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Case report

Concomitant hypokalemia and hypocalcemia: a very rare but life-threating combination of reversible causes of cardiac arrest - an unusual first manifestation of celiac disease

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Abstract. The causes of cardiac arrest are extremely heterogenous. Among these, both hypokalemia and hypocalcemia are known reversible factors that can lead to cardiac arrest. In this report, we present a unique case report of a patient with previously undiagnosed celiac disease who experienced cardiac arrest due a combination of hypokalemia and hypocalcemia resulting from malabsorption. A 66-year-old male presented to the emergency department with symptoms of malaise, weakness, weight loss, and persistent diarrhea. The patient exhibited characteristic signs of hypokalemia and hypocalcemia, including fasciculations, weakness, and swelling. An electrocardiogram showed a normal rhythm, and blood tests confirmed the electrolyte imbalances. Despite initial treatment, the patient experienced sudden cardiac arrest. Prompt resuscitation efforts were successful in restoring spontaneous circulation. However, recurrent episodes of ventricular arrhythmias and cardiac arrest occurred. Large doses of intravenous potassium chloride, in conjunction with magnesium, were needed prior to restore electrolyte balance. The concomitant severe hypocalcemia required caution calcium supplementation, to avoid further decreases in serum potassium levels. Appropriate ion replacements ultimately led to successful resuscitation with good functional recovery. During the hospital stay, the patient was diagnosed with celiac disease. This case is noteworthy for its uniqueness, as there are no documented instances in the scientific literature linking cardiac arrest directly to celiac disease. It is important to emphasize the need for investigating potential reversible causes of cardiac arrest, such as hypokalemia and hypocalcemia, and implementing appropriate interventions to address these factors. (www.actabiomedica.it)

Key words: hypokalemia, hypocalcemia, cardiac arrest, reversible cause, celiac disease

Introduction

Cardiac arrest (CA) can result from potentially reversible causes, and electrolyte disturbance is among these causes. One such reversible cause is hypokalemia, which is indicated by a serum potassium (K+) level <3.5 mmol/L (1). Mild hypokalemia is defined when potassium levels range between 3-3.4 mmol/L, moderate when it falls between 2.5-3 mmol/L, and severe if it is <2.5 mmol/L (1). There are numerous causes of hypokalemia, which can be categorized into increased excretion (e.g. diarrhea, sweating), renal loss (due to diuretics, mineralocorticoid excess as seen in rimary aldosteronism, Cushing's syndrome, distal tubular acidosis, hypomagnesemia), transcellular shifts (e.g., alkalosis, thyrotoxic crisis, hormonal causes like insulin, α-agonists, exogenous or endogenous β2-agonists), and reduced intake (malnutrition, artificial

nutrition, and alcoholism) (2). While hypokalemia can present with various clinical manifestations, most cases are asymptomatic (3). When symptoms are present, clinical manifestations can be heterogeneous, including: changes in the electrocardiogram (ECG), e.g. U wave, T wave flattening, QTc prolongation, ST segment depression, as well as arrhythmias including sinus bradycardia, atrioventricular blocks, ventricular extrasystole, ventricular tachycardia (including Torsade de Pointes), and ventricular fibrillation; renal manifestations, e.g. increased urinary output (polyuria) and renal insufficiency; gastrointestinal symptoms, like constipation; neuromuscular symptoms, among which cramps, weakness, paresthesia, and paralysis (1–7). Notably, the incidence of hypokalemia in cases of CA is rare. A search of the Medline database from 1967 yielded only 30 CA cases attributed to hypokalemia (8, 9).

Hypocalcemia is a medical condition characterized by an abnormally diminished concentration of calcium (Ca+) in the bloodstream. Suboptimal levels of calcium can have profound repercussions on bodily functions, particularly on the heart, potentially resulting in the occurrence of CA (10). Hypocalcemia is defined as a serum total calcium concentration <8.8 mg/dL (2.20 mmol/L) in the presence of normal plasma protein concentrations, or a serum ionized calcium value <4.7 mg/dL (1.17 mmol/L). There are several factors that can contribute to the development of hypocalcemia, including: vitamin D deficiency; hypoparathyroidism; impaired kidney function; malabsorption disorders (10, 11). The symptoms of hypocalcemia can vary depending on the severity and duration of the condition. Common signs and symptoms include: muscle cramps and twitching; numbness and tingling; fatigue; mood changes and cognitive impairment (10–12).

