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Severe hypokalaemia: is one reason enough?

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Introduction

Hypokalaemia is a common electrolyte disorder with a straightforward differential diagnosis. The usual suspects are diarrhoea, vomiting or intake of diuretics. In some patients, a spot urinary chloride may help to tell the tale. Occasionally, a comprehensive workup is required [1] to elucidate disorders such as Conn's, Bartter's or Gitelman's syndromes. Sometimes, however, the cause of hypokalaemia may be all too obvious and one of the usual suspects later turns out to be an innocent bystander rather than the primary culprit. We present such a case to illustrate a common but dangerous error in medicine, namely our intention to frame all available information into an all too obvious diagnosis.

Case

A 50-year-old woman was referred to our casualty department with muscle pain and weakness. She had experienced pain and weakness in her calf muscles, shoulders and hands for some 3 weeks without any precipitating or aggravating factors. The symptoms were constant during the day and did not depend on exercise. The patient declined malaise, fever, weight loss and dyspnoea. The previous medical history was notable for chronic headache and hypertension, which was controlled with telmisartan and torasemide. Both had been started 9 months prior to admission. There was a history of gynaecological complaints, which were still unresolved. The patient worked as an accountant and the family history was unrevealing. Earlier on the day of referral, she had been seen by a general practitioner, who had admitted her with a tentative diagnosis of connective tissue disease. On examination, the patient was afebrile and did not appear acutely ill. Blood pressure was 150/80 mmHg. The deltoid and gastrocnemial muscles were tender to palpation and a malar rash was seen. The remainder of the clinical examination was unremarkable. The admitting physician concurred that polymyositis was indeed a tempting diagnosis, owing to the age and gender of the patient and the preponderance of polymyositis to affect proximal muscles. Laboratory studies revealed profound hypokalaemia of 1.8 mol/l, pH 7.6, creatine kinase 13 051 U/l and myoglobin 5633 U/l. Urine chloride was 72 mmol/l (elevated). The initial diagnosis was refuted and the hypokalaemia was believed to be due to the intake of torasemide. Both intravenous and oral potassium were administered, yet the serum potassium remained as low as 1.9 mmol/l and the patient was transferred to the intensive care unit. On this occasion, another attempt was made to uncover a second cause of hypokalaemia. The patient declined vomiting, diarrhoea or intake of any medication other than the above mentioned. Intake of laxatives was specifically asked for, again to no avail. When asked for liquorice intake, however, the patient confessed. In particular, she preferred strong liquorice candies, which she obtained in considerable quantities from a local pharmacy. This had been going on for quite some time, perhaps 1.5 years. We were unable to retrieve any previous measurements of electrolytes. Plasma renin was <0.2 ng/ml/h, plasma aldosterone was <6 pg/ml and urinary aldosterone was 3.5 μg/24 h. The patient made an uneventful recovery.

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Discussion

One of the most dangerous errors in medicine is to try and fit all the available information into a tentative diagnosis. First, we tried to fit all symptoms into a diagnosis of polymyositis, until the laboratory results ridiculed such an assumption and demonstrated that our patient had red cheeks rather than a malar rash. Unfortunately, we quickly repeated this type of error in the differential diagnosis of hypokalaemia. Here, we accused one of the usual suspects and assumed that diuretic intake was the only cause of hypokalaemia. This form of error derives form a particular style of clinical reasoning, namely pattern recognition [2]. Other types of reasoning include algorithmic, exhaustive (gathering every possible piece of data) and hypothetico-deductive (generating and rejecting) hypotheses as more and more data are collected. The latter is widely held up as the ideal, while the exhaustive approach is often used for rare diseases or unusual presentations. The pattern-recognition style is commonly used by primary care physicians and in casualty, where instant recognition of a disease is paramount. This strategy has both merits and dangers. In particular, physicians are keen to look for evidence to support the initial diagnosis and ignore any data that might refute it. In other words, physicians try to fit 'a square peg in a round hole' [3]. In our case, one pattern was present but missed: hypertension and hypokalaemia.

Recognition of this pattern would have prompted a search for *Glycyrrhiza glabra* (Figure 1). Unfortunately, we missed the point and believed that diuretics were the sole culprit. Elevated urinary chloride was still in keeping with this assumption (as long as diuretic action is still present), while the results of further laboratory studies were not: use of diuretics provides a stimulus for the renin–angiotensin–aldosterone system, while our patient had low plasma renin and aldosterone, suggesting the presence of an aldosterone-like substance. In addition, the patient reported here had slightly elevated blood pressure, while hypokalaemia due to diuretic intake is commonly associated with low or low-normal blood pressure. Finally, it has been noted that hypokalaemia due to loop diuretics is usually mild and transient [4], unless another effect is at work. Therefore, in the presence of a normal diet, severe hypokalaemia due to a loop diuretic should always prompt a search for additional factors.

Dangerous effects due to intake of liquorice were, in fact, noted as early as in the 1960s, when the pathophysiology of liquorice-induced disorders was not even nearly understood. After liquorice had been

Fig. 1. Literally the root of the matter: radix Glycyrrhizae glabrae (root of *Glycyrrhiza glabra*, the European liquorice).

noted as a cause of hypertension it was first believed to exert a direct mineralocorticoid effect [5]. Accordingly, liquorice treatment for Addison's was recommended. Patients with peptic ulcers were also treated with liquorice derivatives. Today, liquorice ingestion differs markedly from one region to another. Extraordinary amounts of liquorice are consumed in Iceland, succeeded by the Netherlands and Scandinavia. In Germany, the habit is considerably more prevalent in coastal provinces. In the UK, 'Pontefract cakes' are notorious [6] and pay testimony to the centuries-old use of liquorice (liquorice was introduced into Pontefract, Yorkshire, by monks in 1562; sugar was later added by a local chemist and the novel product named Pontefract cakes). Severe hypokalaemia, rhabdomyolysis and tetraparesis due to these cakes have been reported [7].

