CASE REPORT

Gitelman or Bartter type 3 syndrome? A case of distal convoluted tubulopathy caused by CLCNKB gene mutation

António José Cruz, Alexandra Castro

Serviço de Medicina Interna, Centro Hospitalar de Entre o Douro e Vouga—Hospital de São Sebastião, Santa Maria da Feira, Portugal

Correspondence to
Dr António José Cruz,
ajcruzborges@gmail.com

SUMMARY

A 32-year-old woman with no significant medical history was sent to our consultation due to hypokalaemia (<3.0 mmol/l). Her main complaints were longstanding polyuria and nocturia. Physical examination was normal. Basic investigations showed normal renal function, low serum potassium (2.7 mmol/l) and magnesium (0.79 mmol/l), metabolic alkalosis (pH 7.54; bicarbonate 32.5 mmol/l), elevated urinary potassium (185 mmol/24 h) and normal urinary calcium (246 mg/24 h). Thiazide test revealed blunted response. Chronic vomiting and the abuse of diuretics were excluded. Genetic tests for SLC12A3 gene mutation described in Gitelman syndrome (GS) came negative. CLCNKB gene mutation analysis present in both GS and Bartter (BS) type 3 syndromes was positive. The patient is now being treated with potassium and magnesium oral supplements, ramipril and spironolactone with stable near-normal potassium and magnesium levels. This article presents the case of a patient with hypokalaemia caused by CLCNKB gene mutation hard to categorise as GS or BS type 3.

BACKGROUND

Hypokalaemia is one of the most common electrolytic disturbances in clinical practice.

When defined as a value of less than 3.6 mmol of potassium per litre, hypokalaemia is found in over 20% of hospitalised patients.[1]

Hypokalaemia can result from poor potassium intake, increased translocation into the cells or most commonly, increased losses in the urinary or the gastrointestinal tract. The cause of hypokalaemia is in most cases obvious from the history of the patient and in the majority of cases is related to the use of drugs, especially diuretics.[1 2] Nevertheless, in some patients its aetiology is not straightforward and may demand a work-up with sometimes surprising conclusions, which are decisive for correct management and treatment of the patient.

One of the least frequent yet possible diagnoses for hypokalaemia are salt-losing tubulopathies, namely Gitelman (GS) and Bartter (BS) syndromes.[1] Although congenital, these disorders may manifest late in childhood or even adulthood and should always be borne in mind in cases of otherwise unexplained often severe hypokalaemia.[3] In this article we present the case of a patient with chronic hypokalaemia caused by CLCNKB gene mutation hard to categorise as GS or BS type 3.

CASE PRESENTATION

We present the case of a 32-year-old woman sent to our consultation by her family physician due to persistent hypokalaemia (<3.0 mmol/l).

She was married, had one healthy child and worked as a florist. Her medical history as a child was uneventful. She had a history of colic polyps and had mild chronic venous insufficiency for which she took a venotropic. She took no other medication. She was a non-smoker, consumed no alcohol or drugs and denied consuming herbal products. There were no aberrant dietary habits. Her family history was unremarkable.

The only complaints the patient had were longstanding asthenia, polyuria and nocturia, which she could not determine in duration. She also described episodes of what seemed to be carpopedal spasms which should have started by the age of 10.

Her physical examination was normal, with low-normal blood pressure (100–110/50–60 mm Hg). She weighed 67 kg and was 165 cm tall. Body mass index was 24.6 kg/m^2.

INVESTIGATIONS

The patient presented to us with the following laboratory findings: K^+ 2.7 mmol/l (3.5–5.0 mmol/l); Mg^{2+} 0.79 mmol/l (0.85–1.15 mmol/l); Ca^{2+} 8.8 mg/dl (8.5–10.2 mg/dl); Cl^- 90 mmol/l (95–105 mmol/l); Na^+ 138 mmol/l (135–145 mmol/l); creatine 0.6 mg/dl (0.6–1.1 mg/dl); urea 26.0 mg/dl (15.0–40.0 mg/dl).

