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# Hypocalcemic Seizures in Breastfed Infants with Rickets Secondary to Severe Maternal Vitamin D Deficiency

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**Abstract:** This study was done to evaluate if nursing mothers of infants with rickets have vitamin D deficiency, and to evaluate the relationship between maternal vitamin D levels with hypocalcemic seizures in infants with rickets. We selected a cohort of breastfed infants with rickets. Infants were included in this study if they were breastfed and presented with any of the following clinical criteria: delayed motor milestones or delayed teething, were found to have specific rachitic bony signs, or presented with hypocalcemic seizures. We checked serum calcium (Ca), phosphorus (P), alkaline phosphatase, 25 hydroxy vitamin D [25(OH)D] and parathyroid hormone (PTH) levels in both infants and their mothers. Out of 32 children who met the clinical criteria for rickets, 23 (72%) had vitamin D level less than 20 ng $mL^{-1}$. Twenty two mothers (69%) had vitamin D deficiency (25 hydroxy vitamin D <20 ng $mL^{-1}$). Mothers of nine infants who presented with hypocalcemic seizures had severe vitamin D deficiency, ($p = 0.005$). We conclude that maternal vitamin D deficiency is common in nursing mothers of infants diagnosed with rickets. Invariably mothers of infants presenting with hypocalcemic seizures have severe vitamin D deficiency. Hypocalcemic seizures in infants secondary to maternal vitamin D deficiency might be prevented by supplementation of vitamin D.

**Key words:** Vitamin D, breastfeeding, supplementation, 25 hydroxy vitamin D, parathyroid hormone

## INTRODUCTION

Rickets is an example of extreme vitamin D deficiency, with a peak incidence between 3 and 18 months of age. The vitamin D status of an infant depends upon the amount of vitamin D transferred from the mother prenatally and upon the amount of vitamin D ingested or produced by the skin during exposure to ultraviolet light postnatally (Kovacs and Kronenberg, 1997). Human milk contains less than 25 international units of vitamin D per liter (Reeve *et al*., 1982). Vitamin D content of human milk is related to lactating mother's vitamin D status. If a lactating mother is supplemented with 400 IU/day of vitamin D, the vitamin D content of her milk will range from 25 to 78 IU $L^{-1}$ (Hollis and Wagner, 2004a). So breast milk is an insufficient source of vitamin D unless the mother receives vitamin D supplementation in high doses (2000 IU per day) (Hollis and Wagner, 2004a). A small number of studies have examined the effect of higher maternal supplements of vitamin D on the 25(OH)D concentrations in breastfed infants (Hollis and Wagner, 2004b; Saadi *et al*., 2007).

A state of deficiency occurs months before rickets is obvious on physical examination, and the deficiency state may also present with growth failure, lethargy, irritability, and a predisposition to respiratory infections during infancy (Najada *et al*., 2004; Papandreou *et al*., 2010).

Recently, young infants who presented with hypocalcemic seizures, were found to have congenital vitamin D deficiency (Orbak *et al*., 2007; Holick *et al*., 2009).

Vitamin D status of nursing mothers and their breastfed infants are closely correlated (Mehrotra *et al*., 2009; Narchi *et al*., 2010).

Materno-fetal transfer of vitamin D is mostly in the form of calcidiol [25(OH) vitamin D], which readily crosses the placenta (Kovacs and Kronenberg, 1997). The half life of calcidiol is approximately three to four weeks. Thus, the serum concentration of vitamin D falls rapidly after birth unless additional sources are available. The main reasons for inadequate vitamin D supply in infants from western countries are prolonged breastfeeding without vitamin D supplementation and the concomitant avoidance of sun exposure (Welch *et al*., 2000; Ward *et al*., 2007).

Several lifestyles and environmental factors including inadequate exposure to sunlight and decrease in the number of physicians who routinely prescribe vitamin D supplements for breastfed infants are partly responsible for the high prevalence of vitamin D deficiency in the

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developing countries and the resurgence in developed countries (Davenport *et al*., 2004). Nutritional rickets caused by inadequate intake of vitamin D and/ or calcium remains prevalent in many parts of the world (Anatoliotaki *et al*., 2003; Tomashek *et al*., 2001; Bhattacharyya, 1992).

