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Hypocalcemia - A Cause of Reversible Dilated Cardiomyopathy

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Abstract **Case Report**

Hypocalcemiccardiomyopathy (CMP) is a rare but potentially reversible cause of heart failure. The mechanism of hypocalcemia, in adult patientswithsignificant cardiac dysfunction; usually occurs as a result of hypoparathyroidism, either isolated or in combination with vitamin D deficiency. Hypocalcemia induced cardiomyopathy is usually reversible when calcium level returns to normal range. We reportthe cases of threefemalepatientswithhypocalcemiadue to total thyroidectomycomplicated by dilated cardiomyopathy. After supplementation of calcium and vitamin D, symptoms of heart failure and LV function were recovered.

Keyswords: Hypocalcemia - Dilated Cardiomyopathy- heart failure.

INTRODUCTION

Calcium plays an important role in myocardial contractility. Severe extracellular hypocalcemiaaffects cardiac contractility because the sarcoplasmic reticulum is unable to maintain sufficient amount of calcium to initiate myocardial contraction [1, 2]. Hypocalcemia is a rare reversible cause of dilated cardiomyopathy (DCMP).We describe here three cases of DCMP caused by hypocalcemia after total thyroidectomy and recovered completely after supplementation of oral calcium and vitamin D.

CASES REPORT

Case 1

A 56-year-old female patient was admitted to our hospital due to the on-setof dyspnea (NYHA class III) and generalized edema 5 days before her admission. She also complained of generalized seizures and numbness on both hands and feet for 2 weeks. She had a history of total thyroidectomy 14 years ago. She had taken synthyroid as a daily medication after thyroidectomy. She had no history of hypertension, diabetes mellitus or smoking. On physical examination, blood pressure was 96/64 mmHg, heart rate was 75b/min, and body temperature was 37˚C. On chest auscultation, there were coarse breathing sounds with rale and wheezing on both lung fields. A 4/6 systolic murmur at the mitral focus, a positive sign of Chvostek and Trousseau. Chest radiograph showed mild cardiomegaly with increased pulmonary vascularity on both lung field. Her electrocardiogram (ECG) showed normal sinus rhythm with T wave inversion in the anterolateral leads. Laboratory studies revealed C-reactive protein of 2 mg/L (reference range < 5 mg/l), magnesium of 1.9 mg/dL (reference range; 1.8-3.0 mg/dL), albumin of 4.2 mg/dL (reference range; 2.6-5.8 mg/dL), corrected calcemia of 3.8 mg/dL (reference range; 8.5-10 mg/dL), and ionized calcium of 0.40 mmol/L (1.13-1.32). CK-MB and troponin-I were in normal range, whereas brain natriuretic peptide (BNP) was high at 520.7 pg/mL (reference range <100 pg/mL). In the hormone analysis, free T4 and thyroid stimulating hormone (TSH) were in normal range, however parathyroid hormone (PTH-I) was normal at 8 pg/mL (reference range; 14-66 pg/mL).

The transthoracic echocardiography showed global hypokinesia of the LV with 31% of left ventricular ejection fraction (EF) (Fig. 1A). The left ventricular (LV) end-diastolic dimension was 61 mm (Fig. 1B). Mitral regurgitation was observed due to incomplete coaptation of both leaflets. The effective regurgitant orifice (ERO) was 33 mm2 and mitral regurgitation volume was 40 cc in the calculation of proximal isovelocity surface area (PISA) method. The mitral inflow diastolic pattern showed restrictive physiology (Fig. 1C). The E/E' was calculated at 16. There were no significant stenotic lesions on both coronary arteries in coronary arteriogram. We diagnosed as a DCMP due to severe hypocalcemia. We prescribed the oral calcium, vitamin D3, furosemide and candesartan.

Five months after these medications, corrected calcium level increased from 3.8 mg/dL to 9.1 mg/dL. She is free of symptoms such as dyspnea, and numbness of extremities. Chest radiography showed no cardiomegalyor pulmonary congestion. In the follow up echocardiographic evaluation, LV ejection fraction (31% to 58%) and LV end-diastolic dimension (6.1 to 5.4 cm) were normalized. Mitral regurgitationdisappeared. Transmitral inflow patterns changed from restrictive pattern (E/A ratio: 2.77) to abnormal relaxation pattern (E/A ratio: 0.69) (Fig. 2D), and E/E' ratio decreased from 16 to 7,35.

