Case Report

Irreversible End-stage Heart Failure in a Young Patient due to Severe Chronic Hypocalcemia Associated with Primary Hypoparathyroidism and Celiac Disease

Address for correspondence:
Kyriakos P. Aloumanis
3 Filliron str.
14122, N. Heraklion
Athens, Greece
aloumanisk@hotmail.com

Konstantinos Mavroudis, MD,[1] Kyriakos Aloumanis, MD,[1] Panagiotis Stamatis, Dr,[2] George Antonakoudis, Dr,[2] Konstantinos Kifnidis, MD,[2] Chariton Antonakoudis, MD[2]
[1]Department of Endocrinology, Diabetes & Metabolism and [2]Department of Cardiology, General Hospital "Asklipieion", Voula, Athens, Greece

ABSTRACT

Background: Chronic hypocalcemia may cause electrocardiographic (ECG) changes and mimic acute myocardial infarction. It has also been associated with reversible cardiac dysfunction. On the other hand cardiomyopathy and heart failure have been reported in patients with idiopathic hypoparathyroidism or celiac disease.

Clinical Case: A 39-year-old male was admitted to the emergency room with acute retrosternal pain and dyspnea. He exhibited severe hypocalcemia and acute renal failure. High creatine kinase (CK) levels did not correlate with biomarkers of myocardial necrosis (negative troponin test, heart type creatine kinase isoenzyme (CK-MB) <1% of CK value). The ECG showed an extremely long QT interval (0.6 sec) and T-wave inversions on V_4 through V_6. The left ventricular ejection fraction (LVEF) was as low as 25%, while coronary angiography was normal. Investigation of the hypocalcemia revealed primary hypoparathyroidism (Parathyroid hormone (PTH) <3 pg/ml) and concomitant celiac disease with positive antigliadin and endomysial antibodies. The cardiovascular episodes and the dilated heart failure were attributed to the chronic hypocalcemia since no other cause was found. The correction of hypocalcemia has not been sufficient to reverse the end-stage heart failure after more than 6 months of treatment, even though ECG abnormalities have receded, implying permanent cardiac impairment.

Conclusion: This case demonstrates an unusual clinical condition where 2 calcium homeostasis disorders led to severe hypocalcemia with clinical manifestations of end-stage heart failure. The severe cardiac failure appeared to be nonreversible after calcium repletion suggesting permanent cardiac muscle dysfunction due to associated cardiomyopathy.

Introduction

Severe chronic hypocalcemia may predominantly be presented with paresthesias, neuromuscular irritability, and tetany, but can sometimes manifest cardiovascular complications like hypotension, myocardial dysfunction, prolongation of the QT interval, and triggered dysrhythmias like torsades de pointes, decreased myocardial performance, and even heart failure.[1] Hypocalcemia induced heart failure (or hypocalcemic heart failure) has been associated with various clinical entities like idiopathic or postsurgical hypoparathyroidism, vitamin D deficiency, and celiac disease.[2,3,4] The symptoms are often misleading and, consequently, endocrine causes of heart failure are sometimes overlooked.

The case of a 39-year-old man, who upon evaluation for clinical acute myocardial syndrome and end-stage heart failure was diagnosed with primary hypoparathyroidism and celiac disease, is presented and the role of these diseases in heart function is discussed.

Case Report

An obese 39-year-old male was admitted to the emergency room with acute retrosternal pain and dyspnea. He was heterozygous for β thalassemia and had a history of autoimmune hypothyroidism, on T_4 100 μg/d, surgically corrected bilateral cataract, and mild intermittent chronic diarrhea. He reported symptoms of chronic fatigue and muscle weakness. Three years earlier the patient was hospitalized for an "acute coronary syndrome (ACS)" and severe hypocalcemia, with a diagnosis of "non-Q-coronary infarction." Retrospectively, the patient had already had cardiomegaly with a long QT interval on ECG and high muscle enzymes (CK, lactate dehydrogenase [LDH]) with disproportionately low CK-MB at that time. He had been on a β-adrenergic blocker, furosemide, angiotensin converting enzyme (ACE) inhibitor, isosorbide mononitrate, salicylate, and pentoxifylline regiments and was advised to receive daily 1500 mg of calcium supplements, yet his follow-up was inadequate.

