

Hypocalcemic rachitic cardiomyopathy in infants

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Hypocalcemic cardiomyopathy in infants is characterized by heart failure in a previously normal infant with hypocalcemia without organic cardiac lesion. Vitamin D deficiency rickets is increasing in Middle East. In a six month study 136 cases of rickets were diagnosed in the main Children's Hospital in Almadinah but none of them showed evidence of cardiomyopathy. Concerned of missing this serious complication of rickets we searched pub med and present this review article.

Results: 61 cases of hypocalcemic cardiomyopathy were reported as case reports with two series of 16 and 15 cases from London and Delhi, respectively. The major features of these cases: the age ranged from one month to 15 months with a mean age of 5 months. All presented with heart failure and hypocalcemia. There was a minor feature of rickets in a few of the cases. All had high alkaline phosphatase. Echocardiology evidence of cardiomyopathy was found in all. Most of them responded to calcium, vitamin D and cardiotonic and diuretics.

Discussion: We concentrated on pathogenesis of this hypocalcemic cardiomyopathy and reviewed the literature. The evidence available supports that the most likely cause of cardiomyopathy is hypocalcemia. Hypovitamin D also contributes but hyperparathyroidism might have a protective role as we did not detect any evidence of cardiomyopathy with hyperparathyroidism and florid features of rickets.

Conclusion: We need to look out for cardiomyopathy among infants with hypocalcemia. For prevention maternal supplementation during pregnancy and lactation with up to 2000 units of vitamin D and 400 units for their infants.

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Introduction

Cardiomyopathy in infants is characterized by heart failure in apparently normal children without previous organic cardiac lesions. The Pediatric Cardiomyopathy Registry of USA contains clinical and causal information for 916 North American children who were diagnosed as having cardiomyopathy. Cardiomyopathy has been found to comprise four types with different incidence rates; hypertrophic (34.2%), dilated (53.8%), restrictive (3.2%), and other or mixed (8.9%). Only one third of the cases had a known cause. Children with a known cause for hypertrophic cardiomyopathy included more females than males in relatively younger age groups, presenting with congestive heart failure, and increased left ventricular posterior wall thickness without outflow tract obstruction. For dilated cardiomyopathy (DCM), a known cause was associated with older age, lower heart rate, smaller left ventricular dimensions, and greater shortening fraction [1]. In all these cases there was no mention of hypocalcemia as one of the causative factors. In Pakistan, a developing country, the relative incidence of DCM was reported to be 9%, in patients with a mean age of 5 years and none of them were hypocalcemic [2]. The association of heart failure and hypocalcemia was first reported in 1949 by Dodd and Rapport who stated that cardiac manifestations could be linked to hypocalcemia though in the presence of other electrolyte deficiency [3]. In 1955, Schulman and Ratner reported a 12 years old girl with chronic hypoparathyroidism and cardiac failure that improved with a correction of calcium [4]. In 1963 [5] Edge reported congestive heart failure associated with hypocalcemia in infancy. The first case of frank rickets presenting with heart failure occurring in an 18 months old infant was reported by Najjar, in 1967 [6]. Troughton and Singh in 1972 [7] reported six neonates with hypocalcemia and heart failure. The fact that heart function returned to normal as soon as these patients were subjected to calcium regiment, was a clear proof of that low serum calcium was the direct cause of DCM in these individuals. The term hypocalcemic cardiomyopathy was coined by Bas-hour et al. in 1980 while reporting the cases of a 10 years old girl and a 36 years-old woman, both presenting with hypocalcemia and heart failure, and showing a dramatic response to calcium therapy [8]. Gillor et al in 1989 were the first to report that heart failure in a three and a half months old rickets patient is caused by vitamin D deficiency [9]. This patient responded promptly to adequate calcium therapy accompanied by

usual anti-congestive therapy. Since vitamin D deficiency-induced rickets is common in Middle East with hypocalcemia being the most common manifestation during the first year of life among breastfed infants, in this review we will discuss the recent literature on hypocalcemic rachitic cardiomyopathy [10–12]. We will highlight the latest advances in diagnosing and treating this disease, with particular emphasis on the latest advances in the Middle East.

Methods

We searched Pub Med using the key words hypocalcemia, rickets and dilated cardiomyopathy in children. Also, we reviewed cases with a diagnosis of cardiomyopathy admitted to Pediatric Intensive Care Unit (PICU) of Medinah Maternity and Childrens Hospital (MMCH) retrospectively in a period of one year.

As part of the study of rickets in MMCH studied cases seen in outpatient with features of rickets were examined by echocardiography to detect any abnormality suggestive of cardiomyopathy in a period of six months from September 2008 to March 2009.

