

ORIGINAL ARTICLE

Hypocalcemic Seizures in Infancy and its Relationship with Maternal Vitamin D Deficiency

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Abstract

Background: Hypocalcemia accounts for a large number of seizures in infants presented at the emergency department of our hospital.

Objective: To evaluate the role of Vitamin D deficiency as the etiology of hypocalcemic seizures in infancy and its relationship with maternal Vitamin D levels.

Methods: Cross sectional hospital based study over a period of 35 months from July 2016 to June 2019. Total 60 infants with hypocalcemic seizures were enrolled into the study. Blood samples were taken for serum total calcium, inorganic phosphate, alkaline phosphatase, albumin, 25(OH)D and PTH from the child. Maternal serum 25(OH)D levels were measured as well.

Results: The mean age of the studied infants was 3.6 (± 1.2) months. All patients had low total calcium (mean 6.5 mg/dl) and most of them had low inorganic phosphate (mean 3.5 mg/dl), while all of them had raised alkaline phosphatase (mean 1093.50 IU/L) and PTH levels (mean 104 pg/ml) at presentation. Forty percent of infants were severely deficient and 60% were deficient in vitamin D; none of them were vitamin D sufficient. Among their mothers, none were sufficient, 10% were insufficient, 45% were deficient, and 45% were severe deficient of vitamin D. Neonatal 25(OH)D showed strong negative correlation with their serum PTH levels and strong positive correlations with maternal serum 25(OH)D levels.

Conclusion: All infants in our setting presented with hypocalcemic seizures were found due to Vitamin D deficiency and it was mostly related to maternal Vitamin D deficiency.

Keywords: Hypocalcemia, seizures, 25-hydroxycholecalciferol.

Introduction

Seizures are commonly encountered as emergency in pediatric population occurring in 4-7% of infants and children.¹ In the developing countries, hypocalcaemia has been found as a major biochemical cause of seizures in infancy^{2,3}, which constitutes 25.6% of total afebrile seizures in paediatric age group.⁴ Among the notable causes of hypocalcemic seizures, prematurity, birth asphyxia, exogenous

phosphate load, magnesium deficiency, hypoparathyroidism, malabsorption syndromes, pancreatitis, hypoalbuminemia (pseudohypocalcemia) and vitamin D deficiency are well documented.⁵ Furthermore, hypocalcemia due to vitamin D deficiency constitutes an important cause of infantile seizures in developing countries.

Infants are more vulnerable for vitamin D deficiency because of their high rate of skeletal growth.^{2,3,6}

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Vitamin D stores in young infants mostly depend on intrauterine accretion and breastmilk. Breastfed infants born to and nursed by vitamin D deficient mothers found to have low serum 25(OH) D levels.^{7,8} Maternal vitamin D deficiency may therefore be an important risk factor for hypovitaminosis D in early infancy, thereby causing in hypocalcemia and seizures in this age group.^{9,10}

The role of vitamin D has been found in central nervous system as antiepileptics which are mediated through vitamin D receptors.¹¹ Due to its prolonged half life serum 25 (OH) vitamin D level is the best available biomarker for the diagnosis of vitamin D deficiency. Vitamin D concentrations of >20 ng/mL (50 nmol/L) are considered as sufficient, between 12-20 ng/mL (30-50 nmol/L) as insufficient and <12 ng/mL (<30 nmol/L) as deficient.¹²

There is paucity of data studying association of hypocalcemic seizures in infants with hypovitaminosis D in Bangladesh. This study was conducted to evaluate the role of Vitamin D deficiency in the etiology of hypocalcemic seizures in infancy and its relationship with maternal Vitamin D levels.

Materials and Methods

Infants aged 15 days to 12 months of age, presenting with seizures at emergency department of Bangladesh Shishu Hospital & Institute, Dhaka were assessed for the study between July, 2016 and June, 2019. Written informed consent was taken from the mothers enrolled in the study.

Only infants of full term deliveries had normal birth weight and without any congenital malformation were recruited. Infants with history of intake of calcium or vitamin D supplementation, infants with other causes of seizures-meningitis, hypoglycemia, dyselectrolytemia, structural brain malformation, history of birth asphyxia and infants of diabetic mothers were excluded from the study. Finally excluding above causes these who were diagnosed as hypocalcemic were included in the study.

Hypocalcemia was considered to be the cause of seizures when total serum calcium level was <8 mg/dL, with normal levels of serum albumin. The study was approved by the Ethical Review Committee of the hospital.

Mothers known to have hepatic, renal or bone disorders, malabsorption or intake of any drugs or supplements known to affect the calcium-vitamin D-PTH axis were excluded from the study. A structured questionnaire was used to obtain relevant

information for Infants and mothers. The selected mother-infant pairs underwent necessary clinical, biochemical and hormonal assessment on the first visit.