Arterial blood gas analysis showed metabolic alkalosis (pH 7.54; HCO_3^- 32.5 mmol/l; pCO_2 38 mm Hg). ECG revealed normal sinus rhythm, with no alteration consistent with hypokalaemia.

Renal ultrasound was normal, with no signs of lithiasis.

She was admitted in our ward for potassium supplementation and investigation of the aetiology of hypokalaemia.

The 24 h-urine collection electrolyte panel showed: K^+ 185 mmol/24 h (25–125 mmol/24 h); Na^+ 495 mmol/24 h (20–200 mmol/24 h); Cl^- 636 mmol/24 h (110–250 mmol/24 h); Ca^{2+} 246 mg/24 h (100–300 mg/24 h); urinary Ca^{2+}/-creatine ratio of 178 mg/g (<220 mg/g).

Both serum renin and aldosterone were high: 185.4 pg/ml (<27.8 pg/ml) and 481.7 pg/ml (25–160 pg/ml), respectively.

A thiazide test was performed, during which 50 mg of oral hydrochlorothiazide was given and the differential of the fractional excretion of

To cite: Cruz AJ, Castro A. *BMJ Case Reports* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2012-007929

chloride after and before administration of the diuretic was calculated. The final result was a 1.73% rise in fractional excretion of chloride, which meant a blunted response to thiazides (<2.3%).[4]

DIFFERENTIAL DIAGNOSIS

Before a patient with known hypokalaemia and metabolic alkalosis, associated with high renin and aldosterone levels and low-normal blood pressure levels, the main diagnoses to be considered are: chronic vomiting, laxative abuse, diuretic abuse and salt-losing tubulopathies, namely GS and BS.[2 5]

Chronic vomiting, as in the context of bulimia or anorexia nervosa, leads to loss of HCl and volume contraction, which explains the hypokalaemia, metabolic alkalosis and high renin and aldosterone levels. In our case, this diagnosis was excluded both because the patient had no signs of persistent vomit induction, such as scars or ulcers on the dorsum of her hands or dental erosions, and her urinary chloride levels were too high, consistent with active renal salt loss. For this same reason, laxative abuse could be promptly excluded.

The hypothesis of diuretic abuse could fit well with all the laboratory findings of the patient. Unfortunately, a urinary diuretic screen was not available in our laboratory. Nonetheless the patient kept very low potassium levels while she was in our ward and no outer medication was accepted.

The main differential diagnosis stood between GS and BS. The likeliest hypothesis seemed to be GS for a number of reasons: presentation in adulthood, presence of hypomagnesemia and blunted response to hydrochlorothiazide. However, the absence of hypocalciuria was not in favour of this diagnosis.[6–9]

Blood was sent to the Molecular Genetics Laboratory of Addenbrooke's hospital (Cambridge University hospitals) for DNA mutation analysis. No mutations were detected in exons 1–26 of the SLC12A3 gene using fluorescent sequence analysis. DNA screening for mutations and deletions in exons 1–19 of the CLCKNB gene found two mutations, namely: (1) fluorescent sequencing detected single base pair substitution c.610 G>A (p.Ala204Thr) in exon 6, previously reported as a Bartter founder mutation[10] and (2) multiplex ligation dependent probe amplification analysis detected a heterozygotous deletion of exon 1–19, previously reported in BS patients.[11]

TREATMENT

The patient started a four-drug regimen in order to have near normal potassium and magnesium levels: oral potassium chloride supplements, 4800 mg/day in four divided doses; oral magnesium aspartate supplements, 1229.6 mg three times daily; spironolactone, titrated to a maximal dose of 300 mg/day and low dose ramipril (1.25 mg/day).