Results

The Pub Med review for hypocalcemia and cardiomyopathy revealed 23 publications including 59 case reports of infants (see Table 1), as well as 16 cases reported from the London region [13] and fifteen from Delhi [14]. Also 5 cases reported from Delhi in which hypocalcemia and cardiomyopathy were not only presenting features, but also cardiogenic shock [15]. Additionally, we noted four cases from one center in USA as well as reports of two cases in each from UAE, UK and France. The remaining were single case reports from different parts of the world.

Interestingly, a one-year survey of cases at the pediatric intensive care unit (PICU), Al-Madinah Maternity and Children Hospital (MMCH), Kingdom of Saudi Arabia did not reveal any cardiomyopathy that is associated with hypocalcemia. This observation is consistent with our survey conducted by us in the outpatient unit of the same hospital. As a part of our study on rickets to be reported, these 35 outpatient cases with frank rickets that were examined using echocardiography (echo) and did not reveal any cardiac defect suggestive of cardiomyopathy.

To summarize this literature review, that of Maiya et al. [13] reported 16 cases of hypocalcaemia

Table 1. Clinical, biochemical and cardiological features in infants with dilated cardiomyopathy, hypocalcemia and rickets.

Reference yr S(No)	Age(Gen)	Fed on	Origin	Present	Diagnosis	Cardiac Diagnosis	Ca	Ph	V D	AIPIU	PTHpg	Treatment	Out come
Bashour 1980 (7)	10y	Nor	Serya	Tetany	HypoPTH	CF	L	H	L	H	L	Ca VD RCT	G
Gillor1989 (12)	3.5(m)	Bf	Germa	CHF	Rickets	DCM	L	L	L	H	H	Ca vitdCt	G
Yaseen 1993 (17)	Infant	Bf	France	CHF	Rickets	DCM	L	L	L	H	H	Ca vi DCT	G
Memmi 1993(18)	1.5(m)	Bf	France	Dysp	Ricketsm	DCM	1.4	N	L	H	10	Ca vitdCT	G
Karademir1993 (19)	1 m(m)	Bf	Turky	CHF con	HypoCa	HF	L	L	L	H	H	Ca vitDCT	G
Brunvard 1995 (20)	3.5 (f)	Bf	Norwa	CHF	Rickets	DCM	L	H	L	H	H	Cqa vitDCT	G
Lachassinne1992(21)	8 m(ng)	Bf	France	CHF	HypoCa	HF,EBV	L	L	L	H	H	Ca vitDCT	G
Abdulla1999(22)	5 m (m)	Bf	Canada	CHF	Rickets	DCM	L	L	L	H	H	Ca vitDCT	G
Oglun 2003(23)	9 m(F)	bf	Turky	SB	Rickets	DCM	L	L	L	H	H	Ca VitDCT	G
Gulati 2001(24)	4 m(m)	Bf	India	SB	VDDR	pQoTc	L	N	L	H	H	Ca calcitrol	G
Price 2003(25)	5 m	Bf	USA	HF irr	Rickets	DCM	L	L	L	H	H	Ca D digCT	G
C-Conway1004(26)2cases	4.5(f)8(m)	Bf	UK	RD HF	Rickets	DCM	1.3	L	LL	H	H	Ca VitDRCT	G
Goulet 2006(27) 2 cases	1 m	Bf	France	Hf hf	22q11 del	DCM	LL	LL	LL	HH	HH	Ca viit dCT	G
Cramm 2006(28)	3.5 m	Bf	USA	CHF	Rickets	DCM	L	L	L	H	H	Ca VitDCT	G
Roy 2006 (29)	Infant	Bf	UK	DCM	Adibic aciduria	DCM	L	L	L	H	Diet	Diet,Ca	G
Amirlak 2008(30) 2cases	9 m × 2	Bf	UAE	CHF	Rickets	DCM	L	L	L	H	H	Ca vit DCT	G
Brown 2009(31)4cases	8 m(fmmm)	Bf	USA	RDC	Rickets	HF,DCM	L	L	L	H	H	CaVITDCT	G
Kim 2010 (32)	2 m (f)	Bf	Koria	CHF	Rickets	DCM	5 m		2.3	63	15	Ca vit D CT	G
Verma20 11(33)	15 m(m)	Bf	India	CHF	Rickets	DCM	L	L	L	H	H	Ca vD CT	G
Maiya etal 2008 (13)16cases	185.3(mf)	Bf	UK	HF	Rickets	FS 10%	L	L	L	H	H	CavitudCT	3died
Tomar 2010(14) 15cases	Infants	Bf	India	HF	HypoCa	SLVD	L	L	L	H	H	Ca Vit D	allGR
Gupta 2011 (15)5 cases	4.7	Bf+_	India	CS	Rickets	DCM	L	L	L	H	H	CavitDdCT	1died
Kumar2011(16)	2 m	Bf	India	CHF	No R	DCM	L	L	L	H	H	Ca vit D	I died
Total 59	5m	BF	World	CHF	Rickets	FS10-25	L	L	L	H	H	Mortality	8.5%