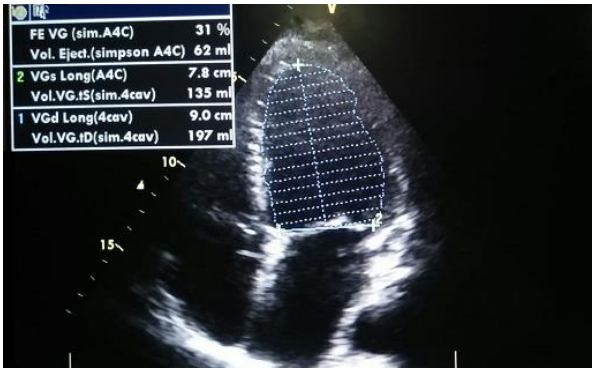

Fig-1A: The transthoracic echocardiography showed a sever left ventricular systolic dysfunction with 31% of left ventricular ejection fraction

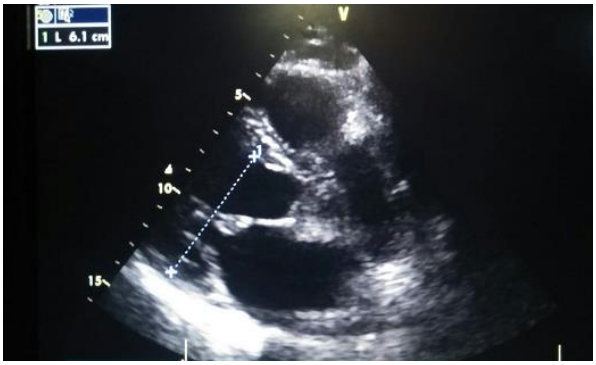

Fig-1B: The transthoracic echocardiography showed the left ventricular (LV) end-diastolic dimension

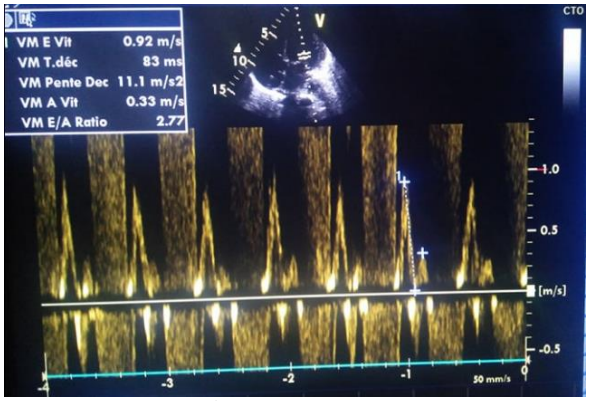

Fig-1C: The mitral inflow diastolic pattern showed restrictive physiology

CASE 2

A 29-year-old female patientsuffering from dyspnea (New York Heart Association class IV) associated with acute crisis of tetany was admitted to our cardiology department. Dyspnea had developed 5 days before admission. She had a history of total thyroidectomy 10 years ago.

On admission, the patient's blood pressure was 90/60 mmHg, and her pulse rate was 85 beats per minute with a 3/6 systolic murmur at the mitral focus. Rales were heard on both sides of the lung field. Physical examination did not reveal neurological dysfunction inregards to muscle tone and sensitivity. Neither edema nor neck vein distension were observed. Electrocardiography showed a sinus tachycardia with prolonged QT interval (432 ms) with nonspecific ST-T changes. Chest X-ray revealed prominent cardiomegaly with pulmonary congestion (Fig. 2A). Echocardiography indicated decreased left ventricular function.

The ejection fraction of the left ventricle (LV) was 24% (Fig. 2B), and the diastolic and systolic dimensions of the LV were 59 and 47 mm, respectively. Moderate mitral and tricuspid valvular regurgitations were identified with global hypokinesia.

Serum levels of creatinekinase-MB and troponin-I were within the respective normal ranges, whereas the brain natriuretic peptide level was elevated.

Based on her symptoms and the results of several previous studies, we made a diagnosis of congestive heart failure and began initial treatment with furosemide injection. The patient had no history of hypertension, diabetes mellitus, or smoking.

Additional studies were performed to determine the etiology of congestive heart failure and acute crisis of tetany. Laboratory studies revealed reduced total serum calcium of 3.2 mg/dL (reference range; 8.5-10 mg/dL), magnesium of 1.6 mg/dL (reference range, 1.8 to 2.5), and ionized calcium of 0.7mmol/L (reference range, 1.13 to 1.4). The creatinine levelwas normal .Hormonal analysis were performed and showed free T4 and thyroid stimulating hormone to be within the respective normal ranges, with intact parathyroid hormone level at 8.14pg/mL (reference range 14-66 pg/mL. Coronary angiography did not detect significantstenotic lesions on the coronary arteries.

We made a diagnosis of DCMP caused by severe hypocalcemia, and treatment was started with intravenous calcium and oral vitamin D3. This was continued in addition to conventional heart failure management. The patient responded to this regimen with remarkable improvement of dyspnea, and chest X-

ray showed a reduction of cardiomegaly with clearance of pulmonary edema.

