CASE REPORT

Licorice-induced apparent mineralocorticoid excess compounded by excessive use of terbutaline and high water intake

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SUMMARY

This case highlights the clinical course of a 54-year-old male patient presenting with hypertension and long-term refractory hypokalaemia. He reported long-term malaise, fatigue and physical discomfort. Diarrhoea, vomiting, over-the-counter drugs, dietary supplements and any kind of medical abuse were all denied. Physical examination was normal. Suppressed plasma renin activity along with a low aldosterone level and elevated urinary cortisone/cortisol metabolite excretion ratio raised the suspicion of apparent mineralocorticoid excess (AME). The patient started treatment with spironolactone, but serum potassium levels were persistently fluctuating and the patient was hospitalised for further evaluation. During hospitalisation, repeated medical history and diagnostic examinations revealed licorice-induced AME complicated by excessive use of terbutaline and massive water intake. Licorice discontinuation, reduction of terbutaline and normalisation of water intake led to fully normalised potassium levels. Despite careful clinical history and diagnostic work-up, hospitalisation may be necessary in selected patients with long-term hypokalaemia.

BACKGROUND

Hypokalaemia is one of the most common medical conditions encountered in clinical medicine. Up to 20% of hospitalised patients and up to 40% of patients on diuretics suffer from hypokalaemia.¹

Approximately 90% of the daily potassium intake is excreted in the urine, whereas 10% is excreted by the gastrointestinal tract.² Diarrhoea, vomiting and use of diuretics make up the most common causes of hypokalaemia, whereas hypokalaemia due to transcellular shifts or renal wasting is less common.³ Clinical manifestations of hypokalaemia include weakness, fatigue and polyuria. Severe hypokalaemia can cause muscle necrosis, paralysis, cardiac arrhythmia and impaired respiration. Even small changes in serum potassium levels can affect outcomes in patients with comorbidities such as hypertension, heart failure, renal dysfunction and diabetes. Consequently, even mildly decreased potassium levels demand attention and treatment.^{4,5}

In many cases, a thorough medical case history and physical examination may be enough to provide the cause of hypokalaemia. However, the diagnostic approach to a patient with hypokalaemia

also includes measurement of blood pressure, evaluation of plasma renin activity, aldosterone levels, potassium urinary excretion and acid–base status. Further examination of urinary cortisol metabolite excretion (free cortisol–cortisone ratio or tetrahydrocortisol + allo-tetrahydrocortisol/tetrahydrocortisone ((THF + allo-THF)/THE)) may occasionally be necessary.

We present an uncommon, elaborate case of long-term refractory hypokalaemia induced by a mixture of exogenous factors.

CASE PRESENTATION

A 54-year-old Caucasian man was referred with long-term malaise, fatigue and physical discomfort. Initial blood samples established at the general practitioner had shown severe hypokalaemia (2.3 mmol/L). The patient had a medical history involving asthma and hypertension. He reported a tobacco consumption of 20 cigarettes per day, a water intake of 4–5 L per day and medical treatment with amlodipine (10 mg/day), budesonide (2 inhalations/day), terbutaline (4 inhalations/day), glycopyrroniumbromide (44 µg/day) and bromazepam (24 mg/day). A thorough medical history was obtained; diarrhoea, vomiting, alcohol, over-the-counter drugs, dietary supplements and use of nature medicine were all denied. The patient had two adult sons and no family history of endocrine disease. At admission, there were no signs of dyscrina appearance but the patient had hypertension (160/100 mm Hg). Telemetric monitoring did not show any signs of cardiac arrhythmias.

INVESTIGATIONS

Biochemical tests showed low P-aldosterone <27 pmol/L (reference interval: 38–490 pmol/L) and low P-renin <2 mIU/L (reference interval: 2.8–40 mIU/L). Acid–base status indicated metabolic alkalosis (pH 7.49). Twenty-four hours urinary collection revealed elevated daily potassium excretion of 45 mmol/L (reference interval: <20 mmol/L). Twenty-four hours urinary cortisol excretion was normal, but (THF + allo-THF)/THE ratio was moderately increased at 1.67 (reference interval <1.5). Serum sodium levels were at first normal, but decreased later in the course with values between 128 and 134 mmol/L.

