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A rare cause of Recurrent Life-Threatening Myopathy

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Abstract:Hypokalaemia is an electrolyte abnormality with several aetiologies and a broad clinical spectrum. Secondary myopathy is sometimes the first symptom in severe cases (<2.5 mmol/L) or sudden onset of hypokalaemia. We report the case of a 36-year-old man, admitted repeatedly in the emergency department due to intense chest pain and myopathy. Laboratory results revealed hypokalaemia (2.5 mmol/L), metabolic alkalemia (pH 7.52, bicarbonates 31.2 mmol/L) and hypomagnesaemia (1.4 mg/dL). Hypokalaemia was always corrected along with pain resolution, and he was discharged for future evaluation in the internal medicine outpatient clinic. After an extensive aetiological study, the SLC12A3 gene was sequenced and confirmed the diagnosis of Gitelman syndrome. Recurrent myopathy is a challenging diagnosis and may be the presentation of Gitelman syndrome onset, secondary to prolonged periods of non-excitability of the muscle membrane. Urgent correction of electrolyte disturbance is essential, and its clinical severity imposes a fast and accurate diagnostic algorithm.

Keywords: hypokalaemia, myopathy, Gitelman syndrome

Introduction

Hypokalaemia is an electrolyte disturbance with multiple possible aetiologies. A frequent cause is excessive excretion of potassium in the urine resulting from diuretic drugs, but endocrine diseases such as primary hyperaldosteronism, kidney disorders and genetic syndromes affecting renal function must also be considered [1].

Clinical symptoms and signs depend on the severity and rate of onset. Hypokalaemic myopathy and cardiac arrhythmias are life-threatening presentations of severe potassium depletion (serum potassium less than 2.5 mmol/L), and despite their reversibility with potassium replacement, high awareness and knowledge of different causes are crucial to prevent a récurrence [2, 3]. Gitelman syndrome is a rare recessive salt-wasting tubulopathy, characterised by disruption of the thiazide-sensitive sodium chloride cotransporter activity and leading to severe electrolyte abnormalities, including hypokalaemia, hypomagnesaemia, hypocalciuria and metabolic alkalosis [4]

Case Report:

A 36-year-old man, with a medical history of psoriasis under topical therapy with no arthritis, was admitted to the emergency department with intense chest pain without radiation but worsening with respiratory movements. Additionally, he complained of cramps, fatigue, and cervical and dorsal myalgias. There was no history of trauma or recent intense exercise. At admission, his blood pressure was 110/69 mmHg, with regular heart rate and normal pulse oximetry level. Electrocardiogram showed sinus rhythm, QTc 427 ms, without U waves (Fig. 1). Laboratory findings revealed normal renal and thyroid function, hypokalaemia (2.5 mmol/L), metabolic alkalemia (pH 7.52, bicarbonates 31.2 mmol/L) and hypomagnesaemia (1.4 mg/dL).

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The patient denied fever, diarrhoea, drug use, laxative, diuretic or energy drink consumption. Adequate serum potassium level was achieved by intravenous supplementation along with pain resolution, and he was discharged to a future evaluation in the internal medicine outpatient clinic, with oral potassium chloride and magnesium sulfate. Two weeks later, he was readmitted in the emergency department with persistent and intense chest pain and myopathy. Despite the prescribed treatment, laboratory findings confirmed the recurrence of severe hypokalaemia requiring intravenous supplementation again. He was evaluated in the outpatient clinic a week later, and after starting an extensive aetiology study, began therapy with spironolactone. Gitelman syndrome was considered because of normal blood pressure, metabolic alkalemia, recurrent hypokalaemia and hypomagnesaemia with no hypercalciuria. The SLC12A3 gene was sequenced and confirmed the diagnosis. The hypokalaemia was refractory to the established therapy, and it was decided to initiate indomethacin, achieving a serum potassium average level of 3.1 mmol/L, with no new episodes of myopathy.

Discussion: Gitelman syndrome is a recessively inherited tubulopathy, caused by inactivating mutations in the SLC12A3 gene that encodes the thiazide-sensitive sodium chloride cotransporter expressed in the apical membrane of the distal convoluted tubule [4]. The phenotypic variability, from asymptomatic to severe and life-threatening symptoms, implies a challenging but nevertheless essential correct diagnosis [5]. Indeed, the broad clinical spectrum is related to the severity of electrolyte disturbance, particularly chronic salt loss, hypokalaemia and hypomagnesaemia. The inhibition of thiazide-sensitive sodium chloride cotransporter leads to decreased sodium reabsorption in the distal convoluted tubule, which results in vascular volume contraction and permanent activation of the renin-angiotensin-aldosterone axis [6]. This compensatory mechanism stimulates sodium reabsorption in the collecting tubules and consequently increased secretion of potassium and hydrogen, causing hypokalaemia and metabolic alkalosis. Ionic disturbances are responsible for the deregulation of other ionic channels, leading to hypocalciuria and elevated magnesium excretion, although hypocalciuria is highly variable and hypomagnesaemia may be absent in some cases [4]. After cardiac arrhythmia, hypokalaemic myopathy is one of the most feared consequences. In cases of severe hypokalaemia, muscle membrane may become unexcitable, and myofibre vacuolation and necrosis can occur [2]. Muscle pain and weakness usually begin at proximal muscles and rarely affect the diaphragm or cervical muscles. The diagnostic approach includes an incisive clinical history to rule out diuretic use, vomiting or diarrhoea, chronic alcohol abuse, and liquorice or energy drink consumption. Conversely, pubertal delay, episodes of fainting, palpitations, cramps, paraesthesia, thirst, abnormal drinking behaviour and joint pain are some of the main clinical symptoms and manifestations suggesting a diagnosis of Gitelman syndrome [6, 7]. In the reported case, a typical history of muscle weakness and cramps, associated with multiple episodes of severe hypokalaemia and hypomagnesaemia, along with the acid-base and blood pressure status were of great help in the differential diagnosis. Other laboratory findings may include hypocalciuria, normal or slightly elevated creatine kinase, and high plasma renin activity or levels.