Abbreviations: Af Am, African American; m, male; f, female; yr, year; DCM, dilated cardiomyopathy; L, low; H, high; gen, gender; RD, respiratory distress; Ca, calcium; ALK, alkaline phosphatase; PTH, parathormone; G, good; EBV EBvirus; ng, not given; HF, heart failure; bf, breast feeding; CT, cardiac treatment; m, month; (m), male; (f), female; hypoCa, hypocalcemia; GR, recovery; CS cardiogenic shock; VD, vitamin D.

with heart failure from London area hospitals in six years period as shown in Table 1. Ten were of black ethnicity and six were Indian. Their ages varied between 3 weeks and 8 months with a median age of 5.3 months. All had been breastfed. Median shortening fraction was 10% (range 5–18%) and median left ventricular end diastolic dimension z score was 4.1 (range 3.1–7.0). While six had a periodic cardiac arrest, three infants died. Eight were ventilated, two required mechanical circulatory support and 12 required intravenous inotropic support. Two were referred for cardiac transplantation. The average of biochemical markers on admission were: total calcium 1.5 (1.07–1.74) mmol/l; alkaline phosphatase 646 (340–1057) IU/l; 25-hydroxyvitamin D 18.5 (0–46) nmol/l (normal range >35) and parathyroid hormone 34.3 (8.9–102) pmol/l (normal range <6.1). The clinical markers and echocardiographic indices of all survivors improved upon calcium and vitamin D regimen. The time from diagnosis to achieve normal fractional shortening was ~12.4 months [13]. Based on these observations the authors of this study concluded that vitamin D deficiency and consequent hypocalcaemia were seen in association with severe and life-threatening infant heart failure. In addition, the fact that no infant or mother was receiving the recommended vitamin supplementation highlights the need for adequate provision of vitamin D to ethnic minority populations in UK.

Tomar et al. from India [14] reported 15 infants with age ranging from 45 days to 5 months (median 2 m) among which 12 presented heart failure and the remaining 3 cardiogenic shock. While all these patients had cardiomegaly and seven of them underwent convulsions episodes, no clinical signs of rickets were found. Electrocardiogram (ECG) analysis showed sinus tachycardia and prolonged QT interval. While calcium and phosphorus levels in the serum were low, the levels of alkaline phosphatase and parathyroid hormone (PTH) were high in all the cases described above, except for one where a significant decrease in the level of PTH was found. Hemoglobin ranged from 8 to 10 g/dl. Echo revealed dilated left ventricle and decreased left ventricular ejection fraction. All received decongestive therapy, calcium and vitamin D (600,000 IU IM) and magnesium sulfate. Serum calcium was normalized in all in 2-to-4 days. One infant had recurrent hypocalcaemia with tonic spasm leading to aspiration and death. Ten children received packed cell transfusion. Fourteen infants were discharged after normalization of their calcium levels and QTc interval and

their LVEF normalized in 12 weeks. Five cases presented with cardiogenic shock [15]. The details of the other case reports are shown in the Table 1, showing similar features of all of them including the four cases from one institute in USA [16–33].

Discussion

The survey of available literature showed that all the cases presented from a wide range of countries were among dark skinned breastfed infants with an age ranging from 1 to 15 months with a mean age of 5 months. The main conclusion from all these studies is that this early onset of hypocalcemia with such life threatening cardiomyopathy is most likely due to maternal vitamin D deficiency which was hypothesized by us in 1980 and, as described was later confirmed by subsequent reports [34–36]. In addition, heart failure respiratory distress were noticed in all. Although all were hypocalcemic and presented a hyperactive parathyroid not all of them developed convulsions. Clinical features of rickets were not obvious in all these cases except in some of them which is consistent with the early biochemical phase of rickets. The dramatic response to treatment with cardiac supporting medications in addition to calcium and vitamin D supplementation was an indication of a role of vitamin D deficiency and hypocalcemia in the pathophysiology of these patients. Cardiomyopathy was diagnosed by clinical evidence of heart failure with hepatomegaly, cardiomegaly and low LV ejection fraction (EF%) <60% as indicated by echo analysis.

Since dilated cardiomyopathy is a life threatening syndrome, specifically for hypocalcemic infants, and is spreading in an epidemic form in many countries, in age group below six months in the majority of cases, we will discuss the different factors involved in its pathogenesis. The fact that in the majority of the cases reported so far; this syndrome is associated with biochemical features of rickets, namely hypocalcemia, hyperparathyroidism and hypovitaminosis D and high alkaline phosphatase, each one of the three abnormalities will be discussed in more details in the subsequent sections.