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Figure 1 Diagnostic evaluation of hypokalaemia.

An ACTH (adrenocorticotrophic hormone) test was performed with intravenous bolus of 0.25 mg Synacthen (Novartis Healthcare, Copenhagen, Denmark). Cortisol, 17-hydroxyprogesterone and 11-deoxycortisol levels were measured at 0, 30 and 60 min. Baseline ACTH was 3 pmol/L (reference value: <10 pmol/L). The results for cortisol at 0, 30 and 60 min were 414, 745 and 676 nmol/L (reference value >500 nmol/L). The results for 17-hydroxyprogesterone were 2.8, 13.6 and 12.0 nmol/L (reference value <35 nmol/L). 11-Deoxycortisol (cortodoxone) levels were 0.4, 4.7 and 6.0 nmol/L (reference value <2.7 nmol/L).

Due to elevated urinary (THF +allo-THF)/THE ratio and no other plausible aetiological explanations, a genetic test for a defect in 11-beta-hydroxysteroid dehydrogenase type 2 (11b-HSD2) was performed (figure 1). The test did not show any mutations.

DIFFERENTIAL DIAGNOSIS

Diagnostic measurements and observations indicated different possible diagnoses. Acquired apparent mineralocorticoid excess (AME) seemed probable since all diagnostic criteria were present: the patient presented with a mineralocorticoid excess state, an increased (THF +allo-THF)/THE ratio and reported a non-specific consumption of licorice. Furthermore, genetic testing for defects in the 11b-HSD2 gene was normal. Ectopic ACTH syndrome or Cushing's disease with increased secretion of glucocorticoids may be considered. This condition would imply significantly elevated 24 hours free cortisol excretion, high serum ACTH and Cushingoid symptoms (Moon face, Buffalo hump and so on). The patient had normal clinical appearance, excretion of urinary cortisol was within reference limits and ACTH level was normal, which did not

support a diagnosis of Cushing's syndrome. Liddle syndrome, an autosomal recessive genetic disorder, which causes a gain-of-function mutation of ENaC, should also be suspected in the setting of hypertension, low plasma renin activity and low aldosterone levels. This disease would be investigated through detailed recording of family history and gene testing. Debut of symptoms at older age made a diagnosis of Liddle syndrome less plausible; furthermore, the patient had two healthy adult sons with normal blood pressure and there was no family history of electrolyte disturbance. Deoxycorticosterone (DOC) excess, a condition associated with increased ACTH release and production of steroid precursors such as DOC, was unlikely due to the abnormally urinary cortisol metabolite excretion ratio and a normal urinary cortisol level. A mineralocorticoid receptor mutation seemed very improbable because of its rare occurrence and the absence of juvenile hypertension (figure 1).

TREATMENT

Potassium supplementation was continually adjusted to ensure potassium levels within the reference interval. Treatment with spironolactone was added in order to antagonise the supposed mineralocorticoid excess state and treat the consistently variable potassium levels. Moreover, the patient was advised to decrease water intake because of persistently low sodium levels.

OUTCOME AND FOLLOW-UP

The patient was hospitalised for further diagnostic evaluation due to persistent fluctuating levels of potassium. During repeated clinical interviewing, the patient described 12–14

Figure 2 Potassium variations during clinical course. Shaded area indicates the normal range of serum potassium levels.

inhalations of terbutaline a day and a minor non-specific intake of licorice. Other conspicuous dietary intake (tea, nuts, roots and so on) or any other exogenous factors seemed unlikely after consultation. Water intake was unchanged at 4–5 L/day.

Medical treatment with spironolactone and potassium was fully discontinued, daily water intake was restricted to 1.5 L/day and terbutaline inhalations were reduced to <4/day. Potassium was normalised along with normalisation of plasma renin activity and aldosterone concentration. Urine examinations following pause of medical treatment and no ingestion of licorice indicated a normal (THF +allo-THF)/THE ratio (0.85). The patient was discharged with normal potassium levels, and within a week, his symptoms had entirely resolved.

