blood and urine tests on our patient. These blood tests showed hypokalaemia, hypomagnesaemia and a pH of 7.52. Twenty-four hour urine analysis showed hypocalciuria. With these results our patient was diagnosed as having GS.

She was later referred to the chemical pathology clinic by her rheumatology team for an opinion regarding the long-term management of GS. She was under rheumatology for pseudogout, which had arisen as a consequence of the GS. Her pseudogout would flare up occasionally, but was well controlled with ibuprofen during these times.

Her main concern was that her elective operations were being cancelled by the anaesthetics

team due to concerns regarding her hypokalaemia. Otherwise, she was not experiencing any symptoms of GS at this time and she felt well in herself. No one else in her family had a history of electrolyte abnormalities or had been diagnosed with GS.

INVESTIGATIONS

Initial biochemical testing (prior to starting any electrolyte supplementation/treatment) showed serum adjusted calcium 2.6 mmol/L, urine calcium excretion 3 mmol/24 hours (normal range 15–20 mmol/24 hours), serum magnesium 0.35 mmol/L, urine magnesium excretion 9.8 mmol/24 hours (normal range 3–5 mmol/24 hours), serum potassium 3.3 mmol/L and urine potassium excretion 145 mmol/24 hours (normal range 25–100 mmol/24 hours). Her serum creatinine levels have remained consistently within normal ranges from time of diagnosis to now. These potassium and magnesium results shown here were thought to be consistent with GS.

Our patient then went on to have genetic testing in 2017. This showed two heterozygous pathogenic variants in SLC12A3 which, assuming biparental inheritance, is consistent with a diagnosis of GS.

1. c.1930delC in exon 16, which is predicted to lead to a frameshift and result in an abnormal protein with a premature stop codon.
2. c.2221G>A in exon 18, which is predicted to result in an abnormal protein p.(Gly741Arg).

The SLC12A3 gene is responsible for encoding the thiazide-sensitive sodium-chloride cotransporter.

DIFFERENTIAL DIAGNOSIS

GS shows significant overlap with Bartter syndrome and it is often difficult to distinguish between these disorders. In the past they were considered part of the same spectrum of disease, but now they are distinguished as separate and distinct disorders. Bartter syndrome tends to present at a younger age, urinary calcium excretion is often normal or high and the magnesium is normal or only mildly reduced.³ Bartter syndromes are caused by recessive mutations in the SLC12A1 gene (type 1), the KCNJ1 gene (type 2), the CIC-Kb gene (type 3), the BSND gene (type 4A) or both the CIC-Ka and CIC-Kb genes (type 4B).⁴

TREATMENT

Mainstay of GS treatment is alleviating any symptoms. Patients with GS are at risk of cardiac arrhythmias as a result of the electrolyte imbalance. Other than renal transplantation there is no cure for GS,

To cite: Stimson L, Reynolds T. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-223680

we can only treat the electrolyte levels with supplements or other pharmacological treatments. From the literature there was only evidence of one patient who developed chronic renal insufficiency and subsequent progression to end-stage renal disease, so renal transplantation is extremely rarely, if ever, indicated.⁵

At the time of diagnosis, the patient was started on potassium supplements and magnesium supplements. She believed that these were making her feel unwell. After being referred to pathology clinic we trialled a course of indomethacin, with a good response on the potassium levels, but little response on the calcium or magnesium levels. However, this caused diarrhoea and was not tolerated by the patient. Naproxen 500mg/day was also not tolerated due to gastrointestinal side effects. It was therefore decided that we would only treat her electrolyte levels when necessary, for example, several weeks before any anaesthetic was needed.

The patient was discharged from the ophthalmology department after several years of follow-up. Her calcium deposits had remained unchanged during this time and she had remained symptom free. The ophthalmology team suggested a prompt referral back to the eye department if any symptoms occurred.

OUTCOME AND FOLLOW-UP

We have opted to monitor her blood electrolyte levels and treat as her symptoms as she requires. We will continue to see this patient approximately every 6 months in chemical pathology clinic for monitoring of her serum electrolytes.