The role of hypocalcemia in cardiomyopathy

The importance of normal calcium in controlling activation of several cellular enzyme cascades and smooth muscle and myocardial contraction is well recognized. As described above, the main causes of hypocalcemia in infants include low vitamin D

leading to biochemical abnormalities that result in the development of frank rickets. Numerous studies, some of which have been discussed above, have indicated that during the onset of hypocalcemia heart muscle is affected giving rise to cardiomyopathy. In one of the earliest reports on this association, Troughton and Singh [7] studied 6 cases of neonates and concluded that calcium defect could lead to the development of cardiomyopathy in four ways: First, that the low serum calcium level itself was responsible for the cardiac manifestations. Second, that a decrease in calcium level provided the last straw to a myocardium that had been injured by a previous factor. Third, that the heart failure was caused by other factors of which the hypocalcemia was a by-product. Fourth, that the hypocalcemia was secondary to the heart failure. The fact that hypocalcemia was associated with all the cases reported favors the possibility that the low serum calcium level itself was responsible for the cardiac manifestations. This is supported by its occurrence within the first months of life during which hypocalcemia was found in 70% of patients with rickets [37]. The role of calcium in heart contractility was originally reported in a publication in *Nature* by Bers [38] in which the author discussed, for the first time the term Cardiac excitation–contraction coupling, which describes a process that enables the chambers of the heart to contract and relax. Interestingly, this study clearly established that of the ions involved in regulating heart function, specifically the excitation–contraction coupling process, calcium is considered perhaps the most important. To understand the basic physiology of heart function requires, it is important to determine the exact calcium level and the way by which it is moved around the various organelles of the myocytes in order to modulate the excitation–contraction coupling process. Furthermore, spatial micro domains within the cell are important in localizing the molecular players that orchestrate cardiac function. Cardiomyopathy was also observed in primary hypoparathyroidism in older children and in cases of thalassaemia due to hemosiderosis [7,39]. The majority of these studies have indicated that hypocalcemia is the sole/most important trigger of cardiomyopathy in these patients. We might postulate the possibility that the secondary hyperparathyroidism observed in some of these cases could have a protective role against cardiomyopathy. In fact, the persistence of hypocalcemia in cases with vitamin D deficiency as well as the direct correlation between the onset of primary hypoparathyroidism and cardiomyopathy devel-

opment provided strong evidence in support of this possibility. In addition, the complete recovery of these patients without sequel in response to calcium and vitamin D regimens provides another strong proof in support of this idea.

The role of vitamin D in cardiomyopathy

The cardiomyopathy observed in all these reports was also associated with low 25-hydroxyvitamin D and hence the role of vitamin deficiency as a causative factor has to be considered. Pilz et al. [40] discussed the impact of vitamin D on the heart of an infant and concluded that vitamin D deficiency is common among patients with myocardial diseases because dietary intake and sun-induced production of vitamin D are often insufficient. Knockout mice for the vitamin D receptor develop myocardial hypertrophy and dysfunction. It has also been shown that children with rickets who suffered from severe heart failure could be successfully treated with supplementation of vitamin D plus calcium. In adults, almost all patients with heart failure exhibit reduced 25-hydroxyvitamin D levels, which are used to classify the vitamin D status. In prospective studies, vitamin D deficiency was an independent risk factor for mortality, deaths due to heart failure and sudden cardiac death. Several vitamin D effects on the electrophysiology, contractility and structure of the heart suggest that vitamin D deficiency might be a causal factor for myocardial diseases. Based on these observations, it can be concluded that the obvious beneficial effects of vitamin D on myocardial and overall health strongly argue for the use of vitamin D supplementation to treat all vitamin D-deficient patients with or at high risk for myocardial diseases. Studies by Tishkof et al. [41] have shown, using the Radioligand binding assays (³H-labeled 1,25(OH)(2)D(3), that a t-tubule membrane fraction isolated from homogenized rat ventricles contains a 1,25(OH)(2)D(3)-binding activity similar to the classic vitamin D receptors (VDR). This was the first study to demonstrate that cardiac myocytes isolated from VDR knockout mice present accelerated rates of contraction and relaxation as compared to their wild type counterparts and that 1,25(OH)(2)D(3) directly reduced the contractility and the relaxation of the wild-type but not the knockout myocytes. Moreover, they also observed that a VDR is localized to t-tubules in the heart in a position that allow it to exert an immediate effect on signal transduction mediators and ion channels. The authors of this study think that their novel

discovery is fundamentally important in understanding 1,25(OH)(2)D(3) signal transduction in heart cells and provides further evidence that the VDR plays a role in heart structure and function. These observations make the requirement of vitamin D supplementation in pregnant and lactating mothers and their infants a more urgent issue.