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The clinical examination revealed an obese (body mass index [BMI]: 32.7), afebrile patient with mild psychomotor retardation without neuromuscular signs. Pulmonary auscultation was compatible with acute pulmonary edema. Blood gas analysis on Venturi oxygen mask was as follows: pH 7.36, PCO_2 23 mmHg, PO_2 120 mmHg, HCO_3—13 mmol/l, Oxygen saturation (SaO2): 99%. The ECG was remarkable for an extremely long QT interval (0.6–0.8 sec) and T-wave inversions on V_4 through V_6.

Laboratory tests manifested acute renal insufficiency (urea: 65 mg/dl, chromium Creatinine [Cr]: 2.1 mg/dl), with hyperuricemia (uric acid 12.9 mg/dl), severe hypocalcemia (calcium [Ca]: 5 mg/dl) with normal albumin, and elevated serum phosphate (phosphorus [P]: 7.83 mg/dl). The initiation of treatment with diuretics and inotropes resulted in high fluid output and modest hypokalemia (potassium [K]: 3.1 meq/l). The patient also received aspirin and antithrombotic treatment (IIb/IIIa inhibitors) as the case was considered an acute coronary syndrome.

The second day of hospitalization, a massive subcutaneous hematoma secondary to antithrombotic treatment resulted in severe anemia (Hematocrit (Ht): 22%) and the need for transfusion of 3 units of blood. There was a deterioration of calcium depletion (Ca: 3.5 mg/dl), probably because of blood transfusion, due to citrates, in combination with the high doses of loop diuretics and local muscle rhabdomyolysis, that necessitated the initiation of IV calcium repletion.

Repeatedly measured myocardial necrosis biomarkers were not indicative of ischemic heart disease compared to the high CK levels that gradually reached 128 times the upper normal (CK: 21704 U/L vs CK-MB: 126 U/L, troponin: normal). Inflammation markers were high (C-reactive protein [CRP]: 168.00 mg/l, erythrocyte sedimentation rate [ESR]: 100). Left ventricular ejection fraction was as low as 25%.

Further investigation of the hypocalcemia revealed: basal ganglia calcifications in brain CT scan, celiac disease with positive antigliadin (IgG and IgA) and endomysial antibodies as well as primary hypoparathyroidism (PTH <3 pg/ml, normal 15–68 pg/ml) with mild hypomagnesemia (magnesium [Mg]: 1.31 mg/dl [1.6–2.6]). The 25-(OH)-vitamin D level (40 ng/ml) was normal. Urinary calcium was very low (52 mg/24 h). An extensive search to establish the cause of hypoparathyroidism was unsuccessful. The lack of symptoms and signs of tetany was attributed to the long period of hypocalcemia. Pituitary and adrenal function as well as bone mineral density was normal.

A month later, the patient was discharged after gradual decrease of muscle enzymes (normalization of transaminases and CK-MB, while CK and LDH equaled 1.7 and 3.4 times the upper normal limit respectively). Upon discharge, the serum calcium was still low (4.7 mg/dl) in spite of vigorous Ca treatment. Alfacalcidol up to 4μg, calcium carbonate 1500 mg, magnesium, and a gluten free diet was prescribed daily with Ca levels reaching 8.2 mg/dl and ionized Ca 0.82 mg/dl. Intramuscular vitamin D2 40000 IU was added every 2 months and Ca levels increased at 9.1 mg/dl (ionized Ca 1.08 mg/dl). Compliance was extremely poor before admission, but was fairly good for the last 2 years. The gluten free diet was not followed though.

A coronary angiography performed after the stabilization of the patient did not demonstrate cardiovascular disease. The chronic correction of hypocalcemia reversed the ECG abnormalities. However, it has not been sufficient to reverse the end-stage heart failure. This could imply permanent cardiac impairment as a consequence of chronic hypocalcemia and associated cardiomyopathy.

After 27 months of follow-up (15 months with normal corrected calcium levels) the patient's ejection fraction remains low (30%) although the QT interval has been markedly shortened (0.4 sec).

Discussion

Calcium is a multifunctional regulator of diverse cellular functions. Hypocalcemia is reported to be a reversible cause of myopathy, either due to tetany from the decrease in calcium concentration which causes an increase in excitability at the neuromuscular junction, or due to functional alterations in the sarcolemma (increased membrane permeability) that leads to the release of CK, which explains in part the patient's high CK levels and muscle weakness.[5,6] Creatine kinase increase must also be attributed to local muscle involvement at the area of hemorrhage, which could precipitate hypocalcemia in the first few days because of both deposition of calcium salts in damaged muscle and decreased bone responsiveness to parathyroid hormone. Moreover, hypocalcemia has been described as a cause of acute rhabdomyolysis with high CK.[7] In this case the presence of elevated CK-MB reflects a small amount found in skeletal muscle rather than the presence of myocardial disease. Elevation of serum aminotransferase enzymes and LDH due to muscle damage and hyperuricemia from the release of purines are frequent as well and were evident in our patient.

