Hypocalcemic Cardiomyopathy—Different Mechanisms in Adult and Pediatric Cases

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Background: Hypocalcemic cardiomyopathy (CMP) is a rare but potentially reversible cause of heart failure. However, the mechanism of hypocalcemia seems to differ between infants and adults. Although severe vitamin D deficiency alone is the usual cause of hypocalcemic CMP in infants, in adult patients significant cardiac dysfunction usually occurs as a result of hypoparathyroidism, either isolated or in combination with vitamin D deficiency. We present two cases of hypocalcemic CMP—one adult and one pediatric—to highlight these differences.

Case Presentation: The first patient was a 47-year-old female who presented with progressive dyspnea and fatigue and was found to have severe left ventricular (LV) systolic dysfunction (LV ejection fraction, 25%). Her serum calcium level was 3.5 mg/dL, serum phosphorus level was 5.7 mg/dL, and serum 25-hydroxyvitamin D level was 14.1 ng/mL, along with a serum PTH level of 11.8 pg/mL. Her LV ejection fraction normalized completely over 6 months with calcium and calcitriol treatment. In contrast, the second patient was an infant who had presented in cardiogenic shock. Investigations revealed serum calcium of 4.5 mg/dL, serum phosphorus of 11.9 mg/dL, 25-hydroxyvitamin D of 8.9 ng/mL, and serum PTH level of 670 pg/mL. Calcium and calcitriol supplementation resulted in rapid and complete clinical and hemodynamic recovery.

Conclusion: Hypocalcemia is a rare but treatable cause of dilated CMP. In infants, hypocalcemia is usually due to maternal vitamin D deficiency and is accompanied by compensatory hyperparathyroidism. In contrast, in adult patients, hypocalcemic CMP is usually a result of hypoparathyroidism, with or without concomitant vitamin D deficiency. **(*J Clin Endocrinol Metab* 99: 2627–2632, 2014)**

Dilated cardiomyopathy (CMP) is a common clinical condition associated with significant morbidity and mortality and is usually irreversible. Hypocalcemia is one of the few treatable causes of dilated CMP, and its recognition is therefore important in patients presenting with unexplained left ventricular (LV) systolic dysfunction (1). Although hypocalcemic CMP is commonly encountered in children, it has been reported less frequently among adults. The differences in the underlying metabolic abnormalities may account for this discrepancy. Whereas the pediatric cases are predominantly due to vitamin D deficiency, most adult cases occur as a result of hypoparathyroidism, either isolated or in combination with vitamin D deficiency (2, 3). We present one adult and one pediatric case of dilated CMP associated with hypocalcemia to highlight the differences between the two.

Case Presentations

Case 1

A 47-year-old female reported to the hospital on July 13, 2012, with complaints of weakness, progressively increasing dyspnea on exertion, sudden onset of chest heaviness, and palpitations associated with a tingling sensation in hand and arm for 1 month. She had type 2 diabetes for 3 years and was on oral antidiabetics with optimal glycemic control. On presentation, her pulse rate was 72 beats

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Abbreviations: CMP, cardiomyopathy; LV, left ventricular.

per minute, and her blood pressure was 120/70 mm Hg. Chest auscultation revealed bilateral basal crepitations with an unremarkable rest of the systemic examination. Laboratory tests revealed normal blood counts, renal functions, and serum electrolytes, but serum calcium and phosphorus levels were not checked. Cardiac enzymes were also normal. Her electrocardiogram revealed normal sinus rhythm with borderline atrioventricular conduction delay, nonspecific T wave abnormalities, and prolonged QT interval. Echocardiography showed global LV hypokinesia with LV ejection fraction of 24%. LV global longitudinal strain, an objective parameter of LV contractile performance (4), was measured using two-dimensional speckle tracking echocardiography and was found to be markedly reduced (−10.4%; Figure 1A). She was subjected to coronary angiography, which revealed normal coronary arteries. She was stabilized with medical therapy and discharged on conventional treatment of heart failure including diuretics, digoxin, β-blocker, and an angiotensin-converting enzyme inhibitor.

The patient presented again on October 3, 2012, with new complaints of episodic dizziness and muscular spasms for the preceding 2 months. She also had a history of generalized seizures in August 2012, unrelated to hypoglycemia. On examination, her Trousseau sign was positive. She had bilateral pedal edema and bilateral lung crepitations. In view of these new findings, hypocalcemia was suspected, which was confirmed by her lab reports that showed severe hypocalcemia with hyperphosphatemia (Table 1). Subsequent investigations showed insufficient serum 25-hydroxyvitamin D (henceforth, vitamin D) levels and low serum PTH values (11.8 pg/mL). She was given 10 mL of 10% calcium gluconate iv, followed by five ampoules of 10% calcium gluconate in 5% dextrose infused over 10 hours. Her antidiabetic medications were changed from glimepiride and pioglitazone to metformin and sitagliptin. She was simultaneously initiated on oral calcium and calcitriol in doses of 3 g/d and 1.5 μg/d, which were tapered after 2 months (to calcium carbonate 1 g/d and calcitriol 0.25 μg/d) when her serum calcium level was found to be elevated beyond the normal range.