The treatment of Gitelman syndrome is also a clinical challenge. Diverse options exist to restore potassium, magnesium and salt serum levels, although knowledge about long-term efficacy, tolerability and safety of these treatments is limited [6]. Depending on severity at diagnosis, intravenous replacement should be considered. Symptoms may improve over an hour, while some patients with severe weakness may take more time to improve. Chronic management usually includes liberal salt intake, and high doses of oral magnesium and potassium supplements. In most cases, potassium-sparing diuretics are also necessary, along with renin-angiotensin system blockers if the patient's blood pressure allows it. Additionally, there are refractory cases similar to the reported case [8]. In these cases, nonsteroidal anti-inflammatory drugs, most frequently indomethacin, are sometimes used to inhibit prostaglandin E2 synthesis in the kidney. However, because some side effects such as gastrointestinal complaints and decreased estimated glomerular filtration necessitate careful management [9]. The prognosis and long-term consequences of Gitelman syndrome are unknown. Cruz et al. reported a significant reduction in quality of life, similar to patients with heart failure or diabetes [10]. In cases of early onset, severe manifestations and future consequences may include growth retardation, chondrocalcinosis and epilepsy. Long-term outcomes in adult onset, such as chronic kidney disease, secondary hypertension and cardiac arrhythmias, need to be considered, as well as management during pregnancy [5, 6]. Long-term studies are needed for better individualised treatment and prognosis.

The authors emphasise the importance of being alert and pursuing uncommon causes of electrolytic disturbance, and highlight the fact that in Gitelman syndrome, physician awareness and patient education are crucial to improve quality of life and prevent related complications.

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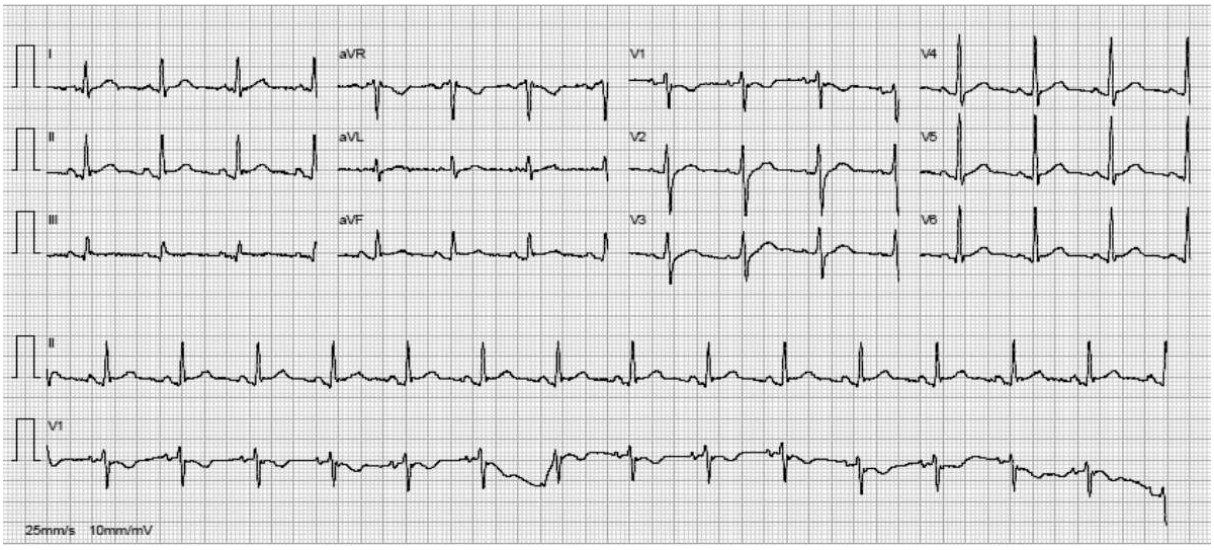

Figure 1: Electrocardiogram showed sinus rhythm, QTc 427ms, without U waves

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