

# Rachitic hypocalcemic cardiomyopathy in an infant



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Cardiomyopathy in infants is characterized by heart failure in apparently normal children without previous organic cardiac lesions. Cardiomyopathy has been found to comprise four types. Rickets is common in Saudi Arabia, that is why I reviewed this subject. Recently this case with classical features of rickets being admitted in a serious state we thought of publishing it. The infant responded well to treatment and full recovery was achieved. Follow up biochemistry, radiology cardiac function completely recovered and bony abnormalities showed evidence of healing. This case might have been missed as respiratory infection. We recommend meticulous look for biochemical features of rickets in infants admitted with respiratory symptoms.

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## Introduction

Although rickets is becoming a serious epidemiological problem, even in sunny countries, it is still considered a benign disease. However, it has some serious life-threatening associations (one of which is described herein) with cardiomyopathy which may be fatal had it been missed. Cardiomyopathy in infants is a rare complication of hypocalcemia. Although rickets is common in the Middle East, this complication was only reported recently [1]. We came across

this case after reviewing the association of cardiomyopathy and hypocalcemia, as we thought it needed acknowledgment as a life-threatening situation in association with rickets [2]. To highlight this association and its significance in relation to hypocalcemia, we are reporting this case which was seen in Medinah Maternity and Children's Hospital in Medinah, Saudi Arabia.

## Case report

A 6-month-old girl with dark skin was taken to the Accident and Emergency Department (A&E)

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of Medinah Maternity and Children's Hospital because she had collapsed suddenly and had convulsions. Before this episode she was said to be complaining of coughing and had difficulty in breathing, ongoing for 3 days and associated with poor feeding. She recovered after being resuscitated in A&E and was admitted to the Pediatric Intensive Care Unit, where she was ventilated. She had more attacks of convulsions which were controlled with anticonvulsive medications. Clinical exam revealed a well-built infant. The anterior fontanel was wide open and had evidence of a rachitic rosary in the chest with wide wrists (Figs. 1 and 2).

No murmur was heard on cardiac examination; however, there was tachycardia and the liver was 4 cm below the costal margin but the spleen was not palpable.

The patient was delivered at full term at another hospital by *cesarean section* due to oligohydramnios with failure of advance in labor. The child was admitted to the Neonatal Intensive Care Unit for 4 days due to respiratory distress which recovered and continued being breastfed without remarkable problems.

All necessary investigations were performed. The biochemical findings on admission were: alkaline phosphatase was 992 IU/L, calcium was 1.18 mg/dL, phosphate was 1.51 mg/dL, urea was 4.36 mg/dL, chloride was 100 mEq/L, creatinine was 28.5 mg/dL, Na was 136.5 mEq/L, K was 5.2 meEq/L, uric acid 3.6 mg/dL, hemoglobin was 10.2 g/dL, white blood cells were 10.8 mm<sup>3</sup>, and platelets were 661,000 mm<sup>3</sup>. Cardiac echocardiography revealed a dilated left atrium and ventricle with a fractional shortening of 22.5%, with impaired systolic function. There was also a mild degree of mitral regurgitation due to a dilated annulus. Electrocardiography showed sinus tachycardia.



Figure 1. Wrist distally wide indicating rickets.



Figure 2. Rachitic rosary due to widening of the ends of the ribs.

She was treated with digoxin, captopril, phenobarbitone, vitamin D, calcium iv, iron, and magnesium. She was kept in the Pediatric Intensive Care Unit for 15 days with steady progress leading to clinical and biochemical recovery. At the final follow-up, echocardiography revealed that the left ventricular systolic function returned to normal with a fractional shortening of 32%. The left ventricular size was normal and no more mitral regurgitation was noted. The biochemical findings on discharge were: alkaline phosphatase was 698 IU, calcium 2.4 mg/dL, phosphate 1.08 mg/dL, urea 4.19 mg/dL, chloride 100.2 mEq/L, creatinine 27.9 mg/dL, Na 135.9 mEq/L, K 4.9 meEq/L, and uric acid 153 mg/dL (Table 1).