In view of her relatively low serum PTH level, she was evaluated for secondary causes of hypoparathyroidism, but none was found. There was no associated autoimmune illness; thyroid function, serum cortisol level, and iron studies were normal. There was no evidence of Albright's hereditary osteodystrophy phenotype or mucocutaneous candidiasis. She had no cataract, and her computed tomographic brain scan also did not reveal any calcification.

She reported significant symptomatic improvement during her follow-up visit on October 16, 2012. Serum calcium level at that time was 8.2 mg/dL. Echocardiography revealed improved LV systolic function with LV ejection fraction of 35%. She was advised to return for a follow-up visit after 4 weeks but delayed it and presented on December 10, 2012. By then, her symptoms had completely resolved, and the echocardiography revealed near normal LV systolic function (LV ejection fraction, 52%) with significant improvement in LV global longitudinal strain (−15.2%; Figure 1B). However, she had developed hypercalcemia (13.5 mg/dL) due to a continued high dose of calcium supplementation, which was immediately stopped and later restarted at lower doses (500 mg once a day). She presented for another follow-up visit 3 weeks ago (Jan 29, 2014) when she was found to be com-

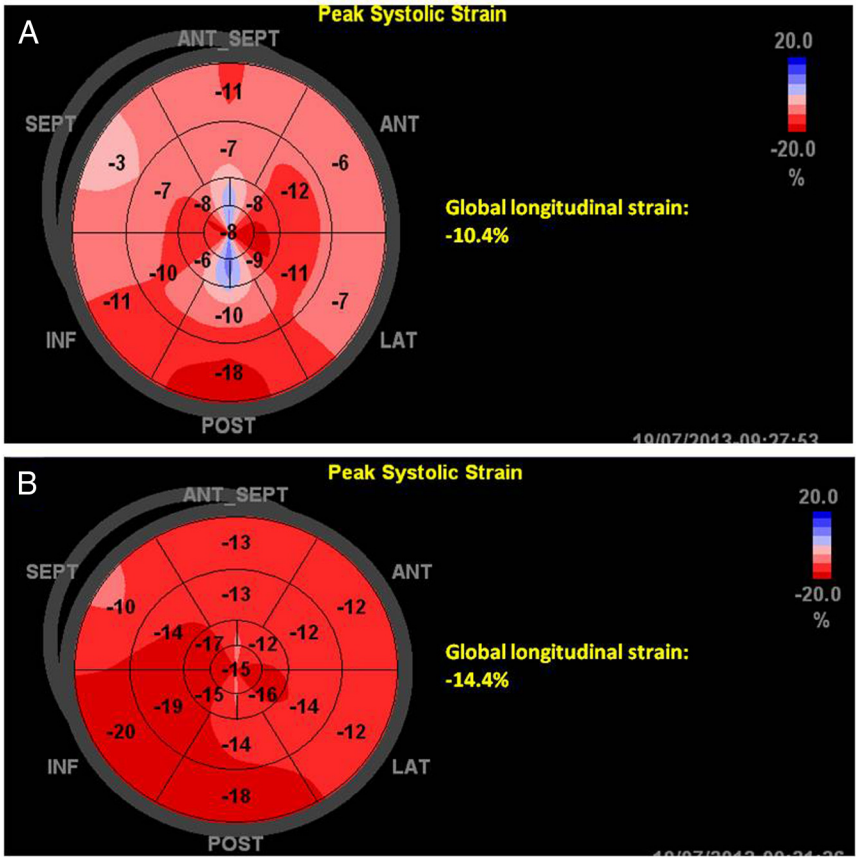

Figure 1. Bull's eye plot of LV segmental longitudinal strain at baseline (A) and after correction of hypocalcemia (B). The segmental longitudinal strain values were markedly reduced at baseline with global average −10.4% only but improved significantly with correction of hypocalcemia. SEPT, septum; ANT_SEPT, anterior septum; ANT, anterior wall; LAT, lateral wall; POST, posterior wall; INF, inferior wall.