Severe hypocalcemia can profoundly impact cardiac function. ECG can reveal distinct changes, including QT interval prolongation, ST segment depression, and T-wave abnormalities. These abnormalities can give rise to dangerous arrhythmias and, in severe cases, CA.

The treatment of both hypokalemia and hypocalcemia involves addressing the underlying cause and replenishing appropriate ion levels. Indeed, prompt diagnosis and appropriate management can help prevent life-threatening complications (13).

Celiac disease is an immune-mediated response to gluten present in wheat, barley, and rye, with a prevalence of approximately 1% in most populations (14). The disease has a wide spectrum of clinical manifestations, e.g. small intestinal enteropathy, systemic symptoms related to malabsorption, immune activation, and autoantibodies to tissue transglutaminase (14, 15). Although, most patients present diarrhea as the most common symptom (15), detection of specific serum antibodies is helpful for the initial screening, while intestinal biopsy and genetic tests are needed for a final diagnosis (16).

Case report

The patient agreed to the use of his data in the publication of this case report for scientific and clinical purposes and the informed consent has been acquired.

A 66-year-old male self-presented to the emergency department with symptoms of malaise and widespread stiffness upon waking up in the morning, followed by speech difficulties, weakness in the right upper limb, and stiffness in the lower limbs, with walking difficulty. The patient reported a weight loss of ten kilograms over the past two months, along with a lack of appetite, reduced fluid and food intake, and persistent diarrhea (four stools during the day and three at night). Additionally, he had been experiencing worsening edema in the lower extremities over the past twenty days. The patient's medical history included hypertension, hypercholesterolemia, and anxiety, and he was taking olmesartan/amlodipine (20/10 mg), rosuvastatin (40 mg), and bromazepam as needed.

Upon arrival at the emergency room, the patient exhibited stable vital signs but had widespread fasciculations, mostly in the face and the tongue. He also had weakness in the lower limbs and swelling in the thigh area. An ECG showed sinus rhythm with a heart rate of 97 beats per minute, normal atrio-ventricular conduction, and no repolarization changes. A venous blood gas analysis revealed a pH of 7.41, sodium (Na+) level of 134 mEq/L, K+ 3.1 mEq/L, ionized Ca++ 0.68 mEq/L, hemoglobin (Hb) 14.7 mg/dL, bicarbonate (HCO3-) 26 mEq/L, and lactate level of 5.7 mmol/L. Focused cardiac ultrasound did not indicate any acute abnormalities. The patient received treatment with lactated Ringer's solution, two grams of calcium gluconate, one gram of magnesium sulfate,

and 20 mEq of potassium chloride. A neurological evaluation revealed contractures and myoclonus related to the metabolic derangement, but no signs of acute brain injury were observed. Approximately 1.5 hour after admission, the patient developed diffuse rigidity and morsus, followed by sudden CA.