We noticed an increase in the number of infants with nutritional rickets who present early in the first few months of life mostly with hypocalcemic seizures. Most of these infants were exclusively breastfed which raised the high possibility of vitamin D deficiency in their mothers as an important risk factor. So those rachitic infants might have begun their lives with small stores of vitamin D due to maternal vitamin D deficiency during pregnancy.

The aim of this study was to assess vitamin D in rachitic breastfed infants and their mothers. Also we aimed to determine whether hypocalcemic seizures in those infants were related to lower levels of maternal vitamin D.

## MATERIALS AND METHODS

Thirty two infants with vitamin D deficiency or nutritional rickets were identified between September 2008 and August 2009. This was done based on clinical presentation, biochemical results and radiological findings. Infants usually presented with delayed motor milestones and or delayed dentition, hypocalcemic seizures or other illnesses. The study was approved by the research committee at the children's hospital.

The study included 32 infants with nutritional rickets and their mothers. All mothers consented for the study. All infants were breastfed with some being exclusively breastfed. Clinical information were obtained regarding the following: infant's age, infant's dietetic history, history of calcium or vitamin D supplementation to the infant or his mother and history of regular sun exposure. Motor milestones and dentition were assessed by history and clinical examination. Radiological examination of the wrists, ankles and knees was done for all cases. CT scan of the head was done for infants who presented with seizures. None of the infants nor any of their mothers suffered from renal or liver disease, or was on anticonvulsant therapy.

Serum calcium, phosphorus, alkaline phosphatase, 25(OH)D and parathyroid hormones were measured for both infants and their mothers. Serum calcium was measured using colorimetric, o-cresolphtalein complexon (CPC). Reference value 8.6-10.3 mg $dL^{-1}$ (2.15-2.57 mmol $L^{-1}$). Serum phosphorus was measured using phosphomolybate UV, End point. Reference values for Infants: 1-30 days 3.9-7.7 mg $dL^{-1}$, 1-2 months 3.5-6.6 mg $dL^{-1}$ and 1-3 years 3.1-6 mg $dL^{-1}$. For mothers: 2.6-4.5 mg $dL^{-1}$. Serum alkaline phosphatase was measured using enzymatic Kinetic method. Reference values for infants: Age 1 day- 30 days 48-406 IU $L^{-1}$ for females while males 75-310 IU $L^{-1}$. Age 1 month-1 year: 124-341 IU $L^{-1}$ for females while 82-319 IU $L^{-1}$ for males. Age 1-3 years: 108-317 IU $L^{-1}$ for females while 104-345 IU $L^{-1}$ for males. Vitamin D was measured using 25-Hydroxyvitamin D $^{125}I$ RIA Kit. Intact PTH levels were measured with the intact PTH using ELISA. Reference range used was between 13.9 to 75.1 pg $mL^{-1}$.

**Definitions:** For infants, vitamin D insufficiency was considered when 25 (OH)D < 20 ng $mL^{-1}$ which equals < 50 nmol $L^{-1}$ while vitamin D deficiency when 25 (OH) D <10 ng $mL^{-1}$ which equals < 25 nmol $L^{-1}$. For mothers: Vitamin D insufficiency when 25 (OH)D was between 20-32 ng $mL^{-1}$ which equals 50-80 nmol $L^{-1}$. Vitamin D deficiency when 25(OH)D was < 20 ng $mL^{-1}$ which equals 50 nmol $L^{-1}$.

**Statistical methods:** Analysis of the results was done using standard computer program SPSS for Windows, release 13.0 (SPSS Inc, USA). All numeric variables were expressed as Mean±standard deviation (SD). Comparison of different variables in various groups was done using student t-test and Mann Whitney test for normal and nonparametric variables respectively. Chi-square ($\chi^2$) test was used to compare frequency of qualitative variables among the different groups. Pearson's and spearman's correlation test were used for correlating normal and non-parametric variables respectively. For all tests a probability (P) less than 0.05 was considered significant.