OUTCOME AND FOLLOW-UP

The patient has been followed on a twice-year basis for the last 2 years and has been asymptomatic. She has had stable near-normal potassium and magnesium levels (3.2–3.6 mmol/l (3.5–5.0 mmol/l) and 0.8–0.9 mmol/l (0.85–1.15 mmol/l), respectively) with the medication we started. Her creatine levels have always been normal thus far. She and her first-degree relatives have been sent to a geneticist consultation.

DISCUSSION

BS and GS both result from congenital defects in renal tubular handling of chloride, potassium and sodium and are conveyed by autosomal recessive transmission.

They are characterised by hypokalaemia with increased potassium excretion, normal to low blood pressure, hypochloremic metabolic alkalosis and hyperreninemic hyperaldosteronism secondary to volume contraction.

Common features of patients with these syndromes include constipation, muscle cramps and weakness/fatigue but phenotypic heterogeneity is immense according to the nature of the mutation involved.[3 6–9]

Classically, salt-losing tubulopathies were grossly divided into BS and GS in relation to the location of the molecular defect, respectively, the thick ascending limb of the loop of Henle and the distal convoluted tubule. BS was further subdivided into five types according to the gene mutation (types 1–5).[6 9]

Recently, another classification has been proposed of BS and GS as one disease entity divided into three groups according to the location of the channels or transporters (figure 1) and clinical presentation[12]:

- Distal convoluted tubule disorders—GS and BS type 3 or classic BS (SLC12A3 gene mutation encoding the Na-Cl cotransporter—NCCT—and CLCNKB gene mutation encoding the basolateral Cl channel Kb—ClC-Kb, respectively);
- Loop disorders—BS type 1 and 2 (SLC12A1 gene mutation encoding the Na-K-2Cl cotransporter—NKCC2—and KCNJ1 gene mutation encoding the renal outer medullary K channel—ROMK, respectively);
- Compound disorders—BS type 4 and 5 (BSND gene mutation encoding barttin, a subunit of ClC-Ka and ClC-Kb and L125P gene mutation encoding calcium-sensing receptor—CASR, respectively).

This new classification was suggested based on the fact that the genotype–phenotype correlation is not so clear-cut and that phenotype overlap may occur.[13–15]

Traditionally, classic BS or BS type 3 was described as a disorder commonly diagnosed at school age or even adolescence in patients presenting with polyuria, polydipsia and a tendency to dehydration.[9]

When the mutation in the chloride channel gene CLCNKB was identified, it was considered that chloride reabsorption in the loop of Henle was primarily and exclusively impaired. However, later, the spectrum of the clinical presentation with a strong distal convoluted tubule signature became apparent, contrasting with the more severe and life-threatening loop disorders, namely antenatal BS (BS types 1 and 2).[3] Yet the full phenotypic spectrum of the Bartter-like syndromes can result from mutations in CLCNKB.[13 15]

The mixed thiazide-furosemide-like clinical presentation of a tubular disorder with ClC-Kb-defect is most likely explained by differences in the expression of the chloride channels ClC-Ka and ClC-Kb in the distal nephron. Expression of both chloride channels occurs in the thick ascending limb of Henle's loop, but ClC-Kb is the only one expressed in the distal convoluted tubule, where it predominates. Thus, there is a potential for compensation for an isolated ClC-Kb defect in Henle's loop by ClC-Ka, whereas no such option exists in the distal convoluted tubule (figure 1). Other channels in Henle's loop have been described that may compensate for the defective ClC-Kb, such as the potassium-chloride cotransporter, cystic fibrosis transmembrane regulator and CLC-5. That is why BS type 3 is now primarily regarded as a distal convoluted tubule disorder.[3 13 15]

The majority of patients share symptoms with patients with a pure thiazide type of disorder (ie, GS), such as postnatal

