Hypokalemic rhabdomyolysis and tetany as a presentation of celiac disease in an adult

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SUMMARY

We describe the case of a 38-year-old man with an hypokalemic rhabdomyolysis and tetany as a presentation of celiac disease. We disuss the several electrolitic disturbances found in this patient with chronic diarrhoea and malabsortion syndrome and also the treatment which conduced to complete clinical resolution. We conclude that celiac disease should be considered a cause of hypokalemic rhabdomyolysis.

Key words: *Rhabdomyolysis. Hypokalemia. Tetany. Celiac disease.*

RESUMEN

Describimos el caso de un paciente de 38 años de edad con una rabdomiólisis hipopotasémica y tetania como forma de presentación de una enfermedad celíaca. Discutimos las diversas alteraciones electrolíticas que presentaba como consecuencia de la diarrea crónica y el síndrome de malabsorción así como el manejo terapéutico que condujo a una evolución clínica favorable. Concluimos que la enfermedad celíaca debería considerarse como una posible causa de rabdomiólisis hipopotasémica.

Palabras clave: Rabdomiólisis. Hipopotasemia. Tetania. Enfermedad celíaca.

INTRODUCTION

Hypokalemia maybe the most common electrolyte disturbance.[1] When severe, hypokalemia may cause severe changes in various organs, including rhabdomyolysis. Various diseases have been reported to be able to cause hypokalemia, and muscle necrosis as a result of this.[2-19] Celiac disease is one of such conditions, though very few cases have been reported to date, and most of them occurred in children or young patients.[20-25]

We report the case of an adult who had severe hypokalemia leading to subsequent rhabdomyolysis and tetany as most salient findings, as well as other electrolyte disturbances, in the setting of chronic diarrhoea and a malabsorption syndrome caused by celiac disease.

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CASE REPORT

A 38-year old male patient with an unremarkable history. He reported progressive weight loss over the past months, together with generalised fatigue and muscle weakness. In the last two months, the patient experienced liquid diarrhoea with no pathological products that further worsened the condition. Treatment with loperamide achieved no improvement. Muscle weakness increased in the days before admission, mainly affecting the deltoid area and legs. The patient had great difficulty to walk and especially to climb stairs, and had to stop to rest very frequently.

The following findings were made at the emergency room: BP 129/79, HR 84 bpm, temperature 35.2ºC, SAT O2 98%. Poor general condition, asthenic habit. Glasgow 15. Skin pallor, no signs of dehydration. Eupneic. CA: Rhythmic sounds with no audible murmurs or rubs. PA: normal. Abdomen soft and amenable to pressure, no tenderness. Peristalsis present. Generalised decrease in bone and tendon reflexes Indifferent plantar reflex. No meningeal signs. During his stay at the hospital ward and coinciding with stress from blood sampling, the patient experienced bilateral carpopedal spasm that subsided spontaneously after inspiration and expiration in a plastic bag. Spasm subsequently recurred in the left arm when the cuff for measuring blood pressure was inflated.

A chest X-ray film on admission was normal. The ECG showed sinus rhythm with normal atrioventricular conduction with a tray-shaped ST segment descent with late negative U wave and a diffusely long QT, suggesting hypokalemia.

Table I shows the main laboratory changes on admission and their changes over time. Myoglobin was not tested. A spot urine sample taken on admission showed: potassium 8.1 mEq/L, sodium 14 mEq/L, chloride 74 mEq/L, pH 6.5 with normal sediment.

Intensive therapy with parenteral fluids and electrolyte replacement was started. Table 1 details the treatment started. Adequate urine output volumes were maintained throughout hospital stay. No additional episodes of tetany occurred, and muscle weakness gradually subsided. ECG changes had disappeared on the sixth admission day. Both potassium and all

other electrolytes progressively normalised, as well as haemostatic changes.

