CASE REPORT

Two cases of hypokalaemic rhabdomyolysis: same but different

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SUMMARY

In this paper, we present two women with hypokalaemic rhabdomyolysis in the context of increased diuretic intake and gastroenteritis, respectively. While their clinical manifestations and laboratory results were strikingly similar, two different underlying disorders were subsequently unveiled. The first patient was diagnosed with Conn syndrome, and adrenalectomy led to significant improvement of hypertension and sustained normokalaemia. The diagnosis in the second patient was Gitelman syndrome. Electrolyte supplements improved long-term lassitude and the frequency of muscle cramps declined significantly. These case vignettes illustrate the importance of establishing the underlying cause of hypokalaemia.

BACKGROUND

Hypokalaemia is frequently encountered in hospitalised patients. Potassium depletion, as opposed to diminished intake, accounts for the majority of cases. Increased renal potassium excretion is often an adverse effect of therapy, with diuretics as typical culprits. Significant gastrointestinal losses are usually apparent from the patient's history. In the acute setting, abrupt cell shifts of potassium need also to be considered. However, the cause of potassium deficiency may occasionally not be apparent, and a structured approach is indicated in such cases. A useful concept is to consider the potential mechanisms of hypokalaemia from urinary potassium wasting in terms of a primary increase in aldosterone secretion or a primary increase in sodium delivery to the distal nephron.¹ The clinical spectrum of potassium deficiency is wide. Patients with mild hypokalaemia are often asymptomatic; when potassium concentration decreases to less than 2.5 mmol/L, muscle damage can occur, and at serum values of less than 2 mmol/L an ascending paralysis can develop, which can be life-threatening.²

CASE PRESENTATION**Case 1**

A 55-year-old Caucasian woman presented to our hospital with a history of weak and painful extremities. Her medical history comprised papillary thyroid cancer 8 years earlier and hypertension, which had been well controlled with an angiotensin receptor blocker and a beta-blocker until 4 months earlier, when systolic readings up to 190 mm Hg necessitated the addition of amlodipine and hydrochlorothiazide. Oedema developed (in hindsight,

likely due to the calcium channel blocker), and xipamide was added by her general practitioner 2 weeks prior to her admission. Three days before admission, weakness in both legs developed and gradually worsened and she had difficulty walking. On examination, her blood pressure (BP) was 144/90 mm Hg and pulse rate 64/min. Residual ankle oedema was present. Her calves were tender to touch, and reflexes were blunted. Initial investigations revealed profound hypokalaemia (1.5 mmol/L; normal range 3.5–5 mmol/L), rhabdomyolysis with a creatine phosphokinase (CPK) of 2900 U/L (normal range <145 U/L) and metabolic alkalosis. Kidney function was normal, and she was biochemically euthyroid. Review of previous laboratory results showed borderline hypokalaemia. A provisional diagnosis of hypokalaemic rhabdomyolysis was made, presumably triggered by the recent addition of a second diuretic agent. Diuretics were stopped; following oral and intravenous potassium substitution, her potassium levels increased to 3 mmol/L and CPK normalised.

Case 2

A 21-year-old Caucasian woman was admitted because of rapidly progressive weakness of the legs, unsteadiness and myalgia. She had just recovered from a severe bout of norovirus enteritis. She denied diuretic or laxative use. Family history was unremarkable. On admission, vital signs were as follows: afebrile, BP 105/65 mm Hg, pulse 86/min. She appeared euvoalaemic. On neurological examination, her gait was waddling, and proximal leg weakness was evident; reflexes were decreased. Laboratory results demonstrated severe hypokalaemia (1.9 mmol/L) and concomitant magnesium deficiency (0.53 mmol/L; normal range 0.7–1 mmol/L), metabolic alkalosis and hypocalciuria (1.19 mmol/24 hours; normal range 2.5–7.5 mmol/24 hours). CPK peak was 1454 U/L. Thyroid function was normal. Based on the clinical picture and biochemistry, hypokalaemic rhabdomyolysis was diagnosed. Oral and intravenous potassium and magnesium replenishment was instituted, and the patient's symptoms abated within few days.