Studies of Weishaar et al. [42] have shown that histological examination of ventricular muscle from vitamin D3-deficient rats revealed a significant decrease in myofibrillar area and a significant increase in extracellular space. The increase in extracellular space was accompanied by a significant increase in myocardial collagen. However, exposing these vitamin D3-deficient rats to a calcium regiment failed to prevent/reverse this phenomenon. Such alterations in the physical and morphological properties of myocardial tissue might represent the basis for the change in myocardial contractile function that accompanies lengthy periods of vitamin D3 deficiency. The importance of vitamin D in heart function was further confirmed in a study conducted by Judd et al. [43]. They showed that vitamin D supplementation significantly decreased both blood pressure levels and inflammatory responses as well as improved insulin sensitivity resulting in a reduction in cardiovascular disease complications and death. Although a growing body of evidence suggests that nutritional vitamin D supplementation and potentially even treatment with synthetic analogues of vitamin D may be cardio protective, relatively few studies have examined either of these compounds in a randomized, controlled fashion. In a recent review Weber et al. [44] have concluded that vitamin D levels play an important role in maintaining myocardial viability and ECM integrity in patients with cardiac hypertrophy and fibrosis that accompanies vitamin D deficiency and VDR ablation. On the contrary to the previous findings Wang and De Luca [45] indicated that the results from their investigations showed that the vitamin D receptor was undetectable in skeletal, cardiac, and smooth muscle, suggesting that the function of vitamin D on muscle is either indirect or did not involve the known receptor. The numerous reports describing the systematic association between cardiomyopathy and vitamin D deficiency in dark skinned infants, provides us with strong indications that vitamin D plays a key role in heart function, whether directly through its effect on cell differentiation or indirectly through its association with calcium defect in cardiomyopathy. While the indirect role of vita-

min D deficiency in this disease is widely accepted, more work is required to demonstrate its direct implication in the onset of cardiomyopathy. It will be particularly interesting to know why not all cases of hypocalcemia and hypovitaminosis D develop cardiomyopathy? It is plausible that hypocalcemia and hypovitaminosis D act synergistically in precipitating the cardiomyopathy, and that is why not every case of rickets develop cardiomyopathy.

The role of parathormone (PTH) in cardiomyopathy

Both high and low levels of PTH were observed in cardiomyopathy as seen in hypocalcemia due to hypovitaminosis D with secondary hyperparathyroidism and in cases of hypocalcaemia in primary hypoparathyroidism, making the role of parathormone per se in pathogenesis of cardiomyopathy unlikely, yet it needs to be discussed.

In an extensive review by Wellenhiemer in 2004, [46] the relation of PTH and cardiac diseases was discussed. Primary hyperparathyroidism (pHPT), caused by solitary parathyroid adenomas in 85% of cases and diffuse hyperplasia in most of the remaining cases, overproduces parathyroid hormone (PTH), which mobilizes calcium to the blood stream. A symptomatic phase of the disease has been reported to be long and patients suffering from symptomatic pHPT have increased mortality. Recently, studies have indicated an association between pHPT and heart disease, and studies in vitro have produced a number of theoretical approaches. An increased prevalence of cardiac structural abnormalities such as left ventricular hypertrophy (LVH), valvular and myocardial calcification has been observed. Associations have been found between PTH and LVH, and between LVH and serum calcium. LV systolic function does not seem to be affected in patients with pHPT, whereas any influence on LV diastolic performance needs further evaluation. The aim of this review was to clarify the connection between pHPT and cardiac disease. Although hyperparathyroidism also leads to myocardial hypertrophy and diastolic dysfunction through many mechanisms, this extensive review did not provide convincing evidence supporting this connection in adult patients. Therefore, in our opinion it is difficult to make such a connection in the case of cardiomyopathic infants with hypocalcemia and secondary hyperparathyroidism. In fact, Wellenhiemer did not provide convincing argument and/or described strong evidence supporting a

role of hyperparathyroidism in the development of cardiomyopathy in infants. An interesting finding is that cardiomyopathy is seen in rickets in which parathormone is high but it was not high enough to normalize calcium. This supports that an increase in PTH secretion per se does not play a role in pathogenesis of cardiomyopathy.

It is difficult to pin point the role of parathormone but further clinical observations have shown that the combination of lower 25-OHD and higher PTH concentrations appears to be associated independently with sudden cardiac death (SCD) risk among older adults without cardiovascular disease [47]. However, further studies are needed to confirm these interesting observations.