Blood sample was drawn from the children by venipuncture with all aseptic precautions without using tourniquet for total calcium, inorganic phosphate, alkaline phosphatase, albumin, creatinine, 25(OH)D, PTH and only for 25(OH)D from the mothers. Routine investigation to exclude other causes of seizures in Infants were also performed accordingly. Total calcium, inorganic phosphate, alkaline phosphatase, albumin and creatinine were analysed by BECKMAN COULTER AU-680, whereas 25(OH)D and PTH were analysed with ARCHITECT-1000 plus by Chemiluminescence method. Vitamin D concentrations of >20 ng/mL are considered as sufficient, between 12-20 ng/mL as insufficient, <12 ng/mL as deficient and severe deficiency as levels less than 5 ng/mL.^{12,13}

We analyzed data using the Statistical Product and Service Solutions version 26.0 software (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). The categorical variables were represented as percentages and measurable variables as the mean±standard deviation (SD) or median (interquartile range, IQR). Pearson correlation test was used to see the correlations of neonatal serum 25(OH)D levels with other variables. *P* value <0.05 was considered statistically significant.

Results

Total 60 infants with hypocalcemic seizure were enrolled in this study. The mean age of the studied neonates was 3.6 (±1.2) months, youngest one was 2 months old and oldest one was 8 months old. They consisted of 36 (60%) males and 24 (40%) females. All of our patients were breastfed with 36 (60%) exclusive breastfed. Neither the infants nor the mothers were receiving calcium or vitamin D supplementation. Most of our patients were of middle and lower social classes. All the infants and mothers had history of limited sun exposure.

All patients had low total calcium (mean 6.5 mg/dl) and most had low inorganic phosphate (mean 3.5 mg/dl), while all of them had raised alkaline phosphatase (mean 1093.50 IU/L) and PTH levels (mean 104 pg/ml) at presentation (Table I).

Table I
Characteristics of the studied neonates (N=60)

Variables	Mean ± SD or Median (IQR)	Range
Age (months)	3.6 ± 1.23.5 (3.0-4.0)	2.0-8.0
S. Calcium (mg/dL)	6.72 ± 0.696.80 (6.20-7.38)	5.6-7.9
S. Inorganic Phosphate (mg/dL)	3.39 ± 0.593.50 (3.05-3.80)	2.1-4.5
S. ALP (IU/L)	1222.03 ± 455.821093.50 (977.25-1244.50)	685-2678
S. PTH (pg/mL)	111.25 ± 25.94104.00 (93.25-123.00)	82-187
S. 25(OH)D (ng/mL)	5.35 ± 1.595.65 (4.13-6.28)	1.4-9.8
Maternal S. 25(OH)D (ng/mL)	6.10 ± 3.175.45 (3.90-7.40)	1.5-14.6

Forty percent of neonates were severely deficient and 60% were deficient of vitamin D; none of them were vitamin D sufficient. Among their mothers,

none were sufficient, 10% were insufficient, 45% were deficient, and 45% were severe deficient of vitamin D (Fig.-1).

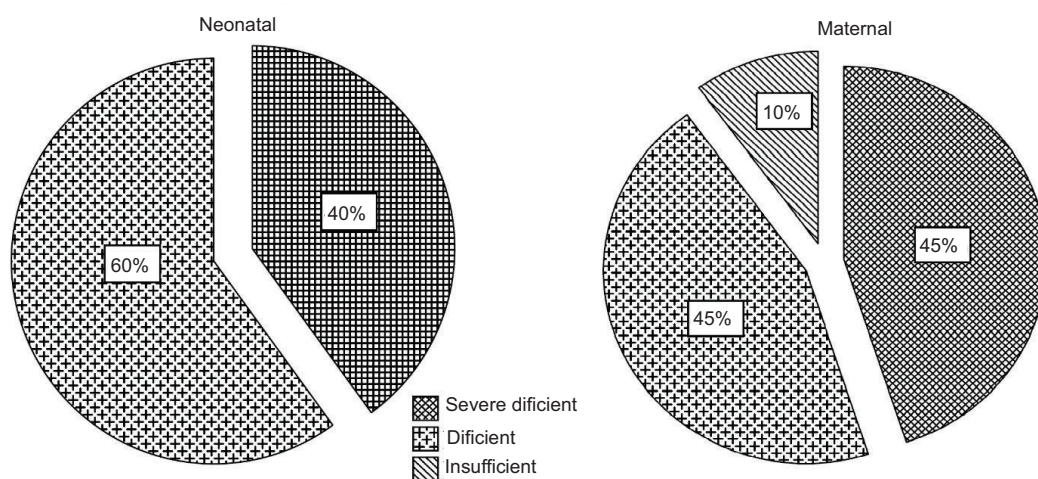


Fig.-1 Neonatal and maternal vitamin D status

Correlations of serum 25(OH)D levels with other variables are shown in Table-II. Serum 25(OH)D showed strong negative correlation with their serum PTH levels and strong positive correlations with maternal serum 25(OH)D levels.