Supplemental tests included fecal cultures and detection of *Clostridium difficile* toxins, that were negative. Serologic tests for HIV and hepatitis B and C viruses were also negative. TSH, cortisol, ACTH, and aldosterone levels were normal, as well as those of vasoactive intestinal peptide and catecholamines in 24-hour urine. PTH levels were increased (113 pg/mL), and vitamin D levels decreased (8 ng/mL). Vitamin B_{12} and folic acid levels were normal. Imaging tests (ultrasonography and abdominal CT scan) revealed no pathology. No changes were seen in the EMG-ENG. Colonoscopy was normal up to the hepatic flexure. Gastroscopy revealed a normal gastric mucosa, showing an obvious atrophy of duodenal mucosa, from which biopsies were taken. Pathological findings are described in Figure 1 caption. IgA antitransglutaminase and antigliadin antibodies were detected (> 100 U/mL and 120 U/mL respectively).

Based on diagnosis of celiac disease, a gluten-free diet was started, with a good response and gradual normalization of bowel motions.

DISCUSSION

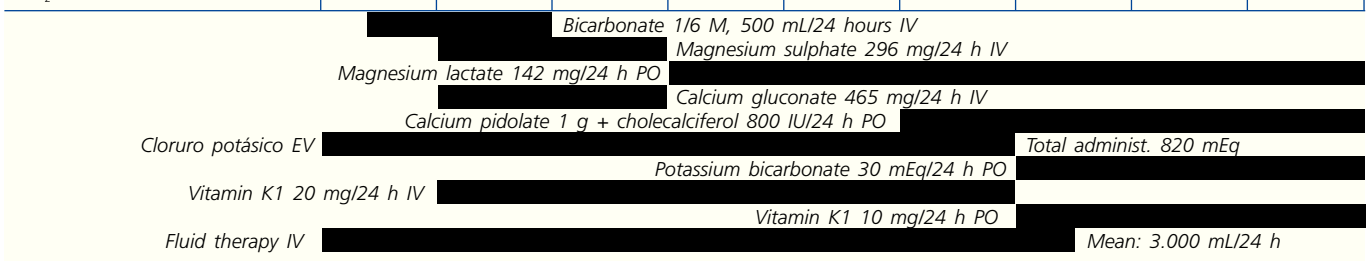
Severe hypokalemia, while rare, is a recognised cause of rhabdomyolysis. This association has previously been reported. The reported causes of hypokalemia include renal tubular acidosis,[2] Bartter syndrome,[3] Gitelman syndrome,[4] licorice intake[5] (mineralocorticoid effect of glycyrrhicic acid), diuretics,[6] laxative abuse,[7] Conn's syndrome,[8] pheochromocytoma,[9] alcoholism,[10] amphotericin B,[11] HIV,[12] chronic intestinal obstruction,[13] Crohn's disease,[14] neuroendocrine pancreatic tumour,[15] ureterosigmoidostomy,[16] short bowel syndrome,[17] itraconazole therapy,[18] and hyperemesis gravidarum.[19] With regard to celiac disease, since the first case was reported in 1982,[20] five additional cases have been reported in which the disease started with rhabdomyolysis induced by hypokalemia.[21-25]

Until recently, celiac disease was considered an uncommon condition mainly affecting children. In the past 15 years, however, celiac disease has become an increasingly frequent diagnosis, and it is now considered an extremely common condition affecting patients at all ages and causing symptoms in multiple organ systems.[26] A change in its clinical presentation has reported in recent years. Symptomatic cases with diarrhoea and weight loss are now less common, and availability of serological tests has allowed for an increasingly earlier diagnosis in the subclinical stages.[27] In our patient, there was no doubt about diagnosis because of both the clinical presentation and the positive serological tests and duodenal biopsy.

