

## Exceptional Case

# Chronic hypokalaemia in a hypertensive patient

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### Abstract

Hypokalaemia in hypertensive patients is a ‘red flag’ bringing to mind various classic secondary and genetic causes related to both hypokalaemia and hypertension. We encountered a patient who had an unusual cause for his disturbance that, to our knowledge, has not been described in hypertensive patients.

**Keywords:** Gitelman syndrome; hyperaldosteronism; hypokalaemia; hypomagnesaemia

### Introduction

A 45-year-old man of Turkish extraction was referred to us for evaluation of hypokalaemia. Hypertension had been diagnosed about a year earlier and treatment with amlodipine 10 mg daily had been given. Serum potassium concentrations <2.5 mmol/L had been observed 3 months earlier that were not associated with hydrochlorothiazide administration. A brief workup for primary aldosteronism revealed plasma renin activity and plasma aldosterone values within normal limits. Treatment with 120 mmol potassium citrate (Kaliner Brause®) daily had not ameliorated the problem. Past medical history revealed a penchant to ingest Chinese herbal preparations. The patient had spasticity of his left leg, which was attributed to multiple sclerosis; however, this condition was quiescent and not under treatment. The patient had several siblings. Some family members exhibited diabetes, angina pectoris and renal stones. The patient had worked in the chemical industry but was currently unemployed. The patient was 169 cm tall, weighed 81 kg, blood pressure was 130/90 mmHg under treatment and the heart rate was 76 b.p.m. Other than spasticity of the left leg, the patient’s physical examination was entirely unremarkable.

The complete blood count and all serum chemistries other than electrolytes were normal. The sodium was 140, chloride 96, potassium 2.81, calcium 2.41, magnesium 0.46, bicarbonate 26.5, urea 4.8, blood sugar 5 (all expressed in mmol/L) and creatinine 85 µmol/L. The arterial pH was 7.47, PaCO<sub>2</sub> 37 and PO<sub>2</sub> 92 mmHg. We next obtained a urine specimen and measured the transtubular potassium gradient (TTKG) from the formula U/P potassium/U/P osmolality. The urine potassium was 75 mmol/L and the urine osmolality was 763 mOsm/kg H<sub>2</sub>O, which gave us a TTKG of 10.4. The result established that the kidneys were the source of the potassium loss. Renin was measured directly with a radioimmunoassay method at 43 ng/mL, which is slightly elevated. Aldosterone was 468 pmol/L, and cortisol was 636 nmol/L. We gave dexamethasone 2 mg in the evening, which suppressed cortisol to 27 nmol/L.

In short, these findings ruled out glucocorticoid remediable aldosteronism, Liddle’s syndrome, apparent mineralocorticoid excess, Cushing’s disease and syndrome and licorice gluttony. All these conditions should have resulted in very low renin values [1]. Glucocorticoid remediable aldosteronism should feature low renin and relatively elevated aldosterone values, Liddle’s syndrome features low renin and low aldosterone, as does mineralocorticoid excess and licorice gluttony [2]. We favoured the latter possibility because a traditional Turkish liquor (Raki) is high in licorice content and other compounds, perhaps associated with Chinese herbs, can inhibit the 11-beta hydroxysteroid dehydrogenase-2 enzyme that converts cortisol to cortisone [3]. The former stimulates the mineralocorticoid receptor, while the latter does not. Thus, the favourite candidates in the line-up, suggested by our chief-of-service, had been eliminated. What now?

Nephrologists, quite appropriately, collect urine and so we did. Our patient had a low serum magnesium serum value, so that electrolyte was included in our measurements. Over 24 h, our patient excreted 0.51 mmol/24 h calcium (less than the expected 2.5–8 mmol/24 h) and his 24-h magnesium excretion was 3.65 mmol/24 h (normal 2.5–8 mmol/24 h). However, at a serum magnesium level of 0.46 mmol/L, the magnesium excretion should have been (towards) zero ([4] review). What causes hypokalaemia, hypomagnesaemia, hypocalciuria and hypermagnesaemia in an hypertensive patient?

Gitelman *et al.* described such a syndrome in 1966 [5]. They observed three patients with hypokalaemia, hypomagnesaemia, mild metabolic alkalosis and potassium wastage. Two were sisters and the parents were related. This state-of-affairs resulted in a more careful family history in our patient and so we constructed a family tree (Figure 1). We found that our patient had married a first cousin and that three of his wife’s brothers were dead. We could not trace the tree to back generations. We believed our patient had a constellation consistent with Gitelman’s syndrome. We have no explanation for any kidney stones since our affected persons should excrete less calcium and more

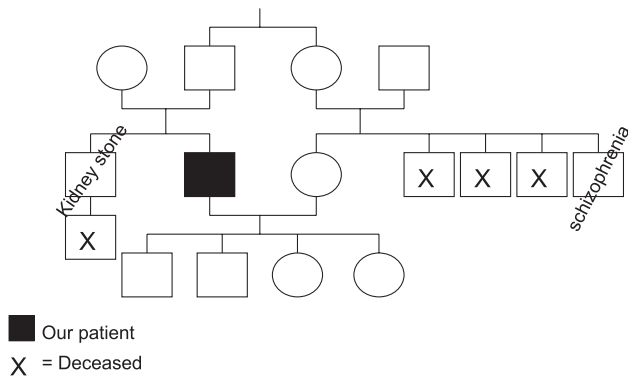


Fig. 1. Family tree of our patient.

magnesium, which should protect from kidney stones. Our chief-of-service pointed out that Cruz *et al.* [6] had found Gitelman's mutations in the Na-Cl cotransporter earlier and that Gitelman's mutations protected from hypertension, which was exactly the opposite of what our patient had. In addition, Cruz *et al.* [6] observed that the NCCT genotype was a significant predictor of blood pressure, with homozygous mutant family members having significantly lower age- and gender-adjusted systolic and diastolic blood pressure than those of their wild-type relatives. Heterozygous children, but not adults, had significantly lower blood pressure than those of the wild-type relatives. Their findings provided a formal demonstration that inherited mutations that impair renal salt handling lower blood pressure in humans. So what? Our patient was hypertensive and not hypotensive? The words 'hypertension' and Gitelman's syndrome occur in a sole report involving central nervous system increases in blood pressure [7].

After some debate and (obviously) without support from any 'third party' payers, we invited family members into the department for genetic testing after written informed consent and internal review board procedures had been satisfied. We identified a previously known sodium-chloride

cotransporter (SLC12A13) mutation (Figure 1) [8]. We found the mutation in both parents of the proband, the (first cousin) wife and the patient (homozygous). Clearly, the impact on the four children of this couple will be extremely important. Gitelman's syndrome is not rare and doctors need to have awareness of this condition [7]. The message of our report is that genetic variance is not exclusive to those patients that we might expect to have the genetic disease. These mutations exist in the population at large and conceivably, our patient would have had malignant hypertension without this mutation.

Conflict of interest statement. None declared.

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