Calcium levels reached the normal range after 5 days of calcium supplementation. The prolonged QT interval was also reduced.

Follow-up visits revealed progressive improvement of myocardial function; the LV ejection fraction was 42% by the first month and 58% by the third month (Fig. 2C). In addition, the LV diastolic and systolic dimensions were decreased to 52 and 35 mm, respectively.

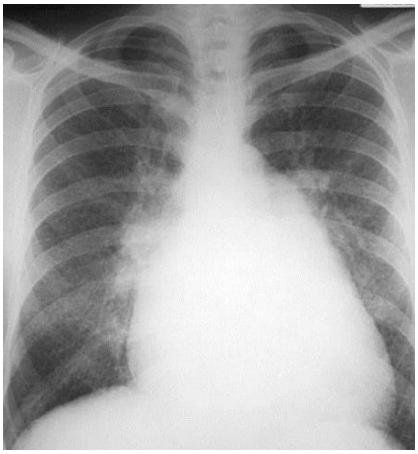

Fig-2A: Chest X-ray revealed prominent cardiomegaly with pulmonary congestion

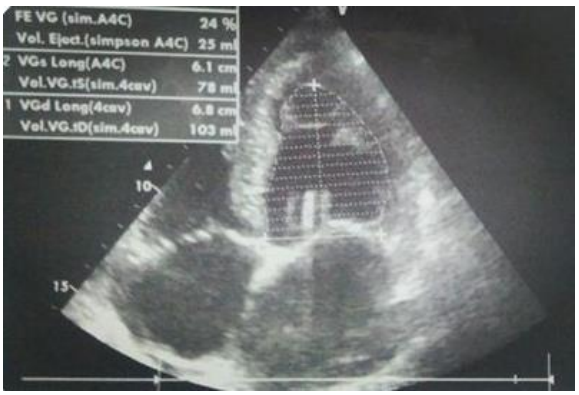

Fig-2B: The transthoracic echocardiography showed a sever left ventricular systolic dysfunctionwith 24% of left ventricular ejection fraction

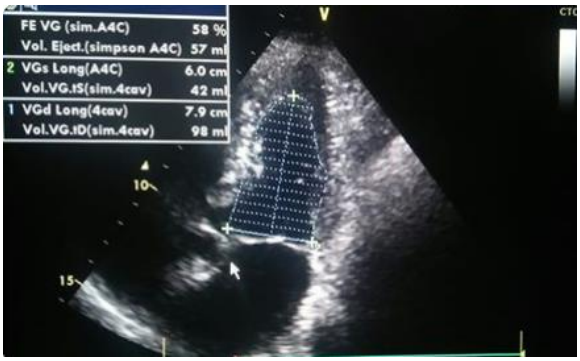

Fig-2C: The follow up echocardiographic evaluation showing improvement of LV ejection fraction to 58%

CASE 3

44-year-oldfemale patient, thyroidectomized 2 years ago, admitted for global heart failure with limb paresthesia.

On physical examination, heart rate was 95/min, BP was 100/60 mm Hg. Trousseau's sign and Chvostek's sign were positive.

Serum Calcium was 3.7 mg/dland serum albumin 4.4 g/ dl. Free T4 and thyroid stimulating hormone (TSH) were in normal range and intact parathormone levels were very low at 2.5 pg/ml.

ECG was without abnormalities. Echocardiography revealed dilated cardiac chambers, global hypokinesia with left ventricular Ejection fraction of 21%

Initially calcium gluconate infusion was administered and later switched to oral calcium supplements and 1,25hydroxy D3. Improvement was noticed with decreased seizures and improvement in functional class. Echo parameters of LV function along with LV dimensions showed improvement at 6 weeks follow up.

DISCUSSION

We present three cases of hypocalcemia-induced DCMP which is improved by calcium and vitamin D replacements. Although hypocalcemia-induced DCMP was previously reported in several papers, it is a rare cause of reversible DCMP after thyroidectomy [2].

Hypocalcemia is a well-known but rare cause of dilated CMP [3-5]. It is important to look for hypocalcemia in every patient with dilated CMP because calcium supplementation has been shown to reverse the otherwise difficult to treat heart failure in such patients [3, 6, 7].

The pathophysiology of hypocalcemic CMP is still unclear, although the physiological role of calcium on muscle contraction is well recognized. Ionized calcium has a central role for regulating myocardial contraction [2, 3].

During the cardiac action potential is activated, ionized calcium enters intracellular through depolarizationactivated calcium channels. Entered ionized calcium triggers calcium release from the sarcoplasmic reticulum (SR). Ca2+ bind to the myofilaments proteins such as troponin C initiate contraction of myocardium [2, 8].There are two main ways to change contractility of myocardium. One is alteration of amplitude or duration of Ca2+ transient, another is alteration of sensitivity of the myofilaments to Ca2+ [8]. Therefore, hypocalcemia induced DCMP is developed by the alteration of amplitude or duration of Ca2+ transient [2, 3].