DISCUSSION

This report presents an unusual, complicated case involving several factors leading to persistent hypokalaemia. Clinical and biochemical signs, including hypokalaemic alkalosis, hypertension, suppressed renin activity and low aldosterone levels, suggested that acquired AME might have been the underlying factor. AME is a rare condition, where cortisol acts as a strong mineralocorticoid stimulant due to impairment of 11b-HSD2, which normally catalyses the conversion of active cortisol to inactive cortisone in kidneys.^{6,7} Acquired AME is predominantly caused by consumption of licorice, containing an active component, glycyrrhizin acid, acting as a competitive inhibitor of 11b-HSD2.^{8,9} Patients consuming excessive quantities of licorice present with hypertension and hypokalaemia that may be severe enough to cause myopathy and cardiac arrhythmia. Both plasma renin activity and aldosterone levels are suppressed. The condition responds to spironolactone and is reversible upon stopping licorice ingestion.¹⁰

Since our patient had no history of juvenile hypertension, it was reasonable to believe that potassium disturbances were caused by acquired impairment of 11b-HSD2 in the present case. The patient reported a non-specific intake of licorice, which may be consistent with the marginally elevated cortisol metabolite excretion pattern (THF +allo-THF)/THE ratio (1.67), whereas the inherited form of AME typically provides ratios between 3 and 70.¹⁰ Furthermore, continuous fluctuations in plasma potassium, despite relevant treatment, also suggested

an underlying exogenous factor (figure 2). Genetic testing for defects in the 11b-HSD2 gene was normal.

Thorough assessment of the medical case history revealed an inappropriate use of terbutaline. Terbutaline is used for the management of asthma by interacting with adrenergic receptors (β_2) in airways. Furthermore, β_2 -agonists are known to promote cellular potassium uptake by increasing the activity of Na^+/K^+ -ATPases in cell membranes.¹¹ This feature might explain low potassium plasma levels, but not increased urinary excretion of potassium or elevated (THF +allo-THF)/THE ratio. This indicates that another factor than terbutaline may have had a contributory role in the preliminary potassium derangement.

After cessation of licorice ingestion, urinary examinations provided a normal (THF +allo-THF)/THE ratio, which again supported the suspicion of exogenous licorice intake as a cause of AME.

High levels of cortisol precursors were detected during the short Synacthen test. Increased mineralocorticoid receptor activation and elevated urinary potassium losses might be ascribed to these precursor substances. The reasons for elevated plasma levels of cortisol precursors remain unclear. Earlier research has indicated that water intake of more than 1.5 L may influence cortisol and cortisone levels.¹² Baseline cortisol precursors prior to the short Synacthen test were normal. Following the test, high levels of cortisol precursors were detected, which might have been due to an inadequate conversion of precursor substances because of saturated enzyme capacity. Additionally, the patient did not appear Cushingoid, which makes water intake an even more probable cause.

During hospitalisation, it was possible to stop medical treatment with spironolactone and simultaneously eliminate all possible causes of hypokalaemia by controlling diet (licorice and water intake) and medicine (terbutaline) with close monitoring of the patient's potassium levels. Licorice ingestion, terbutaline inhalations and high water intake contributed to the biochemistry in different ways, thus making it difficult to determine a definite cause of the patient's hypokalaemia. A sequential phase-out might have made it possible to determine the principal offending agent.

In conclusion, the presented case demonstrates a long-standing and complicated cause of hypokalaemia.

Identification of licorice-induced AME and improper medical use of terbutaline was pivotal in clarification of the aetiology. Careful diagnostic follow-up and switching between outpatient and inpatient medical settings were necessary to reassess medical history and retrieve important biochemical data.

Learning points

- ▶ Licorice can be a potent, reversible promoter of mineralocorticoid effects of cortisol, with the ability to conceal other underlying clinical conditions.
- ▶ Excessive use of terbutaline causes cellular potassium shift resulting in hypokalaemia.
- ▶ Thorough clinical interviewing provides essential information regarding the cause of hypokalaemia.
- ▶ Prompt recognition and identification of dietary intake, supplementation or medications can prevent unnecessary investigations and potential side effects.
- ▶ Careful information and proper compliance are important in administration of medications.

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