The causative ingredient of liquorice is glycyrrhicinic acid, a pro-drug. Interestingly, glycyrrhicinic acid is also found in a broad variety of herbal preparations, pastis and surprisingly Belgian beer. Its metabolite, glycyrrhetenic acid, acts as an inhibitor of 11β-hydroxysteroid dehydrogenase (11β-HSD), a key enzyme of steroid metabolism. The function of this enzyme is to convert cortisol (which has glucocorticoid *and* mineralocorticoid activity) into cortisone (glucocorticoid but *no* mineralocorticoid activity). To fully appreciate the importance of this enzyme, we must step back and understand that mineralocorticoid action of aldosterone is needed in a minority of cells, such as the distal tubule, colon and salivary glands. But how can these tissues sense aldosterone, given that cortisol with its inherent mineralocorticoid action is abundantly present? The answer lies in the action of 11β-HSD. The enzyme is present where aldosterone action is needed and degrades cortisol so that aldosterone alone binds the mineralocorticoid receptor (Figure 2). Like many other endocrine disorders, these events were delineated with a little help from a rare genetic syndrome, apparent mineralocorticoid excess. The hallmark of this disease is absence of 11β-HSD and binding of cortisol to the mineralocorticoid receptor [8]. These observations ultimately led to the finding that glycyrrhicinic acid acts as an inhibitor of 11β-HSD. Thus, cortisol can escape inactivation and bind to the mineralocorticoid receptor with equal affinity, leading to an apparent excess of aldosterone. Recent research has elucidated two isoforms of 11β-HSD: 11β-HSD1 acts as an oxoreductase that generates cortisol, while 11β-HSD2 is crucial for inactivation of cortisol as described above. It has been speculated that 11β-HSD1 may be involved in truncal obesity and metabolic syndrome, with the exciting prospect of therapeutic manipulation. Hypertension is the most common disorder caused by liquorice, but life-threatening electrolyte disturbances have been reported also [9]. It is conceivable that our patient first developed liquorice-induced hypertension, then received a loop diuretic and finally sustained severe life-threatening hypokalaemia. Finally, it has been suggested that furosemide also inhibits 11β-HSD, but this assumption has also been refuted [10].

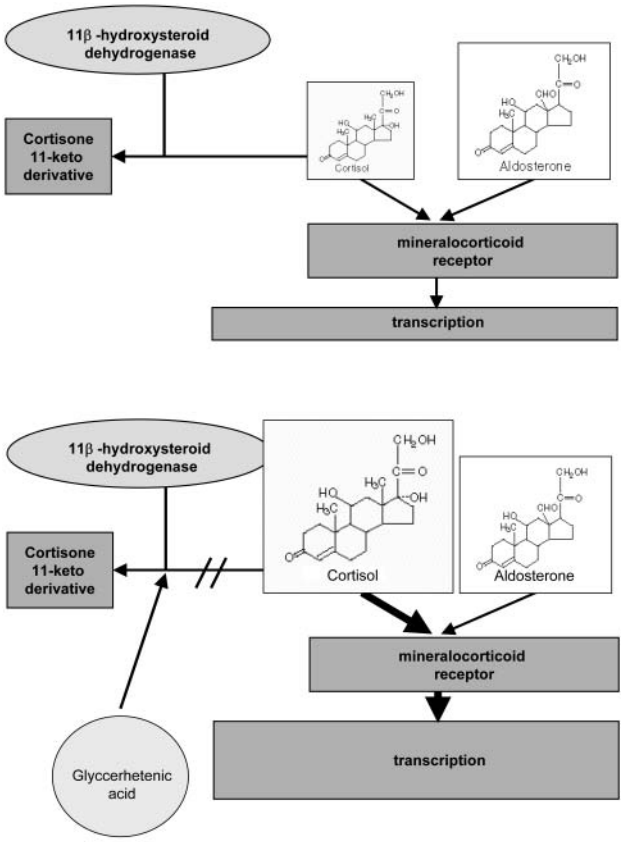

Fig. 2. Steroid metabolism and the syndrome of apparent mineralocorticoid excess. Under normal circumstances, mineralocorticoid receptors in aldosterone-sensitive tissues (kidney, colon, salivary glands) are protected from the action of cortisol by 11β-HSD, which converts cortisol to its keto-derivative. Glycyrrhetenic acid inhibits the enzyme and the mineralocorticoid receptor is 'swamped' by cortisol.

Teaching points

(i) In cases of severe hypokalaemia, consider more than one underlying reason.
(ii) Pattern recognition is an important but potentially dangerous approach during the diagnostic process. Beware of the patient with a label, be prepared to question your tentative diagnosis and try to construct other patterns from the available information.
(iii) Liquorice ingestion is an important cause of hypokalaemia and hypertension. All patients with hypokalaemia and/or hypertension must be evaluated for liquorice ingestion. Uncommon sources of glycyrrhicinic acid, such as herbal preparations, must not be forgotten.
(iv) Hypokalaemia is a very common finding in patients who receive a loop diuretic. However, the effect often disappears over time and severe life-threatening hypokalaemia should always prompt a search for other factors.

Conflict of interest statement. None declared.

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