The studies described above clearly indicate that cardiomyopathy associated with rickets is caused by hypocalcaemia in infants but when secondary hyperparathyroidism develops, leading to normalization of calcium, it may act as a protective factor against cardiomyopathy. Further studies are needed, and in our opinion echocardiography examinations should become mandatory for all infants with hypocalcaemia enabling the detection of cardiomyopathy in an early phase. In the study conducted by us (described above) on 35 infants with rickets, we were unable to detect any abnormal heart function by echocardiography study and most of cases were from the age groups above one year most of them obvious bow legs and having normal serum calcium.

The significance of early diagnosis

Rachitic hypocalcemic cardiomyopathy is a serious life threatening complication of infantile vitamin D deficiency rickets which is a growing community health problem, among breastfed infants born to vitamin D deficient mothers; despite protein calorie nutritional status being normal in the majority of cases [48]. The cardiomyopathy presenting with respiratory distress might be missed as respiratory illness specially the clinical features of rickets, namely bone deformities are not apparent at this early age leading to late diagnosis and fatality with possible cardiogenic shock. As described above, the excellent response to the appropriate cardio-supportive treatment together with calcium and vitamin D regiment highlights the importance of the early diagnosis of cardiomyopathy in infants. In trying to pursue early diagnosis Uysal et al. [49] performed a study in which they surveyed three groups of hypocalcemic patients. They found that echocardiography examination revealed left ventricular dysfunction in the pretreatment stage. The most striking finding

was the increase in the ratio of inter-ventricular septal thickness to left ventricular posterior wall thickness in 8 patients from group (III) and fewer from other groups. The group 111 are cases with severe biochemical findings [49]. From the cardiomyopathy reviewed all of them had hypocalcemia without marked changes in their bone structure. It seems that the persistence of hypocalcemia in these cases is what triggers the development of cardiomyopathy, an observation that is consistent with the of patients of group (111) described by Uysals et al. [49]. We performed echocardiography studies on 35 cases of frank rickets from outpatient cases but none of them revealed any abnormality suggestive of cardiomyopathy. This might be explained by the fact that all of them were classical cases of rickets and most of them were having a normal calcium as seen in patients presenting after one year of age [50]. We postulate that the prolonged hypocalcemia during early age could explain the rapid development of cardiomyopathy in infants. This conclusion is supported by studies describing cases of primary hypoparathyroidism in older children [8] and many adults [51–53] where the onset of cardiomyopathy is associated with a long-standing hypocalcemia.

Conclusion

Vitamin D deficiency is not a benign disease as it might cause cardiomyopathy, hypocalcemic convulsions, myelofibrosis, anemia, juvenile diabetes mellitus, and many other complications. Plans for prevention by antenatal supplementation of vitamin D to pregnant mothers with 1000–2000 IU of vitamin D3 is vital. All breastfed infants should be given vitamin D supplementation of 400 units daily from birth.

Conflict of Interest

Authors have no conflict of interest to declare.

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References

- [1] Cox GF, Sleeper LA, Lowe AM, Towbin JA, Colan SD, Orav EJ, et al. Factors associated with establishing a causal diagnosis for children with cardiomyopathy. *Pediatrics* 2006;118(4):1519–23.

