eSELF ASSESSMENT QUESTIONS

Unexplained hypokalaemia and metabolic alkalosis

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A 23 year old girl was admitted to the medical admission unit with a three month history of malaise and generalised muscle cramps. Her general practitioner performed routine biochemistry and had revealed a potassium concentration of 2.0 mmol/l. She was investigated four years before for a similar electrolyte disturbance which was found to be inconclusive. She was currently taking the combined oral contraceptive pill. There was no history of diarrhoea or vomiting. There was no family history of endocrine disease. On examination the patient appeared well, her body mass index was 19, and her blood pressure was 118/70 mm Hg. She was euvoelaemic clinically. She had no evidence of postural hypotension nor did she have any peripheral oedema. Her skin turgor was normal.

Biochemical investigations revealed a marked hypokalaemic metabolic alkalosis (see table 1). Full blood count, liver function tests, and serum calcium were within normal limits.

Table 1 Biochemical investigations

Investigation	Value
Sodium (mmol/l)	128
Potassium (mmol/l)	2.0
Chloride (mmol/l)	73
Bicarbonate (mmol/l)	40
Calcium (mmol/l)	2.32
Magnesium (mmol/l)	0.64
Urea (mmol/l)	2.8
Creatinine (μ mol/l)	71
Urine osmolality (mosmol/l)	460

Despite aggressive oral potassium supplementation the patient remained hypokalaemic (potassium = 3.0 mmol/l).

Questions

- (1) What are the causes of a hypokalaemic metabolic alkalosis?
- (2) What further investigations may be warranted in this patient?
- (3) What is the underlying diagnosis and what are the treatment options for this condition?

Answers**QUESTION 1**

The causes of hypokalaemic alkalosis can be divided into loss in the gastrointestinal tract or loss in the urine (see box 1).¹

Box 1: Causes of hypokalaemic alkalosis*Potassium loss in gastrointestinal tract*

- Vomiting.
- Laxative abuse.
- Infectious diarrhoea.
- Tumours (for example, VIPoma).
- Enteric fistula.
- Cancer therapy (for example, radiation enteropathy).

Potassium loss in urine

- Mineralocorticoid excess: primary hyperaldosteronism, congenital adrenal hyperplasia (17 α -hydroxylase deficiency), renin secreting tumours, Cushing's syndrome, renovascular hypertension.
- Apparent mineralocorticoid excess: Liddle's syndrome, 11 β -hydroxysteroid dehydrogenase deficiency.
- Impaired chloride associated sodium transport: Gitelman's syndrome, Bartter's syndrome.
- Drug induced: diuretics, fludrocortisone, licorice, aminoglycosides, high dose glucocorticoids.

QUESTION 2

A careful physical examination should be undertaken to look for signs of self induced vomiting which include calluses and scarring of the dorsum of the hand (Russell's sign), dental erosions caused by chronic exposure to acid gastric secretions, and puffy cheeks resulting from hypertrophy of the salivary glands. A urine chloride estimation may help to contribute to the aetiology of hypokalaemia. Urinary chloride is normally very low in patients who have been vomiting and have a metabolic alkalosis. The value of urinary chloride with surreptitious diuretic use is variable—high if the diuretic effect is still acting, but low when the diuretic effect has worn off. A high urine chloride concentration, on the other hand, suggests either continued diuretic therapy or Bartter's or Gitelman's syndrome. A urinary chloride less than 20 mmol/l is seen in a patient with low serum chloride and conversely more than 20 mmol/l if the serum chloride is raised.² The urine chloride concentration was raised in

this patient at 60 mmol/l, which was inappropriately raised for the low plasma chloride concentration (73 mmol/l).

Due to her normal blood pressure, it could be safely concluded that she did not have a condition with mineralocorticoid excess. We did not suspect any psychopathology or access to diuretics. Her laxative and diuretic screen were negative on two separate occasions.

QUESTION 3

Due to the high urine chloride concentration and normal diuretic screen, this suggests that the patient may have either Bartter's or Gitelman's syndrome. Because our patient presented in adulthood, was able to concentrate her urine, had a low urinary calcium excretion and low serum magnesium, she best fits the diagnosis of Gitelman's syndrome (see table 2).³ The primary defect is an abnormality in the gene coding for the thiazide sensitive Na-Cl cotransporter in the distal tubule.⁴ This defect accounts for both the magnesium wasting and the decrease in calcium excretion. The treatment which must be life long, is aimed to minimise the effects of the secondary increase in prostaglandin and aldosterone production. The combination of a non-steroidal anti-inflammatory and an aldosterone antagonist can raise the plasma potassium concentration towards the normal range and reverse the metabolic alkalosis.⁵

Final diagnosis

Gitelman's syndrome.

- 1 Gennari FJ. Hypokalaemia. *N Engl J Med* 1998;339:451–7.
- 2 Walmsley RN, Watkinson LR, Koay ESC. *Cases in chemical pathology*. PG Publishing, 1988.
- 3 Monnens I, Bindels R, Grunfeld JP. Gitelman syndrome comes of age. *Nephrol Dial Transplant* 1998;13:16–17.
- 4 Simon DB, Nelson Williams C, Bia MJ, et al. Gitelman's variant of Bartter's syndrome. *Nat Genet* 1996;12:24–30.
- 5 Colussi G, Rombola G, De Ferrari ME, et al. Correction of hypokalaemia with antialdosterone therapy in Gitelman's syndrome. *Am J Nephrol* 1994;14:127–35.

Table 2 Characteristics of Bartter's syndrome and Gitelman's syndrome

	Bartter's syndrome	Gitelman's syndrome
Localisation of defect	Ascending limb of Henle	Distal tubule
Age of presentation	Prenatal, during infancy or early childhood	Late childhood or at adulthood
Biochemical differences	Serum magnesium may be decreased Urinary excretion of calcium increased or normal	Serum magnesium decreased Urinary calcium excretion reduced
Molecular differences	Na-K-2Cl transporter or apical K channel or basolateral Cl channel in thick ascending limb of Henle	Na-Cl cotransporter in the distal tubule
Functional studies	Concentrating capacity severely impaired	Concentrating capacity normal or slightly impaired