Table 1. Serial Investigations in Case 1

Laboratory Investigation	July 13, 2012	Oct 3, 2012	Oct 16, 2012	Oct 10, 2012	Jan 29, 2014
Hemoglobin, g/dL	13.1				
Total leucocyte count, $\times 10^3$/mL	10.77				
Blood urea, mg/dL	0.9				
Serum sodium, mmol/L	138				
Serum potassium, mmol/L	5.3	3.3			
Random blood glucose, mg/dL	149				
Glycosylated hemoglobin, %		7.5			
Serum calcium, mg/dL		3.5	8.2	13.5	8.9
Serum phosphorus, mg/dL		5.7			
Serum 25-hydroxyvitamin D level, ng/mL		14.1			37.7
Serum magnesium, mg/dL		1.2			
Serum PTH level, pg/mL		11.8			38.8
LV ejection fraction on echocardiography, %	25		35	56	

pletely asymptomatic, with near-normal LV systolic function (LV ejection fraction, 52%) and normal serum calcium (8.9 mg/dL), PTH (38.8 pg/mL), and vitamin D (37.7 ng/mL) levels (Table 1).

Case 2

A 2-month old infant presented on November 17, 2010, with a history of cough for 2 weeks and respiratory distress for 5 days. He was the second of the two siblings and was a product of normal vaginal delivery with no history of birth asphyxia or of any other significant perinatal events. He had had normal neonatal development, weighed 5.0 kg, and was exclusively breast-fed. The growth pattern of the baby was well within normal limits for age and sex. There was no significant antenatal maternal history, except the fact that his mother had not taken calcium supplementation during the entire pregnancy.

At the time of presentation, he was irritable and was crying excessively. His heart rate was 150 beats per minute, and blood pressure was 78/46 mm Hg, with muffled heart sounds and evidence of severe respiratory distress in the form of prominent intercostal retraction. Chest x-ray revealed cardiomegaly. Echocardiography showed dilated left atrium and LV, with LV ejection fraction of only 15% and grade 2 mitral regurgitation. He was urgently managed with dobutamine, iv furosemide, enalapril, digoxin, and iv Ig. His condition deteriorated over the next few hours with worsening respiratory distress, cyanosis, and grunting. Arterial blood gas analysis showed severe metabolic acidosis. In view of his deteriorating clinical condition, he was intubated and ventilated. Meanwhile, his investigations showed anemia and severe hypocalcemia (Table 2). Consequently, he was immediately put on iv calcium supplementation. Ten milliliters (2 mL/kg) of 10% calcium gluconate was given over 30 minutes, followed by 80 mg/kg/d as iv infusion for the next 48 hours. This was followed by oral calcium carbonate 100 mg/kg/d in three divided doses and oral calcitriol 0.125 μg/d.

With this treatment, his condition steadily improved. He was extubated over next 2 days, and inotropic support was withdrawn on the third day of initiating calcium supplementation. His clinical status and LV function im-

Table 2. Serial Investigations in Case 2

Laboratory Investigations	Nov 17, 2010	Nov 20, 2010	Jan 18, 2011
Hemoglobin, g/dL	9.0		
Total leukocyte count, $\times 10^3$/mL	9.37		
Serum TSH, IU/L	0.96		
Blood urea, mg/dL	39.0		
Serum creatinine, mg/dL	0.5		
Serum sodium, mmol/L	134.0		
Serum potassium, mmol/L	5.3		
Serum calcium, mg/dL	4.0	8.3	11.1
Serum phosphorus, mg/dL	11.5		4.6
Serum alkaline phosphatase, U/L	765		
Serum magnesium, mg/dL	1.3		
Serum 25-hydroxyvitamin D level, ng/mL	8.9	32.6	
Serum PTH level, pg/mL	620	170.2	
LV ejection fraction on echocardiography, %	15		50

Table 3. Comparison of Salient Biochemical Findings in Cases 1 and 2

	Case 1	Case 2
Age	45 y	2 mo
Serum calcium, mg/dL	3.5	4
Serum phosphorus, mg/dL	5.7	11.5
Serum magnesium, mg/dL	1.2	1.3
Serum 25-hydroxyvitamin D level, ng/mL	14.1	8.9
Serum PTH level, pg/mL	11.8	625

proved, and he was discharged after 5 days on oral calcium and calcitriol. During follow-up, his cardiac function normalized completely in 3 months. He was last evaluated in January 2014 and was found to have normal growth and development, no rachitic features, and normal LV ejection fraction with normal cardiac chamber dimensions.

The vitamin D deficiency in this child was attributed to maternal vitamin D deficiency because he was exclusively breast-fed and his mother herself was vitamin D deficient (13 ng/mL). He also had significant hyperphosphatemia at presentation, which was likely to be because of poor tissue perfusion secondary to congestive heart failure.