## RESULTS AND DISCUSSION

There were 32 breastfed rachitic infants. Fourteen (43%) presented because of delayed motor milestones or delayed teething. Nine infants (28%) had hypocalcemic seizures. Signs of rickets were found during physical examination of other infants who presented with chest infection 5 (16%), gastroenteritis 2 (6%) or dietetic counseling 2 (6%) (Table 1). There were 20 males (62.5%) and 12 females (37.5%) (Table 2). All 32 infants were breastfed with 20 (62.5%) exclusively breastfed (Table 2). Neither the infants nor the mothers were receiving calcium or vitamin D supplementation. Infants with dark skin were 17 (53%) out of the rachitic infants in the study (Table 2). All the infants and their mothers had limited sun exposure. All the mothers wore covered dress (exposing the face and hands only). Some of them were veiled (covering their faces). Infants who presented with hypocalcemic seizures

Table 1: Clinical manifestations of rachitic breastfed infants at the time of presentation

| Clinical manifestations | No. |
|---|---|
| Delayed closure of the fontanelles | 22 (68) |
| Parietal and frontal bossing | 26 (81 |
| Enlargement of the wrists | 22 (68) |
| Rachitic rosary | 17 (77) |
| Delayed motor milestones | 14 (43) |
| Or delayed teething | |
| Hypocalcemic seizures | 9 (28) |
| Chest infection | 5(16) |
| Gastroenteritis | 2 (6) |

Values in brackets indicate percentage

Table 2: Demographic Characteristics of rachitic infants in the study

| Studied parameter | No. |
|---|---|
| First birth order | 6 (18) |
| Sex: | |
| Males | 20 (62) |
| Females | 12 (37) |
| Prevalence of hypocalcemic convulsions in rachitic infants | 9 (28) |
| Exclusively breastfed | 20 (62.5) |
| Prevalence of dark skin among rachitic infants | 17 (53) |

Values in brackets indicate percentage

were younger than other rachitic infants ($p = 0.005$) (Table 3). Their mothers were more vitamin D deficient ($p = 0.005$) (Table 3, Fig. 2). Serum PTH levels in rachitic infants showed negative correlation with serum 25(OH)D ($r = -0.365$, $p = 0.04$) (Fig. 1).

We report severe maternal vitamin D deficiency as a cause of rickets and hypocalcemic seizures in breastfed infants. All our patients were breastfed and 62.5% of infants were exclusively breastfed.

This is in agreement with Daaboul *et al.* (1997) who found that exclusively breastfed infants who do not receive supplemental vitamin D or adequate sunlight exposure are at increased risk of developing vitamin D deficiency and/or rickets. None of our rachitic infants had received vitamin D supplementation. This finding is supported by Taylor *et al.* (2010), who observed that minority (15.9%) of breastfed infants received vitamin D supplementation. In this study 47% of rachitic infants had vitamin D insufficiency and 25% had vitamin D deficiency. Vitamin D deficiency and/ or nutritional rickets is still commonly diagnosed in Egypt and other developing countries, especially in the Middle East (Hatun *et al.*, 2005; Baroncelli *et al.*, 2008). This high prevalence of vitamin D deficiency in Egypt was reported by El-Khayat *et al.* (2006). The prevalence of nutritional rickets in developed countries also appears to be rising (Wagner and Greer, 2008).

Many factors affect vitamin D synthesis by the skin. The most important of which is the degree of skin pigmentation which makes it difficult to determine what is adequate sunshine exposure for any given infant or child. (Wolpowitz and Gilchrest, 2006). Dark skin is an additional risk factor for developing rickets in breastfed infants in our study. In this study, 53% of the infants had dark skin.