In a patient such as the one reported here, with long-term diarrhoea causing severe electrolyte deficiencies, metabolic acidosis caused by gastrointestinal bicarbonate losses would be expected, with a normal anion gap and a negative urinary net charge (that would reflect urinary excretion of ammonium, a usual renal response in metabolic acidosis of an extrarenal origin).[28] While the latter two conditions were met in our case: Serum anion gap $[Na^+ - (Cl^- + HCO_3^-)] = 11.4$ and urinary net charge $[(Na^+ + K^+) - Cl^-] = -51.9$, venous blood gases were virtually normal on admission. An explanation for this apparently paradoxal situation may be the existence

Table I. Changes in blood laboratory test results during hospital stay. Treatment started is also detailed. Black bars indicate duration of each medication

	Day 1	Day 2	Day 3	Day 4	Day 6	Day 7	Day 8	Day 14	Day 17
CPK (IU/L)	7,489	9,368	12,596	12,271	12,250	7,519	5,459	249	93
Potassium (mEq/L)	1.83	2	1.96	2.22	3.14	3.97	3.68	4.6	4.5
Calcium (mg/dL)	7.6	7.9	7.95	8.1	7.7	8	8	9.1	9
Creatinine (mg/dL)	0.72	0.6	0.6	0.5	0.4	0.4		0.6	0.6
Chloride (mEq/L)	106	102	104	106	104	107	97	104	105
Sodium (mEq/L)	146	143	145	143	139	140	140	142	142
Phosphorus (mg/dL)		1.36				2.7			3.89
Magnesium (mg/dL)		1.4				1.7	1,6	2.1	2.1
Prothrombin activity (%)	38.16	36.44				55.43		80	87
Haematocrit (%)	38.2	36.8	34			32		34.8	35.1
LDH (IU/L)		423				419	415	234	203
AST (IU/L)		190				296	203	75	50
Albumin (g/dL)		3.42				2.6	3.05	3.95	3.8
Total cholesterol (mg/dL)		80				66	79	125	120
pH	7.49	7.55	7.54	7.50	7.43	7.38			
$[HCO_3^-]$ (mmol/L)	28.6	36.3	37.6	31.4	24.5	26.7			
PCO_2 (mmHg)	38.5	41.8	45	41	37.1	45.9			



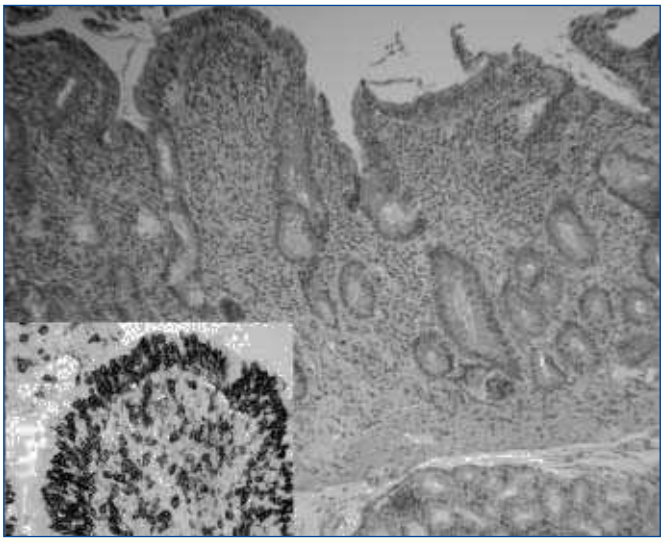


Figure 1. Duodenal biopsy showing villous atrophy and severe inflammation in the lamina propria (haematoxylin-eosin x 400). In the left lower inset, enlarged image showing T lymphocyte infiltrate inside epithelium and in the lamina propria (CD3 immnunochemical stain x 400).

of a mixed disorder of acid-base balance. When metabolic acidosis coexists with metabolic alkalosis, virtually normal values of pH, pCO2, and [HCO^-_3] may occur.[29] Severe hypokalemia (< 2 mEq/L) may cause alkalosis. This is because, in response to low potassium levels, potassium is released from intracellular deposits and a flow of sodium and hydrogen ions into the cell is generated, resulting in a paradoxal situation: the existence of intracellular acidosis in the setting of an extracellular alkalosis. Intracellular acidosis is one of the main mechanisms that stimulate the systems secreting hydrogen ions into the renal tubule lumen, and bicarbonate is secondarily reabsorbed. In addition, by an ill-defined mechanism, potassium depletion is associated to an obligate chloride loss in the distal tubule, which promotes a hypochloremic state.[30] Chloride depletion itself may play an essential role in maintenance of alkalosis together with other well known mechanisms, such as depletion of the effective circulating volume. In this latter situation, the renal tubule reabsorbs virtually all filtered sodium, which is associated to an excess bicarbonate reabsorption. The possibility that our patient had volume depletion as a consequence of diarrhoea cannot be ruled out. We may therefore hypothesise that acidosis resulting from gastrointestinal losses of bicarbonate and the alkalosis caused by severe hypokalemia together with volume contraction due to diarrhoea counteracted each other in our patient.