## Discussion

This breastfed infant presented with respiratory distress at 6 months of age showing evidence of dilated cardiomyopathy with hypocalcemia on admission. The biochemical findings were characteristic of rickets with no obvious clinical bony changes, but appreciated when looked for. These included swollen wrists, rachitic rosary as shown in Figs. 1 and 2, and bossing of the head. These findings were suggestive of rickets together with dilated cardiomyopathy associated with hypocalcemia, without having obvious clinical bony

Table 1. Biochemical findings at onset and discharge in an infant with hypocalcemic cardiomyopathy.

Biochemical tests	Normal range	Onset	Discharge
Calcium (mmol/L)	(2.41–2.77)	1.1	2.4
Alkaline phosphatase (IU)	(55–265)	992	698
Phosphate (mmol/L)	(1.2–2.1)	1.51	1.08
Magnesium (mmol/L)	(0.74–1.0)	0.8	nd
25 hydroxycholecalciferol (ng/L)	(<25)	7.5	nd

nd = not determined.

features of rickets as has been reported from different parts of the world [3–6]. Radiologically there was evidence in the radius and rachitic rosary in the ribs. This is the second case to be reported from Saudi Arabia in an infant, although the prevalence of rickets is high in this area [3]. The first case was reported by Al Azkawi and Al Mutair [1] where they reported an infant presenting at the age of 1 month with symptoms suggestive of sepsis. The features in our case are typical of a series from India, where the shock was the presenting feature [4]. The hypocalcemia-associated cardiomyopathy was first reported by Dodd and Rappaport [7] in 1949 by stating that cardiac manifestations could occur in hypocalcemia, although in the presence of other electrolyte disturbances. Then Edge [8] in 1963 reported congestive heart failure and hypocalcemia in infancy. Four years later, Najjar et al. [9] in 1967 described an 18-month-old infant with frank rickets and heart failure. Heart failure and neonatal hypocalcaemia was described in six neonates by Troughton and Singh [10] in 1972. It was Bashour et al. [11] in 1980 who coined the term hypocalcemic cardiomyopathy in two patients with cardiomegaly and congestive heart failure who were found to be grossly hypocalcemic secondary to previously undiagnosed hypoparathyroidism. The cardiac failure was refractory to digitalis and diuretics but responded dramatically to calcium therapy that restored the serum calcium to normal. This case of a 6-month-old dark skinned infant is the second to be reported in the Middle East with hypocalcemia and biochemical parameters together with clinical evidence of rickets having dilated cardiomyopathy apart from the Bashour et al. [11] case. By reporting this case we would like to stress the point that rickets is a life-threatening problem, especially in early life when hypocalcemia is the presenting feature and is precipitated in neonates and infants by maternal hypovitaminosis D in almost all cases of infantile rickets. In our original report in 1984 [12] and a recent one in 2012 [5] it was stressed to check for calcium levels as a correctable life-saving parameter if low in infants brought to the

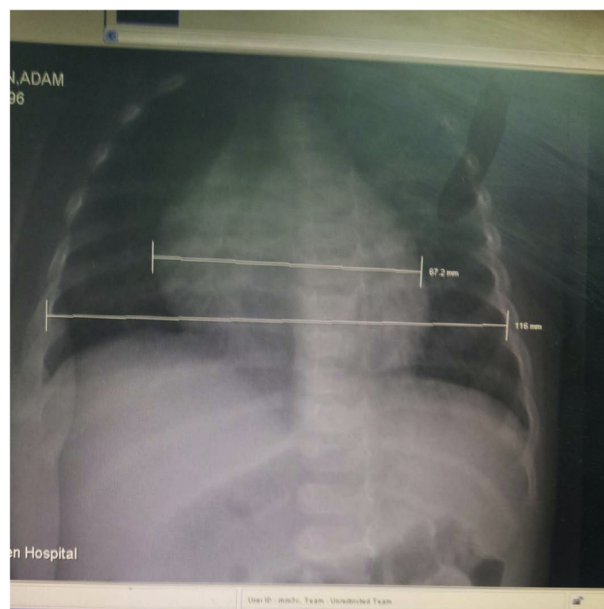


Figure 3. X-ray of chest with a wide heart diameter of 60% suggestive of heart enlargement (normal <50%).

emergency department with sudden collapse and convulsions (see Fig. 3).