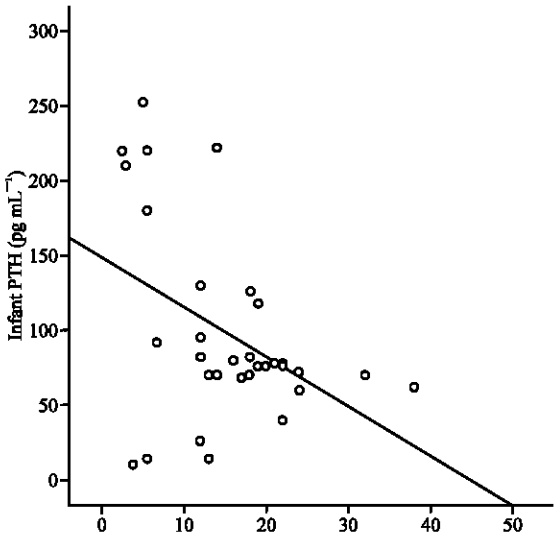


Fig. 1: Correlation between serum 25 hydroxy vitamin D and parathyroid hormone in infants ($r = 0.365$, $p = 0.04$)

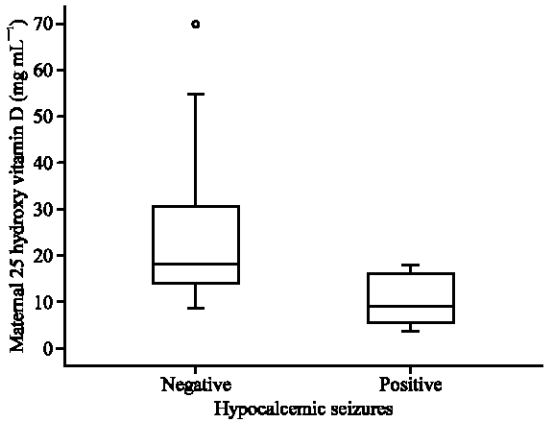


Fig. 2: Mean maternal 25 hydroxy vitamin D level in rachitic infants with or without hypocalcemic seizures

Kreiter *et al.* (2000), found that dark skinned individuals produce less vitamin D in response to sunlight.

We did not include social class of the mother as a risk factor for developing vitamin D deficiency among nursing mothers of rachitic infants. Also we did not compare vitamin D status of nursing mothers living in rural areas and those who live in intercity crowded apartments or high buildings where sun exposure is very limited. Maternal education and work was not included too. Most of our patients were of middle and lower social classes of nonworking mothers living inside the city zone. Atiq *et al.* (1998) found high prevalence of vitamin D deficiency in Pakistani nursing mothers and their infants

Table 3: Infants age and biochemical tests in infants presented with or without hypocalcemic seizures and their mothers

| | Infant values | | | Maternal values | | |
|---|---|---|---|---|---|---|
| Parameters | Group I | Group II | p-value | Group I | Group II | p-value |
| **Infants age (months)** | | | | | | |
| Mean±SD | 3.67±1.6 | 12.35±4.3 | 0.001* | | | |
| Median (IQR) | (3) | (0.335) | | | | |
| **S.Ca (mg dL$^{-1}$)** | | | | | | |
| Mean±SD | 6.5±1.48 | 8.5±1.5 | 0.004* | 8.3±1.1 | 8.8±1.7 | 0.464 |
| Median (IQR) | 6.8 (2.8) | 8.7 (1.530) | | 8.8 (1.8) | 8.7 (9) | |
| **S.P (mg dL$^{-1}$)** | | | | | | |
| Mean±SD | 3.3±0.88 | 3.88±1.19 | 0.184 | 3.7±0.9 | 4.2±1.1 | 0.297 |
| Median (IQR) | 3.5 (1.8) | 4 (1.9) | | 4 (1.8) | 4.2 (1.9) | |
| **S.Alkaline phosphatase (IU L$^{-1}$)** | | | | | | |
| Mean±SD | 286±144 | 189±248 | 0.69 | 119±48 | 102±56 | 0.154 |
| Median (IQR) | 277 (221) | 175 (201) | | 117 (55) | 89 (35) | |
| **S 25(OH)D (ng mL$^{-1}$)** | | | | | | |
| Mean±SD | 9.73±5.9 | 17.4±8.23 | 0.016* | 10.5±5.5 | 26±17.4 | 0.005* |
| Median (IQR) | 6.79 (10) | 18 (10) | | 8.9 (11) | 18 (18) | |
| **S.PTH (pg mL$^{-1}$)** | | | | | | |
| Mean±SD | 3.3±0.88 | 3.88±1.19 | 0.125 | 103±64 | 69±45 | 0.208 |
| Median (IQR) | 3.5 (1.8) | 4 (1.9) | | 88 (184) | 50 (50) | |