INVESTIGATIONS

Endocrine workup in patient 1 initially showed low plasma renin and increased plasma aldosterone concentration. As angiotensin receptor blockers and beta-blockers interfere with measurements of renin and aldosterone, these medications were

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Figure 1 Abdominal MRI (coronal plane) shows a well circumscribed, homogeneously enhancing left-sided adrenal mass (arrow), consistent with an adenoma.

temporarily switched to doxazosin and verapamil before repeat testing 11 days later, and remained in keeping with primary aldosteronism (PA) (aldosterone 209 pg/mL; normal range 10–160 pg/mL; renin 4 μ U/mL; normal range 3–33.6 μ U/mL; aldosterone-to-renin ratio 52). Following a positive saline infusion test, an MRI of the adrenal glands revealed a left-sided nodular mass of 2 cm (figure 1). An aldosterone-producing adenoma (APA; Conn syndrome) was diagnosed, accounting for the chronic hypokalaemia and resistant hypertension.

The possibility of bilateral adrenal hyperplasia (BAH) and a concomitant incidentaloma was discussed with the patient and transfer to another hospital for adrenal vein sampling (AVS) was

offered to differentiate between unilateral and bilateral disease. However, according to the patient's preference, the high likelihood of a unilateral APA and logistic issues, this investigation was not carried out.

In patient 2, the presence of normal BP, metabolic alkalosis, hypomagnesaemia, hypocalciuria and hyper-reninaemic hyperaldosteronism made us consider a congenital tubulopathy. After obtaining informed consent, genetic testing of *SLC12A3*, encoding the thiazide-sensitive sodium chloride cotransporter (NCC), was performed. Molecular analysis revealed the homozygous transition c.741+1G>A at the 5-prime splice position of intron 5, previously described to be causative for Gitelman syndrome (GS) (figure 2).^{3,4}

DIFFERENTIAL DIAGNOSIS

In patients with hypertension, chronic hypokalaemia with increased aldosterone levels points to PA, renal artery stenosis or Cushing disease, while normal or low aldosterone levels are suggestive of Liddle syndrome or increased liquorice intake.²

Individuals with low potassium levels and normal BP typically show increased gastrointestinal or renal losses. Bartter syndrome, a genetically heterogeneous entity, exhibits similar biochemical features as GS. (Surreptitious) diuretic use, laxative abuse and chronic vomiting are pertinent differential diagnosis in this context.²

TREATMENT

Laparoscopic adrenalectomy was performed in patient 1. The nodular mass was histologically classified as an adenoma.

Patient 2 was started on oral potassium and magnesium supplements and was encouraged to follow her lifelong propensity for salty food.

OUTCOME AND FOLLOW-UP

During the course of 1 year, the antihypertensive medication of patient 1 was gradually reduced. Her potassium levels are in the normal range. BP is currently well controlled with two antihypertensive drugs.

Figure 2 The nucleotide sequence of the human *SLC12A3* gene shows the (A) homozygous c.741+1G>A mutation in intron 5 of patient 2 and the (B) corresponding wild-type sequence. The relevant position is marked with a box.

On follow-up, patient 2 remains well, with potassium levels just above 3 mmol/L and magnesium above 0.6 mmol/L. She was issued with a patient information chart including dietary advice and 'Sick day rules', as recommended in a recent review.⁵ Genetic screening has been offered to her parents and siblings.

DISCUSSION

Rhabdomyolysis, defined as necrosis of striated muscle, is a syndrome resulting from the release of intracellular contents into the bloodstream. The diagnosis rests on recognising the symptoms of muscle pain and weakness as well as detecting transient elevations of CPK (with an arbitrary cut-off five times the upper limit of normal) that are not attributable to myocardial infarction.⁶ Acute kidney injury is perhaps its best known complication but seldom develops if CPK levels are in the four-digit range and the patient is not volume depleted.⁷ The aetiology of rhabdomyolysis can be broadly divided into traumatic, exertional, hereditary and other causes. Arguably, it is this latter group which poses the greatest diagnostic challenge.⁸ Hypokalaemia is a common electrolyte disorder and an established cause of rhabdomyolysis. By reducing potassium-mediated vasodilatation and thereby skeletal muscle blood flow, hypokalaemia predisposes individuals to myonecrosis.⁸