DISCUSSION

GS commonly presents in late childhood or early adulthood. It can present with symptoms such as salt craving, musculoskeletal cramps, muscle weakness, aches, fatigue, dizziness, nocturia and polydipsia.⁶ In this case, the patient presented later in life with sclerochoroidal calcification, which has been reported to be associated with GS.⁷ The suggested mechanism is that the sclerochoroidal lesions are crystal deposits of calcium pyrophosphate dihydrate, which possibly develop as a consequence of hypomagnesaemia.⁷ These same deposits have been shown to accumulate in joints, causing pseudogout or chondrocalcinosis.⁷

Diagnosis of GS should still be made on the patient's clinical history plus urine and blood analysis. It is important to rule out other causes of electrolyte abnormalities, for example, by doing a urine diuretic screen. Genetic testing is now possible on the National Health Service (NHS), but is costly and currently only undertaken by very few laboratories. Once a diagnosis of GS has been made, it is important to consider genetic counselling. Adult patients with GS, unless consanguineous, are at low risk of having children with GS; approximately 1 in 400.² There is currently no antenatal testing for GS. At the moment, there are no UK guidelines regarding who should undergo genetic testing for GS. Therefore, it is the decision of the individual clinician as to whether they choose to offer this test in conjunction with the laboratory staff. The current cost for performing sequencing of the entire coding region of gene(s) plus copy number analysis in an NHS setting is £625.⁸

In this case we chose a trial of indomethacin for treatment. Indomethacin has been shown to be more effective than amiloride or eplerenone in increasing mean plasma potassium concentration.⁹ A study looking into treatment options for hypokalaemia in GS proposed that the effect of indomethacin in patients with GS may be caused by the increase in loop NaCl reabsorption, leading, in turn, to a decrease in NaCl delivery to the distal convoluted tubule, and the inhibition of renin release by the juxtaglomerular apparatus.⁹

Most patients remain asymptomatic and the long-term prognosis of GS is good, with progression to renal insufficiency being rare.³ However, studies have shown that GS can negatively impact quality of life in a large proportion of patients with GS.⁶ Therefore, we would recommend reviewing patients with GS one to two times per year in order to address any negative symptoms.

Learning points

- ▶ Consider Gitelman syndrome when investigating a patient with chronic hypokalaemia.
- ▶ Gitelman syndrome is differentiated from Bartter syndrome by the presence of hypocalciuria.
- ▶ Although the diagnosis is made on blood and urine analysis, it is now possible to confirm the diagnosis with genetic testing.

Contributors Written by LS. TR contributed to writing of the case report and approved the final manuscript.

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.

© 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

- 1 Nakhoul F, Nakhoul N, Dorman E, *et al*. Gitelman's syndrome: a pathophysiological and clinical update. *Endocrine* 2012;41:53–7.
- 2 Knoers NV, Levchenko EN. Gitelman syndrome. *Orphanet J Rare Dis* 2008;3:22.
- 3 Gjata M, Tase M, Gjata A, *et al*. Gitelman's syndrome (familial hypokalaemia-hypomagnesaemia). *Hippokratia* 2007;11:150–3.
- 4 Bartter's Syndrome - NORD (National Organization for Rare Disorders). *NORD* 2018 <https://rarediseases.org/rare-diseases/bartters-syndrome/> (accessed 9 May 2018).
- 5 Bonfante L, Davis PA, Spinello M, *et al*. Chronic renal failure, end-stage renal disease, and peritoneal dialysis in Gitelman's syndrome. *Am J Kidney Dis* 2001;38:165–8.
- 6 Cruz DN, Shaer AJ, Bia MJ, *et al*. Yale Gitelman's and Bartter's Syndrome Collaborative Study Group. Gitelman's syndrome revisited: an evaluation of symptoms and health-related quality of life. *Kidney Int* 2001;59:710–7.
- 7 Honavar S, Shields C, Demirci H, *et al*. *Archives of Ophthalmology* 2001;119:833–40.
- 8 UK Genetic Testing Network. Gitelman Syndrome: Postnatal Diagnosis Routine by Sequencing of the entire coding region of gene (s) PLUS copy number analysis at Cambridge RGC in 40 days. 2018 <https://ukgtn.nhs.uk/find-a-test/search-by-disorder-gene/details/524/> (Accessed 15 Feb 2018).
- 9 Blanchard A, Vargas-Poussou R, Vallet M, *et al*. Indomethacin, amiloride, or eplerenone for treating hypokalaemia in Gitelman syndrome. *J Am Soc Nephrol* 2015;26:468–75.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow