

## Review Article

# The Four Serious Complications of Vitamin D Deficiency in Infants

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## Introduction

Rickets is historically known as a disease of bones only, but recently its role in many diseases has been recognized. In this communication would like to shed light on these four major associations of rickets being life threatening if not recognized early enough. These are hypocalcemic convulsions, myelofibrosis, hypocalcemic cardiomyopathy and hypocalcemic stridor. I am discussing them under four titles ending with a recommendation for awareness and prevention being all preventable by vitamin D and adequate calcium supplementation.

## Hypocalcemic Convulsions

Hypocalcemia is the first and the earliest presentation of rickets in infants. Calcium supplementation intrauterine is supplied and maintained adequately independent of Vitamin D or its metabolites. Rickets nowadays is seen commonly in two critical ages of growth, namely infancy and adolescence. Hypocalcemia is forming 30% to 70% of the presenting feature of rickets in the Middle East in the first year of life [1,2]. This makes it mandatory in including testing for hypocalcemia in investigating neonatal and infantile convulsions is mandatory. Neonatal hypocalcemic convulsions may occur as early as the end of the first week of life or later, after the loss of the effect of the trans-placental calcium pump, which is not vitamin D dependent being acting even with low maternal vitamin D status during pregnancy [3]. This low maternal vitamin D was reviewed and confirmed to be the major factor in the etiology of rickets in their breastfeeding infants [4] and noticing an acute drop of calcium in infants at the age of seven days, although it was normal at birth [5]. Neonatal hypocalcemia with its serious complications of severe seizures corrected only by calcium and vitamin D supplementation, have proved to be due congenital rickets which commonly manifests as hypocalcemia and later with classical features of rickets [6-8]. Nineteen cases reported from one hospital in two years are a serious index of a growing epidemic in the Middle East with high buildings without access to the sun [9]. Neonatal hypocalcemia and in the first six months of life and even later, among breastfeeding infants should be considered as due

to maternal vitamin D deficiency. Supplementation with calcium and vitamin D as in the global recommendation is the treatment of choice, also maternal supplementation of vitamin D should seriously be considered together with iron supplementation [9].

## Myelofibrosis in Rickets

Anemia associated with rickets can be iron deficiency anemia was reported in our study [10]. This iron deficiency anemia occurs in 46% of cases of rickets but vitamin D deficiency might play a role, and the difference in incidence might be due to that iron supplementation has become widely accepted while vitamin D supplementation is still under consideration. Another type of anemia associated with rickets is myelofibrosis giving rise to pancytopenia with poor prognosis. Myelofibrosis associated to hypocalcemic, was reviewed by me [11]. The literature review starting with this case report [12]. A female presented with fatigue, and bilateral knee pain and gait disturbance. Primary hyperparathyroidism was diagnosed in association with splenomegaly hypovitaminosis D and anemia, with bone marrow biopsy revealed myelofibrosis. A parathyroid adenoma was discovered and surgically excised. As early as three months after the operation, hematologic parameters improved along with bone markers without any other intervention. Also, Akaya, et al. [13] reported the presence of Hyperparathyroidism (PHP) and myelofibrosis in a 15-year-old boy who presented with generalized weakness, vomiting, and pallor. A parathyroid adenoma was detected on the left distal parathyroid gland. PHP was diagnosed together with hepatosplenomegaly and pancytopenia. Bone marrow biopsy revealed grade 3-4 reticulin fibrosis. As early as 2 months after the left distal parathyroidectomy, hematologic parameters improved without any other intervention. His liver and spleen also gradually decreased in size. It was concluded that the pancytopenia was because of bone marrow fibrosis resulting from primary hyperparathyroidism. These two cases suggest that myelofibrosis secondary to primary hyperparathyroidism as a cause of pancytopenia should be considered in hypocalcemic patients, despite of its rarity. These authors suggest that Parathyroid Hormone (PTH), when in excess, interferes with