Group I: Infants presented with hypocalcaemic seizures. Group II: Infants who did not have hypocalcaemic seizures. S 25 (OH)D: 25 hydroxy vitamin D, PTH: Parathyroid hormone. *Significant, IQR: Interquartile range

Table 4: Biochemical results of breastfed infants with vitamin D deficiency and /or nutritional rickets and their mothers

| Results | Infants | Mothers | Correlation r | p-value |
|---|---|---|---|---|
| **S. Ca (mg dL$^{-1}$)** | | | | |
| Range | 4.5-10.9 | 5.6-14.7 | 0.392* | 0.026 |
| Mean±SD | 7.9±1.7 | 8.7±1.6 | | |
| Median (IQR) | 8.1 (1.6) | 8.6 (1.90) | | |
| **S. P (mg dL$^{-1}$)** | | | | |
| Range | 1.6-6 | 2.5-6.1 | 0.443* | 0.011 |
| Mean±SD | 3.73±1.27 | 4.1±1.07 | | |
| Median (IQR) | 4 (1.6) | 4.1 (1.8) | | |
| **S.alkaline phosphatase (IU L$^{-1}$)** | | | | |
| Range | 77-1250 | 43-227 | 0.054 | 0.769 |
| Mean±SD | 293.6±221 | 107.4±54.44 | | |
| Median (IQR) | 229 (211) | 90 (50) | | |
| **S.25-(OH)D (ng mL$^{-1}$)** | | | | |
| Range | 3-38 | 4-70 | 0.326 | 0.069 |
| Mean±SD | 15.29±8.3 | 21±16 | | |
| Median (IQR) | 15 (13) | 16 (18) | | |
| **S.PTH (pg mL$^{-1}$)** | | | | |
| Range | 10-252 | 18-222 | 0.295 | 0.101 |
| Mean±SD | 98±65 | 78.9±52 | | |
| Median (IQR) | 77 (56) | 57 (73) | | |

S: Serum, Ca: Calcium, P: Phosphorus, 25(OH)D: 25 hydroxy vitamin D, PTH: Parathyroid hormone. *Significant correlation

predominately in the upper social class. They found that women of upper social class mostly preferred to live indoors which decreased their exposure to direct sunlight. Twenty two (69%) of the mothers of rachitic infants had vitamin D deficiency while an additional four mothers (12.5%) had vitamin D insufficiency. This is in agreement with Dawodu *et al.* (2005). They found vitamin D deficiency in over 90% of mothers of rachitic children compared with 52% of mothers of nonrachitic children. In their study the percentage of vitamin D deficiency among rachitic mothers was higher because they used 25(OH)D concentration <25 nmol L$^{-1}$ (<10 ng mL$^{-1}$) to indicate vitamin D deficiency in children.

Present study showed positive correlation between rachitic infants and their mothers but P was insignificant ($r = 0.326$, $p = 0.069$). This is in contrast to Dawodu *et al.* (2005) who found a positive correlation between serum 25(OH)D in mothers and their children ($r = 0.39$, $p = 0.012$). This might be because in their study they included rachitic and nonrachitic children and their mothers while all our infants had nutritional rickets (Table 4).

Serum PTH levels in rachitic infants showed negative correlation with serum 25(OH)D ($r = -0.365$, $p = 0.040$), also this negative correlation was in their mothers ($r = -0.343$, $p = 0.055$). In Dawodu *et al.* (2005) study, serum PTH was available only in rachitic children and their mothers which showed a trend towards negative correlation with Serum 25(OH)D.