- [2] KalimUddin Aziz. Cariomyopathies in childhood; a developing world perspective. *Pak Paed Cardiol J Dec 2001*;3(1-2):3-9.
- [3] Dodd K, Rapoport S. Hypocalcemia in the neonatal period; a clinical study. *Am J Dis Child 1949*;78(4):537-60.
- [4] Schulman JL, Ratner H. Idiopathic hypoparathyroidism with bony demineralization and cardiac decompensation. *Pediatrics 1955*;16(6):848-56.
- [5] Edge WE. Afr Med J. Hypocalcemia in infancy, with special refrence to cardiac failure. *S Afr Med J 1963 Mar 9*;37:262-4.
- [6] Najjar SS, Nassif SI, Khazen AF. Hypocalcemia and congestive heart failure. *J Med Liban 1967*;20(1):69-77.
- [7] Troughton O, Singh SP. Heart failure and neonatal hypocalcaemia. *Br Med J 1972*;4:76-9.
- [8] Bshour T, Shamsi H, Tsung O. Hypocalcemic cardiomyopathy. *Chest 1980*;78:683-5.
- [9] Gillor A, Groneck P, Kaiser J, Schmitz-Stolbrink A. Congestive heart failure in rickets caused by vitamin D deficiency. *Monatsschr Kinderheilkd 1989 Feb*;137(2): 108-10.
- [10] Elidrissy ATH. In: Glorieux FH, editor. Pathogenesis of rickets in a sunny country in rickets. Vevey, Nestele/New York: Raven Press; 1991. p. 123-43.
- [11] Elidrissy ATH, Sedrani S, Lawson DEM. Vitamin D deficiency in mothers of rachitic infants. *Calcif Tissue Int 1984*;36:266-8.
- [12] Belton NR, Elidrissy ATH, Forfar TB, et al. Maternal vitamin D deficiency as a factor in the pathogenesis of rickets in Saudi Arabia. In: Normal AW, editor. Biochemical and clinical endocrinology of calcium metabolism. New York: Walter de Gruyter; 1982. p. 735-7.
- [13] Maiya S, Sullivan I, Allgrove J, Yates R, Malone M, Brain C, et al. Hypocalcaemia and vitamin D deficiency: an important, but preventable, cause of life-threatening infant heart failure. *Heart 2008*;94(5):581-4. Epub 2007 Aug 9.
- [14] Tomar M, Radhakrishnan S, Shrivastava S. Myocardial dysfunction due to hypocalcemia. *Indian Pediatr 2010*;47(9):78.
- [15] Gupta P, Tomar M, Radhakrishnan S, Shrivastava S. Hypocalcemic cardiomyopathy presenting as cardiogenic shock. *Ann Pediatr Cardiol 2011*;4(2):152-5.
- [16] Kumar M, Saikia D, Kumar V, Tomar R. Vitamin D deficiency presenting with cardiogenic shock in an infant. *Ann Pediatr Cardiol 2011*;4(2):207-9.
- [17] Yaseen H, Maragnes P, Gandon-Laloum S, et al. A severe form of vitamin D deficiency with hypocalcemic cardiomyopathy. *Pediatric 1993*;48(7-8):547-99.
- [18] Memmi I, Brauner R, Sidi D, Sauvion S, Souberbielle JC, Garabedian M. Neonatal cardiac failure secondary to hypocalcemia caused by maternal vitamin D deficiency. *Arch Fr Pediatr 1993*;50(9):787.
- [19] Karademir S, Altuntas B, Tezic T, Akinci A, Demirceken F. Left ventricular dysfunction due to hypocalcemia in a neonate. *Jpn Heart J 1993 May*;34(3):355-9.
- [20] Brunvand I, Haga P, Tangsrud SE, Hang E. Congestive heart failure caused by vitamin D deficiency? *Acta Pediatr 1995*;84. 106-8.11.
- [21] Lachassinne E, Gaudelus J, Lacombe F, Lehnert A. Acute heart insufficiency in an 8-month-old infant presenting with hypocalcemia and Epstein-Barr virus infection: acute myocarditis? Or primary hypokinetic dilated cardiomyopathy? *Ann Pediatr (Paris) 1992*;39(3): 179-83.
- [22] Abdullah M, Bigras JL, McCrindle BW. Dilated cardiomyopathy as a first sign of nutritional vitamin D deficiency rickets in infancy. *Can J Cardiol 1999*;15(6):699-701. Erratum in: *Can J Cardiol 1999 Nov*;15(11):1304. Mustafa A [corrected to Abdullah M].
- [23] Olgun H, Ceviz N, Ceviz N, Ozkan A. Case of dilated cardiomyopathy due to nutritional vitamin D deficiency rickets. *Turk J Pediatr 2003*;45(2):152-4.
- [24] Gulati S, Bajpai A, Juneja R, et al. Hypocalcemic heart failure masquerading as dilated cardiomyopathy. *Indian J Pediatr 2001*;68(3):287-90.
- [25] Price DI, Stanford Jr LC, Braden DS, Ebeid MR, Smith JC. Hypocalcemic rickets: an unusual cause of dilated cardiomyopathy. *Pediatr Cardiol 2003*;24(5):510-2.
- [26] Carlton-Conway D, Tulloh R, Wood L, Kanabar D. Vitamin D deficiency and Cardiac failure in infancy. *J R Soc Med 2004*;97(5):238-9.
- [27] Goulet M, Rio M, Jcquette M, Ladouceur M, Bonnet D. Neonatal hypocalcemic dilated myocardiomyopathy due to a 22q11microdeldetion. *Arch Mal Coeur Vaiss 2006*;99(5):520-2.
- [28] Cramm KJ, Cattaneo RA, Schremmer RD. An infant with tachypnea. *Pediatr Emerg Care 2006*;22(11). 728-.
- [29] Roy R, El-Matary W, Gladman G, Isherwood D. Dilated cardiomyopathy and adipic aciduria in nutritional rickets. *Pediatr Emerg Care 2006*;22(3):175-6.
- [30] Amirlak I, AIDhaheri W, Narchi H. Dilated cardiomyopathy secondary to nutritional rickets. *Ann Trop Paediatr 2008*;28(3):227-30.
- [31] Brown J, Nunez S, Russell M, Spurney C. Hypocalcemic rickets and dilated cardiomyopathy: case reports and review of literature. *Pediatr Cardiol 2009*;30(6):818-23.
- [32] Kim BG, Chang SK, Kim SM, Hwang JS, Jung JW. Dilated cardiomyopathy in a 2 month-old infant: a severe form of hypocalcemia with vitamin d deficient rickets. *Korean Circ J 2010 Apr*;40(4):201-3.
- [33] Verma S, Khadwal A, Chopra K, Rohit M, Singhi S. Hypocalcemia nutritional rickets: a curable cause of dilated cardiomyopathy. *J Trop Pediatr 2011*;57(2):126-8. Epub 2010 Jun 15.
- [34] Elidrissy ATH, Taha SA. Rickets in Riyadh. Proceedings of 5th Saudi Medical Meeting 1980; p. 409-418.
- [35] Belton NR, Elidrissy ATH, Forfar TB. Maternal vitamin D deficiency as a factor in the pathogenesis of rickets in Saudi Arabia. In: Normal AW, editor. Biochemical and clinical endocrinology of calcium metabolism. New York: Walter de Gruyter; 1982. pp.735-7.
- [36] Serinius F, Elidrissy ATH, Dandona P, Vitamin D. Nutrition in women at term, and in newly born babies in Saudi Arabia. *J Clin Pathol 1984*;37:444-7.
- [37] Hatun S, Ozkan B, Orbak Z, Doneray H, Cizmecioglu F, Toprak D, et al. Vitamin D deficiency in early infancy. *J Nutr 2005 Feb*;135(2):279-82.
- [38] Bers DM. Cardiac excitation-contraction coupling. *Nature 2002*;415(6868):198-205.
- [39] Tsironi M, Korovesis K, Farmakis D, Deftereos S, Aessopos A. Hypocalcemic heart failure in thalassemic patients. *Int J Hematol 2006*;83(4). 314-78-20.
- [40] Pilz S, Tomaschitz A, Drechsler C, Dekker JM, März W. Vitamin D deficiency and myocardial diseases. *Mol Nutr Food Res 2010 Aug*;54(8):1103-13.
- [41] Tishkoff DX, Nibbelink KA, Holmberg KH, Dandu L, Simpson RU functional vitamin D receptor (VDR) in the t-tubules of cardiac myocytes: VDR knockout cardiomyocyte contractility. *Endocrinology 2008*;149(2): 558-64.
- [42] Weishaar RE, Kim SN, Saunders DE, Simpson RU. Involvement of vitamin D3 with cardiovascular function. III. Effects on physical and morphological properties. *Am J Physiol 1990*;258(1 Pt 1):E134-42.
- [43] Judd SE, Tangpricha V. Vitamin d therapy and cardiovascular health. *Curr Hypertens Rep 2011*;13(3): 187-91.
- [44] Weber KT, William B, Weglicki, Robert U. Simpson, macro- and micronutrient dyshomeostasis in the adverse structural remodelling of myocardium. *Cardiovasc Res 2009*;81(3):500-8.
- [45] Wang Y, DeLuca HF. Is the vitamin d receptor found in muscle? *Endocrinology 2011*;152(2):354-63.
- [46] Willenheimer R. Primary hyperparathyroidism and heart disease-a review. *Eur Heart J 2004*;25(20):1776-87.