The on-call anesthetist was alerted, while cardiopulmonary resuscitation (CPR) was immediately initiated, leading to a 0 min of no-flow time. The presenting rhythm was ventricular fibrillation and the patient received two defibrillations prior to achieve return of spontaneous circulation (ROSC). Orotracheal intubation was then performed, being the patient unconscious (Glasgow Coma Scale score of 3). Another venous blood gas was then performed which showed: K+ 2.6 mEq/L, Ca++ 0.65 mEq/L. Immediately after the blood gas results were obtained, a subsequent cardiac arrest episode with pulseless ventricular tachycardia (pVT) occurred. Since the episode was monitored, the patient received immediate defibrillation followed by a temporary ROSC and a subsequent pVT. This sequence reoccurred several times, such that the patient received a total of four defibrillations, while was administered one gram of calcium gluconate, two grams of magnesium sulfate, 300 milligrams of amiodarone, and a 20 mEq potassium bolus prior to achieve a stable ROSC. Echocardiography showed normal heart chamber dimensions, hypokinesis of the middle apical septum, normal systolic function, and mild mitral and tricuspid regurgitation. There was no indication for urgent hemodynamic intervention, based on the on-call cardiologist's evaluation. A baseline brain CT scan did not reveal any abnormalities, while a subsequent arterial blood gas showed a persistence of hypokalemia and hypocalcemia (K+ 2.8 mEq/L and Ca++ 0.72 mEq/L). The patient experienced new episodes of recurrent VT with significant hypotension, for which amiodarone infusion was started (900 mg/24h) together with concurrent administration of 40 mEq of potassium over two hours, one grams of calcium gluconate and one gram of magnesium sulfate; infusion of noradrenaline and adrenaline was also initiated. Invasive blood pressure monitoring and placement of a central venous catheter were accomplished, and the patient was then admitted to the intensive care unit (ICU).

In the ICU, targeted temperature management at 35.5°C was performed for 24 hours. Antibiotic prophylaxis with amoxicillin/clavulanic acid was initiated to prevent pneumonia due to gastric content inhalation during CPR. The patient was sedated and paralyzed, and adequate sedation was confirmed using bispectral index monitoring for 24 hours. The pupillary light reflex was present and symmetrical. Noradrenaline and adrenaline infusion was continued for hemodynamic support. The arterial blood gas on the ICU admission reported: pH 7.38, Na+ 139 mEq/L, K+ 3.0 mEq/L, chloride (Cl) 108 mEq/L, Ca++ 0.9 mEq/L, Hb 15.4 mg/dL, HCO3- 22 mEq/L, lactate 2.5 mmol/L. Frequent ventricular extrasystoles were initially observed but decreased after six hours. Lactate clearance was achieved within a few hours, and elevated troponin levels were detected, consistent with the post-cardiac arrest syndrome. To address the persistence of a severe electrolyte imbalances including hypokalemia, hypocalcemia, and hypomagnesemia, the patient received in total 220 mEq of potassium chloride, 4 grams of magnesium sulfate, and 4 grams of calcium chloride over a six-hour period. After six hours, arterial blood gas analysis revealed the following values: pH 7.43, Na+ 140 mEq/L, K+3.0 mEq/L, Cl- 109 mEq/L, Ca++1.0 mEq/L, Hb 15.3 mg/dL, HCO3-21 mEq/L, and lactate 2.1 mEq/L. The patient's diuresis spontaneously resumed, and urinary electrolyte levels, including sodium and potassium, returned to the normal range. After 24 hours, the patient regained consciousness and was extubated. No neurological deficits were present. Electrolyte levels and treatments over time are summarized in the Table 1.

On the second day after cardiac arrest, the patient's conditions were stable and the patient was transferred to the cardiology ward, although electrolyte supplementation was still ongoing. During the hospitalization in cardiology, coronary artery disease was discovered, leading the patient undergoing double off-pump coronary bypass surgery. Additionally, in order to investigate the cause of malabsorption and diarrhea, a gastroenterological evaluation was performed, including esophagogastroduodenoscopy with biopsy, which yielded negative results. Thus, a genetic test was executed due to the suspicious of celiac disease, which was then finally diagnosed.

Table 1. Electrolyte values since hospital admission and relative treatments.