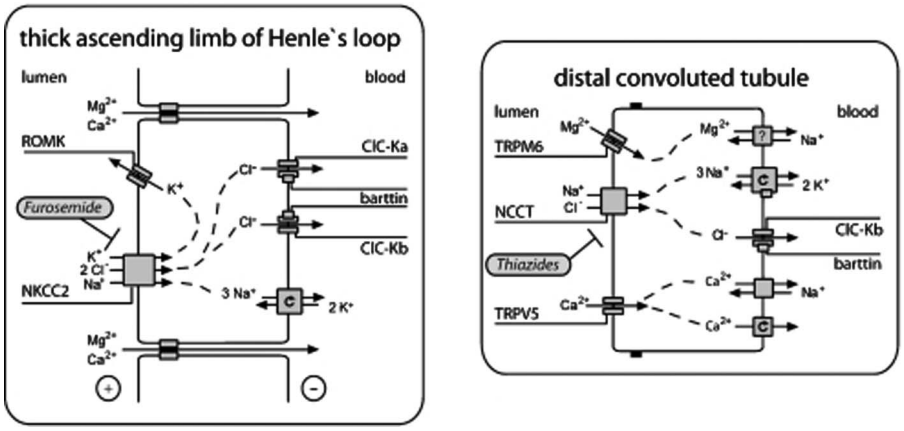

Figure 1 Solute transport mechanisms in Henle's loop and distal convoluted tubule. Expression of ClC-Ka compensates for the ClC-Kb defect in Henle's loop but not in the distal convoluted tubule. Adapted from Seyberth *et al*.[3]

manifestation, a largely preserved renal concentrating capacity, low plasma levels of magnesium and diuretic insensitivity to thiazide administration, which is the case of our patient.[3 8 14]

The occurrence of hypocalciuria was once thought to be pathognomonic of GS and was used as the distinguishing feature between BS type 3 and GS.[6 9] However, among patients with the CLCNKB gene mutation, high, normal or even low urinary calcium levels have been found, once again providing proof of the great clinical variability among patients with this particular gene mutation.[7 8] Owing to its similarity to GS, some authors now state that GS is caused by both the classic SLC12A3 gene mutation encoding NCCT and CLCNKB gene mutation encoding ClC-Kb.[16]

Bearing in mind this possible overlap between the two syndromes and in order to prevent further confusion in the categorisation of these patients, we believe they should be grouped according to the classification presented above and this way said to have a distal convoluted tubulopathy.

Treatment of this disorder demands lifelong supplementation of potassium and magnesium combined with the aldosterone antagonist spironolactone or eplerenone and/or potassium sparing diuretic such as amiloride (in high doses—300 and 40 mg/day for spironolactone and amiloride, respectively). If necessary, one can add other antihypokalemic therapy, such as ACE inhibitors, angiotensin receptor blockers or direct renin inhibitors, taking caution that these may further lower already low blood pressure levels.[3 6–9 16]

Although described in BS patients, we chose not to start treatment with indomethacin, because we did not have a confirmation of renal overproduction of prostaglandin E_2 in our patient, which is in fact usually not very high in BS type 3.[3 7 9]

The prognosis for our patient is overall excellent. Nevertheless, there are certain precautions to be taken.

Being a distal convoluted tubule disorder, there is a tendency of aggravation with age, which means that the therapeutic effort might have to be intensified over time.[3] There are also three potential complications one must be aware of:

- There is a small risk of renal failure.[3 17] Deterioration of the renal function seems to be related not to the state of chronic hypokalaemia (the once stated 'hypokalemic nephropathy'), but to the effects of aldosterone on the proximal tubule epithelium and renal interstitium and the fluctuations in circulating volume. It is therefore important to maintain a long-term blockade of the mineralocorticoid receptor with spironolactone and an adequate fluid status.[17]
- Cardiac arrhythmias and QT prolongation induced by hypokalaemia and hypomagnesaemia put the patient at risk of sudden cardiac death. For this reason, commonly used medicines that prolong QT interval, such as macrolides, antihistamines, psychotropics, antitussives, antimycotics and β_2-agonists, should be avoided.[3]
- Chondrocalcinosis—a possible complication of GS related to chronic hypomagnesaemia.[16]