- [47] Deo Rajat, Katz Ronit, Shlipak Michael G, Sotoodehnia Nona, Psaty Bruce M, Sarnak Ma, et al. Results from the cardiovascular health study. *Hypertension* 2011;58: 1021-8.
- [48] Elidrissy ATH. Nutritional status of children with rickets in Riyadh. *Ann Saudi Med* 1986;6:101-5.
- [49] Uysal S, Kalayci AG, et al. Cardiac functions in children with vitamin D deficiency rickets. *Pediatr Cardiol* 1999;20(4):283-6.
- [50] Elidrissy ATH, Sandoji AM, Al-Magamsi MSF, Al-Hawsawi ZM, Al-Hujaili AS, Babiker NH, Yousif AM. Nutritional rickets in Almadinah: presentation and associated factors. *JTU MedSv* 2012 .07.002.
- [51] Ozerkan F, Güngör H, Zoghi M, Nalbantgil S. Cardiac failure secondary to idiopathic hypoparathyroidism: a case report. *Turk Kardiyol Dern Ars* 2009 Jan;37(1):53-6.
- [52] Babu MS. Hypoparathyroidism and reversible dilated cardiomyopathy. *Indian J Endocrinol Metab* 2011;15(4): 351-2.
- [53] Ari H, Ari S, Koca V, Bozat T. A rare cause of reversible dilated cardiomyopathy: hypocalcemia. *Turk Kardiyol Dern Ars* 2009;37(4):266-8.