Time since ER admission (hour)	**0**	**0.50**	**1**	**1.5**	**3.5**	**7.5**
Hospital location	ER			ICU		
pH	7.41	-	-	7.38	7.42	7.43
Na^+ (mEq/L)	134	-	-	139	139	140
K^+ (mEq/L)	3.1	2.6	2.8	3	2.4	3
Ca^{++} (mEq/L)	0.68	0.65	0.72	0.9	0.9	1
HCO_{3-} (mEq/L)	26	-	-	22	22	21
Lactate (mmol/L)	5.7	-	-	2.5	2.1	2.1
Treatment	Ca^{++} gluconate: 2 g K^+ chloride: 20 mEq Mg sulfate: 1 g	Mg sulfate: 2 g Amiodarone: 300 mg K^+ chloride: 20 mEq	K^+ chloride: 40 mEq Ca^{++} gluconate: 1 g Mg sulfate: 1 g	K^+ chloride 220 mEq Ca^{++} chloride: 4 g Mg sulfate: 4 g		

ER, Emergency Department; ICU, Intensive Care Unit; -, not available since the data was not recorded in the ER electronic chart; K^+, potassium; Ca^{++}, calcium; Na^+, sodium, HCO_{3-}, bicarbonate; Mg, magnesium.

Discussion

Our case report highlights a CA resulting from a concurrent hypokalemia and hypocalcemia associated with a malabsorption disease, specifically coeliac disease. In this scenario, two factors contributed to reduced serum potassium levels: increased excretion due to diarrhea and reduced intake resulting from malabsorption (17, 18). The patient exhibited several signs and symptoms consistent with hypokalemia. As mentioned earlier, hypokalemia is among the reversible causes of CA. In the event of CA, it is crucial to rule out reversible causes (4-T and 4-H) (19, 20). When dealing with a hypokalemic patient, the priority is to restore intracellular potassium levels in order to stabilize cell membranes. Supplement potassium infusion is initiated, typically at a rate of 10-20 mmol/hour. In cases of unstable arrhythmias when CA is imminent rapid infusions or boluses of potassium can be administered at a rate of 2 mmol/min for 10 minutes, followed by 10 mmol over 5-10 minutes (19–21). It is also essential to administer magnesium as an adjuvant therapy for stabilizing cell membranes; moreover, hypokalemia is often associated with hypomagnesemia (22, 23). Magnesium sulfate is infused at a dose of 2 grams over 20 minutes. If, despite these interventions, the patient remains in refractory shockable cardiac arrest, the use of extracorporeal membrane oxygenation may be considered as a bridge to potassium replenishment in the ICU (8, 24).

Furthermore, in this particular case, the clinical scenario was complicated by the concomitant presence of severe hypocalcemia, necessitating prompt supplementation to correct this electrolyte imbalance. It is worth noting that calcium infusion can lower serum potassium levels, which, in this case, could have exacerbated the existing hypokalemic condition. Therefore, the potassium chloride infusion was chosen as first ion supplementation, followed the administration of calcium. Additionally, this administration of calcium likely accounted for an increased requirement of potassium supplementation (25, 26).

In literature, cases of celiac crisis resulting in malabsorption with significant organ function impairment have been reported, and in some cases, like this specific one, the disease was unknown until diagnosed with genetic testing (27, 28). In this case report, it is evident that the combination of malabsorption and excessive loss through profuse diarrhea resulted in a severe multiple ions imbalance. The combination of hypokalemia and hypocalcemia resulted in the 'perfect storm' leading to CA.

This case is notable for its uniqueness, as there are no documented instances in the scientific literature linking CA directly to celiac disease. Unusually, in this case the first manifestation of the disease

was a cardiac arrest; therefore, physicians should remember that malabsorption diseases like celiac one, might cause multiple important electrolyte unbalances potentially leading to rare but fatale life-threating conditions up to CA. Moreover, it is crucial to emphasize the importance of exploring potential reversible factors in cases of CA and implementing suitable interventions to address them (19, 20). In the context of hypokalemia, optimizing magnesium levels may be beneficial, as studies have shown that it can increase serum potassium levels (23, 29). Finally, it is important to highlight the necessity of promptly correcting hypocalcemia, despite concerns about its potential impact on potassium levels. Finally, in this instance, the rapid CPR initiation by the nurses and physicians of the emergency department together with the rapid activation of the CA team, i.e. anesthesiologists, and the optimal handover, led to the successful outcome (30, 31).

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