Learning points

- Hypokalaemia is one of the most common electrolytic disturbances and its aetiology is not always straightforward, demanding a correct work-up.
- In spite of being congenital disorders, salt-losing tubulopathies may present in adulthood and should be borne in mind in the diagnosis of hypokalaemia.
- The distinction between Gitelman and Bartter type 3 syndrome is sometimes blurred and it may be preferable to categorise patients with CLCNKB gene mutation as having a distal convoluted tubulopathy.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Gennari FJ. Hypokalemia. *N Engl J Med* 1998;339:451–8.
2 Assadi F. Diagnosis of hypokalemia: a problem-solving approach to clinical cases. *Iran J Kidney Dis* 2008;2:115–22.
3 Seyberth HW, Schlingmann KP. Bartter- and Gitelman-like syndromes: salt-losing tubulopathies with loop or DCT defects. *Pediatr Nephrol* 2011;26:1789–802.
4 Colusi G, Bertinelli A, Tedesehi S. A thiazide test for the diagnosis of renal tubular hypokalemic disorders. *Clin J Am Soc Nephrol* 2007;2:454–60.
5 Groeneveld JH, Sijpkens YW, Lin SH, *et al*. An approach to the patient with severe hypokalaemia: the potassium quiz. *QJM* 2005;98:305–16.
6 Fremont OT, Chan JC. Understanding Bartter syndrome and Gitelman syndrome. *World J Pediatr* 2012;8:25–30.
7 Unwin RJ, Capasso G. Bartter's and Gitelman's syndromes: their relationship to the actions of loop and thiazide diuretics. *Curr Opin Pharmacol* 2006;6:208–13.
8 Jeck N, Schlingmann KP, Reinalter SC, *et al*. Salt handling in the distal nephron: lessons learned from inherited human disorders. *Am J Physiol Regul Integr Comp Physiol* 2005;288:R782–95.
9 Naesens M, Steels P, Verberckmoes R, *et al*. Bartter's and Gitelman's syndromes: from gene to clinic. *Nephron Physiol* 2004;96:65–78.
10 Simon DB, Bindra RS, Mansfield TA, *et al*. Mutations in the chloride channel gene, CLCNKB, cause Bartter's syndrome type III. *Nat Genet* 1997;17:171–8.
11 Rodríguez-Soriano J, Vallo A, Pérez de Nanclares G, *et al*. A founder mutation in the CLCNKB gene causes Bartter syndrome type III in Spain. *Pediatr Nephrol* 2005;20:891–6.

12 Nozu K, Iijima K, Kanda K, *et al*. The pharmacological characteristics of molecular-based inherited salt-losing tubulopathies. *J Clin Endocrinol Metab* 2010;95:E511–18.
13 Konrad M, Vollmer M, Lemmink HH, *et al*. Mutations in the chloride channel gene CLCNKB as a cause of classic Bartter syndrome. *J Am Soc Nephrol* 2000;11:1449–59.
14 Zelikovic I, Szargel R, Hawash A, *et al*. A novel mutation in the chloride channel gene, CLCNKB, as a cause of Gitelman and Bartter syndromes. *Kidney Int* 2003;63:24–32.
15 Colussi G, De Ferrari ME, Tedeschi S, *et al*. Bartter syndrome type 3: an unusual cause of nephrolithiasis. *Nephrol Dial Transplant* 2002;17:521–3.
16 Knoers NV, Levtchenko EN. Gitelman syndrome. *Orphanet J Rare Dis* 2008;3:22.
17 Walsh SB, Unwin E, Vargas-Poussou R, *et al*. Does hypokalaemia cause nephropathy? An observational study of renal function in patients with Bartter or Gitelman syndrome. *QJM* 2011;104:939–44.