Parathyroid hormone has been known to stimulate renal calcium ion reabsorption. In the parathyroidectomy rats, sodium and calcium ion exchange activity was decreased by 40% and this activity was restored by infusion of PTH [9].Reduced urinary excretion of sodium leads to water retention and it may cause heart failure [9, 10]. At the same time, more recent evidence suggests that vitamin D and PTH may also have an independent role to play [3].

Of late, there has been increasing recognition of the autocrine functions of vitamin D in several organs including cardiomyocytes. Ablation of the vitamin D receptor in mice and vitamin D deficiency in rats have been shown to result in cardiac hypertrophy and fibrosis [11]. This cardiac hypertrophy in vitamin D receptor null mice is not prevented by normalization of calcium levels with a highcalcium, high-phosphate rescue diet, suggesting an independent role of vitamin D in cause of cardiac manifestations [11]. Similarly, in experimental models, vitamin D deficiency in mothers has been shown to result in delayed maturation and abnormal growth of cardiomyocytes in the offspring, even when serum calcium levels were kept unchanged [12]. Numerous epidemiological studies have also shown association between vitamin D deficiency and heart failure. In a community-based study among the elderly, higher circulating vitamin D concentrations were found to be associated with better LV systolic function at baseline [3].

Similar to vitamin D, PTH also plays an important role in the maintenance of normal cardiac contractile function. It acts on voltage-gated calcium channels and has been demonstrated to exert positive chronotropic effect in neonatal cardiomyocytes [3, 13]. In addition, PTH also stimulates intracellular protein synthesis through stimulation of protein kinaseC [3, 13]. Several case reports have shown isolated hypoparathyroidism to be associated with significant, reversible LV systolic dysfunction [3, 14]. Despite the above-mentioned pathogenic associations between myocardial contractile function and calcium homeostasis [3].

Common cardiac manifestations of hypocalcemia include prolonged QT interval refractory, life threatening hypotension, ventricular arrhythmias and dilated cardiomyopathy. Chronic hypocalcemia is a relatively uncommon and reversible cause of congestive heart failure [15].

Hypocalcemiacauses not only heart failure, but also elevating cardiac enzyme and ST segment changes in ECG which mimics acute myocardial infarction [2, 16]. Walters explained that cell membrane potential is lower in case of hypocalcemia, which increases cell membrane permeability and muscle enzyme leakage from the cells. However, the elevated cardiac enzymes usually return to normal after treatment of hypocalcemia [2].

Tingling sensation is a typical symptom of hypocalcemia. Severe hypocalcemia or rapid occurrence of hypocalcemia are associated with chvostek and trousseau's sign [2].

In our cases, serum levels of hypocalcemiawere corrected within several days after calcium supplement. However, improvement of phenotype, such as restoration of LV systolic function and chamber size, was achieved by far later.

Correction of serum levels of calcium was not sufficient for restoration of myocardial function. Rather, it is thought that restoration of intracellular calcium levels is more important to restore myocardial function. It would take a few months to oobtain normalized tissue calcium levels [2, 17].

The echocardiographic and hemodynamic improvement of hypocalcemia-induced DCMP could not be achieved by conventional medical treatments of heart failure [2, 18]. In the experience of Gurtoo *et al*. [19] discontinuation of calcium supply leaded to thereappearance of heart failure. Calcium and vitamin D are themost important treatment forhypocalcemia induced cardiomyopathy. Furthermore, furosemide may aggravate hypocalcemia by increasing urinary calcium excretion. So, closer monitoring of serum calcium levels in the treatment of heart failure patients with severe hypocalcmia is necessary.

Hypocalcemia is an important cause of reversible cardiomyopathy and lack of awareness of this etiology may lead to inappropriate therapy of cardiac failure with loop diuretics, leading to a worsening of hypocalcaemia and its possible acute life threatening manifestations (laryngeal spasm, prolonged QTc, ventricular arrhythmias, and refractory hypotension), by increasing renal excretion of calcium [15].

We speculate that hypocalcemia-induced heart failure occurs more frequently than reported because of asymptomatic hypocalcemia. In our cases, LV systolic function and additional symptoms were improved after calcium treatment. Hypocalcemia should be included in the differential diagnosis of all patients with congestive heart failure as a possible cause of reversible congestive heart failure.

CONCLUSION

Hypocalcemia should be considered as a possible cause of dilated cardiomyopathy when the patient presents with heart failure due to left ventricular systolic dysfunction in association with seizures and other neurologic manifestations and /or prolonged QT interval in the electrocardiogram. Recognition of the condition is important as it is highly treatable.

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