A comparison of these two cases shows that in the pediatric patient, vitamin D level was much lower, whereas PTH level was significantly elevated. In contrast, in the adult patient, vitamin D deficiency was less severe, but there was associated hypoparathyroidism that appeared to be the dominant metabolic abnormality (Table 3).

Discussion

Hypocalcemia is a well-known but rare cause of dilated CMP (5, 6). 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 (7, 8).

The pathophysiology of hypocalcemic CMP is still unclear, although the physiological role of calcium on muscle contraction is well recognized. During membrane depolarization, extracellular calcium ions flux into the myocytes through voltage-gated L-type calcium channels. This triggers release of calcium from sarcoplasmic reticulum. Subsequent binding of calcium ions to troponin-tropomyosin complex stimulates cross-linking of actin and myosin filaments leading to muscle contraction (9). Accordingly, in experimental models, hypocalcemia has been shown to reduce cardiac contractility (9). However, at the same time, more recent evidence suggests that vitamin D and PTH may also have an independent role to play.

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 (10). This cardiac hypertrophy in vitamin D receptor null mice is not prevented by normalization of calcium levels with a high-calcium, high-phosphate rescue diet, suggesting an independent role of vitamin D in causation of cardiac manifestations (10). 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 (11). 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. The association persisted after adjusting for several potential confounders, including cardiovascular risk factors and calcium, phosphate, and PTH levels (12). In yet another study in patients undergoing coronary angiography, low levels of vitamin D were associated with lower LV ejection fraction and increased cardiovascular mortality during follow-up (13).

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 (14). In addition, PTH also stimulates intracellular protein synthesis through stimulation of protein kinase C (14). Several case reports have shown isolated hypoparathyroidism to be associated with significant, reversible LV systolic dysfunction (1–3, 15, 16).

Despite the above-mentioned pathogenic associations between myocardial contractile function and calcium homeostasis, the mechanisms and cardiac manifestations of hypocalcemia seem to differ between neonates and adults. In neonates, vitamin D deficiency is common and is an important cause of hypocalcemic CMP (17–23). Maternal vitamin D deficiency is the usual cause of vitamin D deficiency in this age group. In a recent study, 96% of pregnant women were found to be vitamin D deficient, and there was a positive correlation between vitamin D levels in mothers and the same in their infants (24). In contrast, in adults, although vitamin D deficiency is widely prevalent, significant LV systolic dysfunction with heart failure is only uncommonly reported. Only about 27 adult cases of "hypocalcemic CMP" have been reported in the literature, (1–3, 5–8, 25–28) since its first description in 1939 (29). It is therefore intriguing that although infants with vitamin D deficiency manifest with severe hypocalcemia and cardiomyopathy, adult vitamin D deficiency does not usually manifest as hypocalcemic CMP. Certain differ-

ences in the underlying metabolic milieu may explain this discrepancy. In pediatric patients presenting with hypocalcemic CMP, vitamin D deficiency is generally severe and is almost invariably associated with secondary hyperparathyroidism. Although a recent report on infantile hypocalcemic CMP stated that infants with vitamin D deficiency manifested severe hypocalcemia probably due to relatively immature PTH response to hypocalcemia (22), most of the other case studies have reported very high PTH levels in these children. In contrast, in adult patients presenting with hypocalcemic CMP, relative or absolute hypoparathyroidism is commonly encountered and is usually the dominant metabolic abnormality (1–3, 6, 8, 28). Concomitant vitamin D deficiency, if present, may aggravate hypocalcemia and LV systolic dysfunction. Evidence that vitamin D supplementation might improve cardiac function is not yet established, although some recent data point toward potential benefits (30, 31). The differences in age-related maturation of calcium handling mechanisms may account for these differential effects of vitamin D deficiency on serum calcium levels and LV systolic function in neonates and in adults.

In our first patient, pioglitazone was stopped at the time of initial diagnosis of hypocalcemia. Because pioglitazone is known to cause or worsen heart failure, cessation of pioglitazone may have resulted in the observed improvements in cardiac function in this patient. However, it is noteworthy that heart failure secondary to pioglitazone is almost invariably due to fluid retention, and development of severe LV systolic dysfunction is distinctly rare (32). Hence, hypocalcemia was suspected as the primary cause of impaired cardiac function in this case.

Conclusions

Hypocalcemia is a rare but treatable cause of dilated CMP and therefore should be looked for in all unexplained cases of severe LV systolic dysfunction. In infants, hypocalcemia is usually due to maternal vitamin D deficiency and is accompanied by compensatory hyperparathyroidism. In contrast, in adult patients, hypocalcemic CMP is usually a result of hypoparathyroidism, with or without concomitant vitamin D deficiency.

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