normal erythropoietin by suppressing the erythropoietin receptors on erythroid progenitor cells in the bone marrow. Calvi [14] reported that Parathyroid Hormone (PTH), through activation of the PTH/ PTHrP Receptor (PTH1R) in osteoplastic cells, could alter the Hematopoietic Stem Cell (HSC) niche resulting in HSC expansion in vivo and in vitro and improving dramatically the survival of mice receiving bone marrow transplant. This alteration might be the fibrosis observed in association with myelofibrosis. Recently, Brunner [15] found that primary hyperparathyroidism is associated with increased circulating bone marrow-derived progenitor cells, that in addition to the PTH were shown to support survival of progenitor cells in bone marrow. What the release of progenitor cells occurs in physiological and pathological conditions was shown to contribute to neovascularization in tumors and ischemic tissues. Beheaded, et al. [17] stated that anemia is common in patients with symptomatic PHPT, as it was associated with marrow fibrosis in the majority of the patients who underwent bone biopsy. They found that both anemia and marrow fibrosis improved after curative parathyroidectomy, but this improvement in anemia was noticeable only in those who had marrow fibrosis at presentation. Ohishi, et al. [18] while studying, myelofibrosis associated with hyperparathyroidism, performed a study in mice proving that: the BM is a permissive microenvironment for the differentiation of fibrocystic cells and raised the possibility that these cells could contribute to the pathogenesis of BM fibrosis. Further Sikole [19] suggested that Parathyroid Hormone (PTH) when in excessive amounts, interferes with normal erythropoiesis by down regulating the erythropoietin receptors on erythroid progenitor cells in the bone marrow. Therefore, physiologic concentrations of EPO can no longer sustain normal red cell counts, so normocytic and normochromic anemia ensues. In primary Hyperparathyroidism (HPT), this effect is observed with very high concentrations of PTH. In secondary HPT during chronic renal failure, this effect is more pronounced because erythropoietin synthesis is impaired. From these data, we can say that myelofibrosis in rickets is caused by secondary hyperparathyroidism, as it was reported postoperatively. (Myelofibrosis associated with chronic renal failure is also having associated hyperparathyroidism with almost non-functioning vitamin D. In this situation, it can be stated that hypovitaminosis D and hyperparathyroidism have a synergistic role in the development of myelofibrosis. There is a critical level of each of the metabolites that precipitate the myelofibrosis supported and explained by that only few of vitamin D deficiency cases with persistent, hyperparathyroidism will develop myelofibrosis

## Hypocalcemic Cardiomyopathy

Cardiomyopathy in infants is characterized by heart failure in apparently normal children without previous organic cardiac lesions. Rickets is common in the Sunny Middle East. We recently reported [18] a case which the second reported in the Middle East. Although rickets is common, as we reported 136 cases from one clinic in six months, [1] although I reviewed this subject previous-

ly. This case at six months old infant was breastfed well built with classical features of rickets was admitted in a serious state of collapse needing intensive care admission. 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 a respiratory infection. We recommend meticulous look for biochemical features of rickets in infants admitted with respiratory symptoms. This serious complication of hypocalcemia was reported recently by us.



**Figure 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)
992	698			(55-265)
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)
				7.5NDd

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ND = not determine.. 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) 7.5NDd

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sociations (one of which is described herein) with cardiomyopathy which may be fatal had 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 Figure 2-4.



Figure 2: Wrist showing swelling.

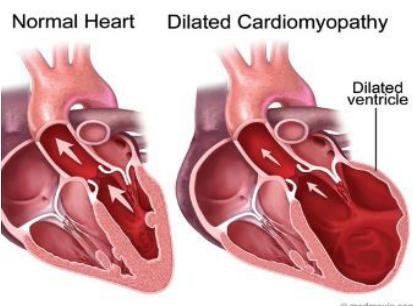


Figure 3: Normal Ventricle.

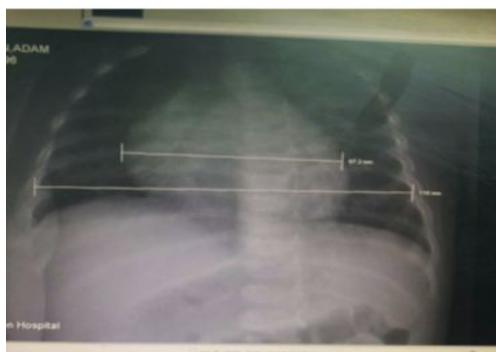


Figure 4: Chest X Ray, Showing enlarged Heart due to cardiomyopathy. This infant is now five years old in good health.

## Hypocalcemic Stridor

Stridor is a noisy breathing in infants or older children, usually frightening to parents. I am quoting a statement by John Apley [19] stating that stridor is derived from Latin Strider, to make gratingly shrill or harsh noise. It needs to be harsh and vibrating, though it should be sustained or repeated, mothers tell me that their child. Stridor is caused partially obstructed airway at the level of the supraglottis, glottis, subglottis, and trachea. Stridor is a symptom,

not a diagnosis or disease, and the underlying cause must be determined. Stridor may be inspiratory, expiratory, or bypass depending on its timing in the respiratory cycle.