In the cardiac muscle, Ca is a direct central mediator of electrical activation and ion channel gating. It is also known that calcium plays a critical role in excitation-contraction coupling (E-C) and is required for epinephrine-induced glycogenolysis in the heart. Finally, Ca-dependent signaling is also involved in long-term alterations in gene expression. These pathways are involved in hypertrophy and heart failure as they can alter the expression of some of the key Ca-regulatory proteins involved in the E-C coupling and their regulation by kinases and phosphatases.[8]

Hypocalcemia induces cardiac dysfunction[9] and should be considered in patients with heart failure and prolonged QT intervals.[1] Myocardial dysfunction occurs in both

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chronic and acute hypocalcemia and has been described in patients from infancy[3] to old age.[1] The symptoms and biochemical, electrocardiographic, and echocardiographic findings may, in rare cases, mislead towards an acute ischemic attack.[10] This may explain our patient's symptoms and the diagnosis of a non-Q-coronary infarction on his previous hospitalization. Hypocalcemia also reduces renal excretion of sodium.[11] This effect of hypocalcemia may also contribute to the development of heart failure and with the use of diuretics could explain the patient's modest hypokalemia.

The underlying mechanisms of hypocalcemic heart failure in our patient seem to be multifactorial. Celiac disease, a major cause of hypocalcemia and secondary hyperparathyroidism, may share a common autoimmune process with myocarditis and can be found in >4% of such patients.[12] Prevalence of celiac disease in a group of 52 Italian patients with idiopathic dilated cardiomyopathy has been shown to be increased.[13] More recently Pradi et al[4] found an increased risk for celiac disease in patients with end-stage heart failure (relative risk: 5.3). Presumably iron deficiency anemia refractory to iron replacement, a common sign of celiac disease, exacerbates myocardial dysfunction. Cardiac function may improve following a gluten free diet with or without immunosuppressive therapy. It is therefore reasonable to detect the history of gastrointestinal complaints or refractory iron deficiency. Our patient had symptoms of intermittent chronic diarrhea not evaluated before. Antigluten antibodies confirmed the existence of celiac disease and a gluten free diet was prescribed.

Dilated and congestive heart failure have also been reported in idiopathic hypoparathyroidism,[2,14] postsurgical hypoparathyroidism,[15] privation osteomalacia,[16] and vitamin D deficiency.[3] There are cases of dilated cardiomyopathy associated with hypothyroidism and hypoparathyroidism. Myocardial biopsy in such a case suggested that hypothyroidism was the main cause for the dilated pattern, but hypocalcemia played a critical role in the evolvement of the disease.[17] Our patient has had hypothyroidism treated with a thyroxin regiment and was euthyroid. Decreased levels of parathyroid hormone per se as well as hypomagnesemia, both present in our patient, may contribute in the development of heart dysfunction. Blood magnesium levels are often a poor indication of tissue magnesium deficiency and magnesium deficiency alone may also induce cardiac disease.[18]

Autoimmune myocarditis has been associated with polyglandular autoimmune syndrome (APS).[19] The constellation of autoimmune diseases that seem to accumulate in our patient (celiac disease, autoimmune hypothyroidism, hypoparathyroidism) though not clearly associated with classical APS, suggest that an autoimmune process might exist. Thus, chronic autoimmune myocarditis leading to dilated cardiomyopathy would be another possible explanation. There are reports of idiopathic hypoparathyroidism and celiac disease attributed to endomysial antibodies co-reacting with the parathyroid tissue and not parathyroid specific antibodies.[20] We were unable to demonstrate such a relationship in our patient.

The case is a unique combination where multiple calcium homeostasis disorders both chronic (hypoparathyroidism, celiac disease) and acute (blood transfusion, muscle necrosis) led to severe hypocalcemia. Chronic hypocalcemia seems to be related with clinical manifestations of ACS and severe cardiac impairment resulting in dilated cardiomyopathy. End-stage heart failure is far from the classical outcome in patients with hypocalcemia induced heart disease. Usually cardiac function improves after calcium repletion. In our patient, the severe cardiac failure appeared to be nonreversible probably due to long standing hypocalcemia and/or associated autoimmune cardiomyopathy.

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