#### Review of previously reported cases

The biggest series is one that was reported from London hospitals by Maiya et al. [3]. To summarize these 16 cases: (16 infants) six were from the Indian subcontinent and 10 were from the Caribbean with a median age at presentation of 5.3 months (range, from 3 weeks to 8 months). All had been breastfed. Ten presented at the end of the British winter (from February to May). 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). Six infants had a cardiac arrest and three infants died. Eight infants were ventilated, two infants required mechanical support, and 12 infants required intravenous inotropic support. Two cases were referred for cardiac transplantation. Median biochemical values 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. The mean time from diagnosis to achieve normal fractional shortening was 12.4 months.

### *Pathogenesis of hypocalcemic cardiomyopathy in infants*

We have recently reviewed hypocalcemic dilated cardiomyopathy and discussed its pathogenesis [2]. That evidence supports the importance of calcium in maintaining contractility of the heart muscle. This was clarified in an editorial by Weber et al. [13] who stated that the heart is normally an efficient physiological pump whose muscular compartment is composed of a syncytium of cardiomyocytes nourished by a coronary vasculature and housed within a scaffolding of structural proteins. The contractile properties of cardiomyocytes were found to be governed by the direct interplay between  $\text{Ca}^{2+}$  and contractile proteins, actin and myosin, and their intracellular handling of  $\text{Ca}^{2+}$ . Likewise, extracellular  $\text{Ca}^{2+}$  handling or  $\text{Ca}^{2+}$  homeostasis can indirectly influence cardiomyocyte contractility. They briefly examined  $\text{Ca}^{2+}$  dyshomeostasis and heart failure. Plasma  $\text{Ca}^{2+}$  concentrations were found to be highly regulated and maintained within a narrow range. If disturbed, a series of controlling factors and feedback mechanisms are called into play. Overall  $\text{Ca}^{2+}$  homeostasis relates to its dietary intake: absorption and excretion from the gut and kidneys, bone storage, and the modifying influence of such calciotropic hormones such as calcitriol and parathyroid hormone. In this statement the role of hypocalcemia in precipitating cardiomyopathy is evident, but among the many effects of hypocalcemia only very few develop cardiomyopathy, suggesting that another protective factor or factors might be present but occult and need to be elucidated.

### *Fetal calcium metabolism*

*In utero*, the availability of  $\text{Ca}^{2+}$  for fetal growth and development, including the bony skeleton, depends on maternal factors such as: (1) dietary  $\text{Ca}^{2+}$  intake, which may be reduced, particularly in vegans or in some women with lactose intolerance, who avoid dairy products; (2) urinary and fecal  $\text{Ca}^{2+}$  losses; (3)  $\text{Ca}^{2+}$  bone stores that may be mobilized if  $\text{Ca}^{2+}$  availability is compromised; and (4) vitamin D status, as assessed by serum 25-hydroxyvitamin D. 25-(OH) D levels are chiefly dependent on supplementation and sunlight exposure that may be limited by culturally imposed dress code and skin pigmentation where melanin is a natural sunscreen