Infants with hypocalcemic seizures had lower serum calcium than infants who did not ($p = 0.004$). They also had lower 25 (OH)D than those who did not have seizures with ($p = 0.016$). The mothers of those infants had less 25(OH)D than mothers of infants who did not have seizures, $p = 0.005$). This suggests that infants with hypocalcemic seizures were born with less vitamin D stores because their mothers were severely deficient in vitamin D.

This finding is supported by Balasubramanian and Ganesh (2008) observation during the study of hypocalcemia in infants and children. Out of 50 cases, 13 exclusively breastfed infants manifesting with hypocalcemic seizures were confirmed to have vitamin D deficiency. All of them had biochemical evidence of hyperparathyroidism and low levels of 25 (OH)D and promptly responded to therapy with vitamin D and calcium. All the mothers of these 13 infants had low levels

of 25(OH) D. Recently, Holick *et al.* (2009) reported a 9 month old infant who presented with seizures. Vitamin D deficiency rickets was the diagnosis which was confirmed by low 25(OH) D, elevated PTH, hypocalcemia. From this study, we found that the younger infants presented with hypocalcemic seizures while the older presented with manifestations of boney affection or delayed motor milestones. This finding is in agreement with a retrospective study of children presented with vitamin D deficiency in the United Kingdom by Ladhani *et al.* (2004). They found two types of presentations. The first was symptomatic hypocalcemia (including seizures) early in infancy long before any physical findings or radiological evidence of vitamin D deficiency occurred. The second clinical presentation was that of a more chronic disease, with rickets and/or decreased bone mineralization and either normocalcemia or asymptomatic hypocalcemia. Infants who presented with hypocalcemic seizures were more exclusively breastfed compared with those who did not ($p = 0.006$).

In spite of the fact that sunlight is abundant in Egypt, in this study vitamin D deficiency was found in 25% of breastfed rachitic infants while 47% had vitamin D insufficiency. In countries where the incidence of hypocalcemic rickets is high despite ample sunlight, researchers have suggested that insufficient calcium intake rather than primary vitamin D deficiency is an important cause of nutritional rickets (Pettifor *et al.*, 1978; Pfitzner *et al.*, 1998). Hypocalcemia was found in 56% of rachitic infants. Hypocalcemic rickets may be due to dietary deficiency of calcium or insufficient intestinal absorption of calcium caused by vitamin D deficiency (Rauch, 2009). This observation is supported by studies in South Africa and Nigeria which suggest that a dietary deficiency of calcium may cause rickets and osteomalacia. Researchers performed a randomized, double blinded, controlled trial of 123 Nigerian children with rickets which showed that these children responded better to treatment with calcium alone or in combination with vitamin D than to treatment with vitamin D alone.

Differential diagnosis of cases of hypocalcemia in infancy should include vitamin D deficiency and/or nutritional rickets. Measurement of serum 25(OH)D level should be included in the work up of cases of infantile hypoclacemia. We suggest that 25(OH)D should be included in the laboratory work up of mothers of rachitic infants. Vitamin D supplementation to lactating mothers and especially those of rachitic infants should be a priority in the national and international campaigns.

Vitamin D deficiency in exclusively breastfed infants results in various stages of rickets and may present with life threatening hypocalcemic seizures. Every effort should be made to prevent these complications by supplementing vitamin D to all pregnant and lactating mothers. Physicians have to follow the new recommendations of the American Academy of Pediatrics (AAP) which states that breastfed and partially breastfed infants should be supplemented with 400 IU/day of vitamin D beginning in the first days of life. Supplementation should be continued unless the infant is weaned to at least 1 L $day^{-1}$ of vitamin D-fortified formula or whole milk (Wagner and Greer, 2008).

## CONCLUSION

In this study an important relationship was found between hypocalcemic seizures in rachitic breastfed infants and maternal vitamin D deficiency. Assay of vitamin D for breastfed infants and their mothers should be considered in cases of infantile hypocalcemic seizures. Supplementation of vitamin D for mothers and their breastfed infant is important to prevent rickets and hypocalcemic seizures in breastfed infant.

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