## Pathophysiology of Stridor in Hypocalcemia

The narrowing of the upper part of the respiratory tract causes a turbulence of air flow manifested as stridor, usually observed in upper respiratory tract infection or foreign body inhalation. As we are seeing rising cases of rickets presenting with hypocalcemia and occasionally with stridor that might be misdiagnosed as viral croup. The relationship between stridor and hypocalcemia is not widely appreciated. The mechanism of hypocalcemia in causing stridor is most likely a sort of laryngeal collapse due to loss of its rigidity caused by hypocalcemia, and as rickets starts with hypocalcemia due to lack of vitamin D they might coexist, but it is mostly a relation of a cause and effect. Narrowing associated with edema, foreign body, or pressure from outside in addition to softening and narrowing of the larynx due to hypocalcemia is what is causing stridor, also aggravated by upper respiratory infections, that is why the role of hypocalcemia in stridor is not well appreciated. Hypocalcemia stimulates parathyroid glands secrete extra hormone needed to mobilize calcium from bone and cartilage with a more vital objective to maintain enough calcium for brain, heart, and blood. In places with the prevalence of vitamin D deficiency, breast milk is low in vitamin D due to maternal vitamin D deficiency. Stridor caused by hypocalcemia should be recognized early and treated promptly taken as a warning sign of occult rickets that might herald serious complications as convulsions, cardiomyopathy, and myelofibrosis. The development of stridor is not as common as the other features of rickets. Due to the hyper Parathyroid playing a major role in correcting the blood level of calcium. All recovered after surgery F: female M: male The narrowing of the upper part of the respiratory tract causes a turbulence of air flow manifested as stridor, usually observed in upper respiratory tract infection by congestion or foreign body inhalation. Lodged in the larynx causing narrowing the passage

## Mechanism of Stridor in Hypocalcemia

As we are seeing rising cases of rickets presenting with hypocalcemia and occasionally with stridor that might be misdiagnosed as viral croup, I am reviewing the relation between stridor and hypocalcemia. Although stridor is a common respiratory symptom associated with upper respiratory diseases, yet its relationship with hypocalcemia is not widely appreciated.

The mechanism of hypocalcemia in causing stridor is most likely a sort of laryngeal collapse due to loss of its rigidity caused by hypocalcemia which is obvious in the early phase of rickets. In infancy, rickets starts with hypocalcemia due to lack of vitamin D. In this phase, the bony features of rickets are not obvious. It is when the parathyroid glands are stimulated by the hypocalcemia that an excess of parathormone mobilizes calcium from the

bones and cartilage leading to decalcified bones and softening of cartilage, which in this phase present as stridor due to the most likely collapse of the larynx which is a sort of narrowing process. Narrowing associated with edema, foreign body, or pressure from outside in addition to softening and narrowing of the larynx due to hypocalcemia is what is causing stridor, also aggravated by upper respiratory infections, that is why the role of hypocalcemia in stridor is not well appreciated.

Hypocalcemia stimulates parathyroid glands to secrete extra hormone needed to mobilize calcium from bone and cartilage with a more vital objective to maintain enough calcium for brain, heart, and blood. In places with the prevalence of vitamin D deficiency, breast milk is low in vitamin D due to maternal vitamin D deficiency. Stridor caused by hypocalcemia should be recognized early and treated promptly taken as a warning sign of occult rickets that might herald serious complications as convulsions, [2] cardiomyopathy, [3] and myelofibrosis [4]. The development of stridor is not as common as the other features of rickets.

## Discussion

These are four life-threatening features of rickets which was, thought as just a bone disease.

Convulsions, cardiomyopathy, Myelofibrosis and Stridor have been shown to be associated with hypocalcemia and other features of rickets features of vitamin D deficiency, in young as well as adults. These complications need prompt actions to prevent their lethal outcome if not appreciated. I have come across hypocalcemic convulsions where the treatment of a sort of status epilepticus that was alleviated by high doses of calcium and vitamin D to be controlled. As regards to the Hypocalcemic cardiomyopathy is that medical advice was solicited in many cases as acute collapse and shock that is diagnosed as hypovolemic shock and managed with fluid treatment might aggravate the condition. As regards to myelofibrosis, it might be missed as iron deficiency anemia, which is a common association to rickets reaching 46%, or celiac disease or even thalassemia, that why is it is recommended to investigate for the anemias associated with rickets to elucidate its cause.

## Recommendations

As all these problems are related to vitamin D deficiency with hypocalcemia, and as they are life-threatening in infants, it is highly recommended to take all measures of preventing them by supplying vitamin D during pregnancy and lactation, according to the global recommendations [19], it is summarized as:

Rickets, osteomalacia and vitamin D and Calcium deficiencies are preventable global health problems in infants, children, and adolescents. Implementation of international rickets prevention programs, including supplementation and food fortifications is urgently required. It is essential and vital to think of vitamin D deficiency as an important factor among infants brought to the emergency unit with collapse, convulsion, pallor, anemia, and noisy breathing. Investigation for the biochemical features of rick-

ets is mandatory in such cases.

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