that mandates longer exposure to the UV-B component of sunrays. Calcium transplacental pump is used to maintain enough calcium in the fetus independent of vitamin D [14], except in situations of severe maternal depletion as in florid osteomalacia or malabsorption as in coeliac disease [2]. We discussed in a report cited previously [2] the three biochemical findings that might be precipitating cardiomyopathy. Firstly hyperparathyroidism, which was excluded because cardiomyopathy occurred in hypocalcemia secondary to primary hypoparathyroidism which excludes hyperparathyroidism *per se* as a cause precipitating cardiomyopathy. Still, there is evidence that heart failure in adults is associated with hyperparathyroidism [14]. This finding, although in adults, makes it doubtful to exclude hyperparathyroidism from playing a role in cardiomyopathy associated with hypocalcemia. The next abnormality was the deficiency of vitamin D; this was explained by the role of active vitamin D metabolite 1,25(OH)<sub>2</sub>D effect on cardiac myocytes by accelerating relaxation which indicates that it is important for the maintenance of diastolic function leading to impaired relaxation of cardiac myocytes and subsequent impaired filling of the ventricles which is a main pathological finding in diastolic heart failure [14]. Recently Polat et al. [15], in a controlled study, suggested that vitamins have a potential role in both the development of dilated cardiomyopathy (DCMP) and left-ventricular remodeling. But they did point out that investigations are needed to shed light on the possible causal linkage between vitamin D and DCMP and the precise role of vitamin D in the pathogenesis of the DCMP and/or heart failure in adults. Lastly, further larger randomized, placebo-controlled trials are also required to assess the effectiveness of vitamin D supplementation therapy in patients with DCMP who are vitamin D deficient. These studies are also required in vitamin D deficient infants with hypocalcemia. It seems that both low calcium and vitamin D together form a triad with hyperparathyroidism that when present in one patient at certain degrees, makes a complex that precipitates DCMP. This is supported by the many cases of rickets seen—only very few develop cardiomyopathy. In a recent report it was found that 1,25-dihydroxy vitamin D and its ratio to parathyroid hormone strongly predicted cardiovascular mortality in chronic heart failure [16]. This finding supports our suggestion of a triad complex precipitating this infantile cardiomyopathy that needs to be looked into seriously with the objective of preventing this serious issue that needs further study especially in the 1<sup>st</sup> 6 months of life.

Rickets, although becoming a serious and a big epidemiological problem especially in sunny countries, should not be considered as a mere benign disease of bones, as it has serious life-threatening associations more likely to be missed. Even in neonates, as seen in this 14-day-old infant recently reported on [17], which was the youngest ever case presenting with hypocalcemic seizures and dilated cardiomyopathy. He developed life-threatening respiratory distress and heart failure. Respiratory support, and administration of diuretic and inotropic drugs, as well as the correction of his hypocalcemia and hypomagnesemia saved him. The patient promptly responded to treatment and was well during the 1-year follow-up period. The importance of this rare, life-threatening but reversible disorder is stressed indicating that this problem has to be considered in neonatal postpartum or even before delivery in communities with endemic maternal vitamin-D deficiency. This is a complication with high mortality and morbidity and is likely to be mismanaged. There are only 59 cases reported in 53 years since the first report by Edge [8] in 1963. The lessons to be learned from this hypocalcemic dilated cardiomyopathy is that it has to be thought of in any infant brought in collapse to A&E especially in places with a high incidence of vitamin-D deficiency. Correction of calcium levels together with heart supporting medications is life-saving, but prevention is of vital importance.

### Prevention

What is most important is preventing neonatal hypocalcemia by treating maternal vitamin-D deficiency which was proved by many studies to be the predominant cause if not the only cause of neonatal and infantile hypocalcemia leading to such serious complications [18,19]. Supplementing breastfed infants is highly encouraged. The new recommendation by Hollis and Wagner [20] with strong data indicate that 4000 IU/d vitamin D during pregnancy will “normalize” vitamin D metabolism and improve birth outcomes including primary cesarean section and comorbidities of pregnancy with no risk of side effects. In spite of this statement, to be on the safe side, we recommend starting vitamin D during early pregnancy by supplementing pregnant mothers with 2000 units of vitamin D3 daily, which is considered effective and very safe. The Endocrine Society defined vitamin-D deficiency as a 25-hydroxyvitamin D <20 ng/mL, insufficiency as 21–29 ng/mL, and sufficiency as 30–100 ng/mL. To prevent vitamin-D deficiency, guidelines recom-

mend vitamin D intake should be: children <1 year 400 IU/d, children 1–18 years 600–1000 IU/d, and adults 1500–2000 IU/d [21]. In sunny countries the best natural source of vitamin D is regular exposure to the sun.

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