Symptoms of potassium depletion rarely occur unless plasma levels are below 3 mmol/L. Fatigue, muscle cramps and muscular weakness are typical complaints; the latter usually begins in the lower extremities and subsequently progresses to the trunk and arms, a presentation which can mimic other acute neurological conditions such as Guillain-Barre syndrome. Of note, in the context of rhabdomyolysis, pre-existing hypokalaemia may be overlooked by the time of presentation because of potassium leakage from intracellular stores due to muscle breakdown.⁹ Hypokalaemia is not a diagnosis but the result of many different disorders and its underlying cause must be sought for diagnostic as well as for therapeutic reasons, as illustrated by the cases presented.¹⁰

Hypokalaemic myopathy due to aldosterone hypersecretion was already reported by Jerome Conn in the 1960s. In an analysis of 145 patients with PA, muscular weakness was found in 73 per cent, with a female preponderance.¹¹ However, the first manifestation of PA with hypokalaemic rhabdomyolysis remains unusual, with few cases reported in the English literature.¹² The diagnosis of PA is not always straightforward and despite guidelines to the contrary, hypokalaemia in patients with hypertension is still all too often ascribed to concomitant diuretic therapy. When evaluating patients for PA, a structured approach with measuring of renin/aldosterone after adaptation of interfering antihypertensive medications (for instance, switching inhibitors of the renin-angiotensin-aldosterone to doxazosin, verapamil and/or urapidil), followed by a confirmation test, such as saline infusion, and adrenal imaging should be employed.¹³ As several subtypes of PA, including BAH, are recognised, confirmation of unilateral APA by AVS is widely recommended in individuals above the age of 40. However, this procedure is fraught with limitations in real life, and its impact on outcomes has been challenged.^{14 15} Individuals with unilateral adrenal adenomas are usually deemed candidates for surgery, although residual hypertension may persist; however, unlike in BAH, surgery in classic Conn syndrome frequently results in significant improvement in BP.¹³

Hypokalaemia is the best recognised laboratory feature of GS, which is inherited as an autosomal recessive trait and is one of the most common inherited renal tubular disorders, with a

prevalence of 1 in 40 000 for Caucasians. GS is caused by inactivating mutations in the NCC gene (*SLC12A3*).⁵ This results in a thiazide-like effect, consisting of salt wasting with secondary hypovolaemia and subsequent stimulation of the renin-angiotensin-aldosterone axis. Although usually detected in adolescence or young adulthood, the syndrome has been described in all age groups. While considered an asymptomatic syndrome for a long time, a different picture has recently emerged.¹⁶ Fatigue, dizziness and nocturia are frequently volunteered by the patients, and significant neuromuscular complications are increasingly recognised. To date, only a handful of cases of rhabdomyolysis in adult patients with confirmed GS have been reported.^{9 17} The diagnosis of GS mainly rests on typical biochemical abnormalities. Apart from potassium deficiency, hypomagnesaemia and hypocalciuria are frequent but not obligatory laboratory features. Significant overlap with other salt-losing tubulopathies (ie, the various forms of Bartter syndrome) exists; therefore, genetic testing with a panel screening for the most common syndromes is recommended.⁵ Recent KDIGO guidelines provide an excellent overview including detailed treatment and dietary recommendations and include web resources for patients with GS; issuing patients with Sick day rules, akin to diabetes, is proposed.⁵

To summarise, our cases illustrate the hazards of hypokalaemia and the importance of establishing its underlying cause. By digging deeper into these cases of hypokalaemic rhabdomyolysis, two curable and treatable disorders, respectively, were found.

Learning points

- Hypokalaemia is not a diagnosis; its underlying cause should be established.
- Severe hypokalaemia may induce rhabdomyolysis.
- In the absence of obvious other causes, endocrine and renal-tubular causes of potassium deficiency should be considered.
- Gitelman syndrome should be confirmed by genetic testing in order to treat and educate patients.

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