The priority objective at treatment start was to prevent a potential renal failure due to rhabdomyolysis because CPK levels, which were already very high at baseline, showed an ascending curve. Intravenous bicarbonate was therefore administered, but at not very high doses. However, IV bicarbonate was discontinued at 36 hours after finding that kidney function was not impaired and urine output was adequate. Seen in retrospect, bicarbonate use was undoubtedly risky, since alkalosis could have aggravated hypokalemia and the clinical signs of tetany, despite early start of both potassium and calcium replacement. It may also be argued that if acute renal failure had occurred, this would have greatly complicated patient management. It is therefore difficult to establish general guidelines, and each clinician should decide in each individual case which are the most appropriate actions. However, close monitoring of clinical and laboratory parameters should be maintained at all times, as was done in our patient.

Cases of celiac disease starting as tetany have also been reported, but rhabdomyolysis was not found in any of them.[31-34] In our patient, tetany should be attributed to hypocalcemia resulting form vitamin D malabsorption and deficiency. It should be reminded that rhabdomyolysis is usually associated to hypocalcemia due to calcium deposition in muscle tissue. The tetany attack was triggered in the setting of an anxiety state with subsequent respiratory alkalosis and ionic calcium decrease, with the enhancing effect of hypomagnesemia. While calcium treatment is controversial in rhabdomyolysis,[35] it was required in our patient due to the presence of clinical symptoms. No rebound hypercalcemia occurred on normalisation of muscle enzymes.

When serum potassium levels decrease to less than 2.5 mEq/L, muscle necrosis may occur through several mechanisms.[11] The probability of muscle necrosis appears to be related to the rate at which potassium levels decrease. Hypokalemia may sometimes be overlooked due to the compensatory increase in serum potassium levels caused by rhabdomyolysis itself. By contrast, in other cases the initial hypokalemia subsequently becomes severe as a result of muscle necrosis.[36] It is admitted that for acute renal failure to occur in cases of hypokalemic rhabdomyolysis, a number of conditions such as dehydration, acidosis, physical exercise, or nephrotoxic drugs should also be present.[3]

The patient reported had two additional marked electrolyte disorders, hypomagnesemia and hypophosphatemia. Magnesium deficiency is considered to be severe when levels are below 1.2 mg/dL. Symptomatic hypomagnesemia is frequently associated to other biochemical abnormalities such as hypokalemia, hypocalcemia, and metabolic alkalosis. As a result, it is often difficult to attribute specific clinical signs to deficiencies in this mineral.[37]

Hypophosphatemia may be classified as moderate (1-2.5 mg/dL) or severe (< 1 mg/dL). While most cases of rhabdomyolysis associated to hypophosphatemia in humans have been reported in the setting of alcoholism, an association between rhabdomyolysis and hypophosphatemia has also been reported in cases of anorexia nervosa.[38] There is experimental evidence in animals of a causal relationship between both conditions.[39]

Despite such evidence, and though its possible contribution cannot be ruled out, the fact that magnesium and phosphorus depletion was not as severe as potassium depletion suggests that potassium deficiency was the main factor responsible for rhabdomyolysis.

To summarise, we report the case of a patient with celiac disease starting in adulthood as rhabdomyolysis and tetany caused by the severe electrolyte changes induced by the malabsorption syndrome The rarity of the condition and its florid clinical and laboratory changes make the case particularly in-

teresting and may help clinicians rule out similar etiologies in adult patients with a clinical picture consistent with the one reported here.

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