Table II <i>Correlations of neonatal serum 25 (OH) D levels with other variables</i>		
Variables	Pearson Correlation	p value
Age (months)	0.110	0.404
S. Calcium (mg/dL)	0.017	0.896
S. Inorganic Phosphate (mg/dL)	0.025	0.851
S. ALP (IU/L)	0.162	0.217
S. PTH (pg/mL)	-0.631	<0.001
Maternal S. 25(OH)D (ng/mL)	0.279	0.031

Simple scatter diagram showing the correlations of neonatal and maternal vitamin D levels (Fig.-2).

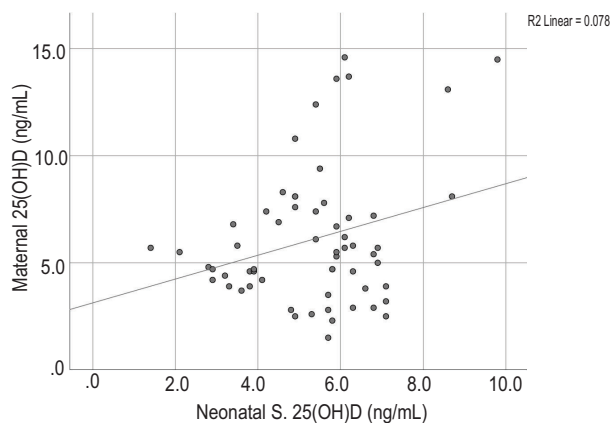


Fig.-2 Simple scatter diagram showing the correlations of neonatal and maternal vitamin D levels

Discussion

Neonatal hypocalcaemia (NH) is a common metabolic event in the neonatal period. NH is classified into early and late, based on the time of presentation. The early NH usually manifests within 72 hours after birth, requiring short term calcium supplementation, and it is a frequent co morbidity in high risk neonates. Another entity, resistant or prolonged hypocalcemia is defined as symptomatic hypocalcemia not responding to appropriate doses of calcium supplementation, calcium requirement beyond 72 h of age in neonates or hypocalcemia manifesting beyond 1st week of life.¹⁴ Our patients belong to this group.

Late NH usually results from increased phosphate load (due to cow milk intake or renal insufficiency), hypomagnesemia and hypoparathyroidism.¹⁴ Maternal vitamin D deficiency leading to neonatal vitamin D deficiency is also reported to be a cause of late NH.^{15,16}

Vitamin D deficiency in neonatal period has been related to several environmental and maternal factors.^{17,18} This study emphasizes the need for the evaluation of infantile and possibly maternal vitamin D status in case of late-neonatal and infantile convulsion due to hypocalcaemia.

All of our patients had hypovitaminosis D with secondary hyperparathyroidism. As mothers' vitamin D level were low, symptomatic early infantile hypocalcemia in these cases can be attributed to the maternal vitamin D deficiency. A strong correlation between child's and mother's vitamin D level is evident in our study. This has been documented in many studies. In Iran 100% of neonates with delayed hypocalcemia were born by mothers with vitamin D deficiency.¹⁹ Some other previous studies showed same results that babies born from mothers having vitamin D deficiency suffering from late onset hypocalcemia and vitamin D deficiency.^{20,21} Exclusive breastfeeding without vitamin D supplementation is another risk factor of vitamin D deficiency in early infancy.^{22,23} Being all of our infants breastfed with 60% exclusive breastfed supports this finding.

Late onset hypocalcemia is usually caused by high phosphate intake²⁴ and usually accompanied by raised ALP and PTH.²¹ However, Do et al.²⁵ showed that most of their patients had hypocalcemia and hyperphosphatemia represented normal or near

normal ranges of PTH and ALP. In contrast, our patients with hypocalcemia do not have history of high phosphate intake or hyperphosphatemia, rather they have hypophosphatemia with raised ALP and PTH. This hypophosphatemia could be attributable to phosphaturia caused by elevated PTH, though this was not investigated.

According to Avery's disease of the newborn, PTH levels are usually high with hypocalcemia with vitamin D deficiency,²⁶ which is truly evident in our study and found consistent with another study.²⁷ However, one study in Korea et al²⁵ observed no elevation of PTH in neonates with late onset hypocalcemia despite vitamin D deficiency.

Among many factors, skin pigmentation may also contribute to less vitamin D synthesis in our study population as Kreiter et al²⁸ found that dark skinned individuals produce less vitamin D in response to sunlight.

We have some limitations in this study. First, we didn't obtain detailed information on sunlight exposure of mothers and infants, diet of mothers. Second, this study is not a case-control study and maternal-infant pair was not assessed case by case. Third, we didn't consider rachitic changes among our infants. Regardless of these limitations, the present study is conducted to evaluate the relationship between early infantile hypocalcemia and maternal vitamin D status in Bangladesh using infant-mother sera.

Conclusion

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

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