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5 Hydroxy Cholecalciferol Levels in Infants with Hypocalcemic Seizures

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Abstract

Objective: To determine the prevalence of vitamin D deficiency (25-hydroxycholecalciferol) in infants with hypocalcemic seizures and the relation of severity of vitamin D (25-hydroxy Cholecalciferol) deficiency with the occurrence of hypocalcemic seizures.

Design: Cross sectional analytical study.

Setting: pediatric emergency department of a tertiary care hospital.

Methods: 60 consecutive term neonates and infants (upto 1 year) presenting with seizures with documented hypocalcemia (total serum calcium was <8 mg/dl, with normal serum albumin levels (≥4 mg/dl) were included as cases and 60 healthy term neonates and infants attending immunization clinic were taken as controls. A structured questionnaire was asked and blood samples taken for serum calcium, phosphorus, alkaline phosphatase, 25 hydroxycholecalciferol, albumin levels. Radiological assessment of rickets was also done in clinically suspected cases.

Results: Majority of the cases had inadequate exposure to sunlight (73.3%) as compared to controls (41.7%). Vitamin D deficiency is seen in 88.3% cases and 68.3% controls (p=0.01). 31.7% of the cases were severely deficient in vitamin D. Thus vitamin D deficiency appears to be a major risk factor for hypocalcemic seizures. No significant relation between 25(OH)D and calcium in both cases and controls using spearman rank correlation. There was a significant inverse relation between 25(OH)D and S.ALP among controls and cases.

Conclusion: High prevalence of vit D deficiency was noted in infants with hypocalcemic seizures however a high prevalence of vitamin D deficiency was also seen in healthy infants. Serum alkaline phosphatase can be taken as surrogate marker for vit D deficiency. Sunlight exposure < 30 minutes/week was likely to develop vitamin D Deficiency.

Keywords: Hypocalcemia; Seizures; 25-hydroxycholecalciferol

Introduction

Seizures are common in pediatric age group occurring in 4-7% of infants and children [1]. Amongst the various etiologies hypocalcaemia is a major biochemical cause of seizures in infancy in the developing countries [2,3]. It constitutes 25.6% of afebrile seizures in children [4]. Causes of hypocalcemic seizures include prematurity, birth asphyxia, exogenous phosphate load, magnesium deficiency, hypoparathyroidism, malabsorption syndromes, pancreatitis, hypoalbuminemia (pseudohypocalcemia) and vitamin D deficiency [5]. Hypocalcemia due to vitamin D deficiency constitutes an important cause of infantile seizures in developing countries. Infants are a vulnerable population for developing deficiency due to their high rate of skeletal growth. A state of deficiency occurs months before rickets is obvious on physical examination and most frequently it presents as seizures.

The role of vitamin D has been found in central nervous system where its functions are mediated through vitamin D receptors [6]. Through its receptor, vitamin D down-regulates interleukin-6 (IL-6) which is a proconvulsant and up-regulates GDNF and NT-3 (anticonvulsant neurotrophic factors). Vitamin D stimulates expression of calcium-binding proteins known to exert antiepileptic effects [7]. Serum 25 (OH) vitamin D level is the best available biomarker for the diagnosis of vitamin D deficiency. A level below 20 ng/ml or 50 nmol/l (cut off) is now considered insufficient by Lawson Wilkins Pediatric Endocrine Society in the USA [8].

There is paucity of Indian data studying association of hypocalcemic seizures in infants with hypovitaminosis D. This study was designed to find out the prevalence of vitamin D deficiency in infants with hypocalcemic seizures so that vitamin D supplementation can be considered as an adjuvant therapy for the prevention and control of hypocalcemic seizures.

Methods

Ours was a crossectional analytical study conducted at a tertiary care hospital (Safdarjung hospital, New Delhi) in the department of Pediatrics. Subjects were recruited between January 2011 to december 2011.

All the term neonates and infants (upto 1year) presenting with seizures and having documented hypocalcemia (total serum calcium was <8 mg/dl, with normal serum albumin levels (≥4 mg/dl) were included as cases in the study. Using the prevalence of hypocalcemic seizure 11% [9], alpha error 5%, power 90%, sample size was taken to be 60. Same number of healthy term neonates and infants attending immunisation clinic were taken as controls. Infants with history of intake of calcium or vitamin D supplementation, infants with other causes of seizures-meningitis, hypoglycemia, structural brain malformation, history of birth asphyxia, congenitally malformed infant or infant of diabetic mother were excluded from study. A written informed consent was obtained from the parents for enrolling their child for the study. The study protocol was approved by the Ethics Committee of the Hospital.

A structured questionnaire was used to obtain information for all cases and controls. A detailed history and clinical examination was done for each child. Breastfeeding was categorised as exclusive breastfeeding for 1st 6 months of life or not exclusively breastfed. Not exclusively breast fed were categorised further as those on mixed feeding (breastfed +animal/toned milk) and those on total animal/ toned feeding before 6 months of age. Season during which an infant presented with seizure was also recorded. Between November to February was taken as winter and between March to October was taken as summer. Information regarding sun exposure was collected. Minimum recommended exposure is defined as when the infant is exposed to sunlight for at least 30 minutes in a week with arms, legs and trunk exposed. 2 hrs is the minimum required period weekly if only face is exposed to sunlight. On examination, anthropometric data was compared. Sign of vitamin D deficiency were recorded by examining clinician as presence of wrist widening. Infants with wrist widening were subjected to radiography of left wrist to detect features of rickets.

Blood sample collection was done under strict aseptic conditions without using tourniquet; 3 ml blood was drawn by venepunture. 1.5 ml blood was immediately sent for measuring serum calcium & serum phosphorus level using autoanalyser, serum alkaline phosphatase level by spectrophotometer and serum albumin level. Remaining 1.5 ml was immediately taken for serum separation by centrifugation. Separated serum was stored at +2 to +8°C in refrigerator to estimate 25(OH)D using ELISA method. Routine investigations to rule out other causes of seizure in infancy were also performed.

Vitamin D (25-hydroxy cholecalciferol) deficiency was defined as 25-hydroxy vitamin D levels < 50 nmol/L or 20 ng/ml (cut off level). Severe deficiency was level are <12.5 nmol/l or <5 ng/ml [8].

Statistical analysis

Data was analyzed using SPSS software version 16.0. Statistical significance of quantitative variables between the study and control group was determined by unpaired student t-test or non-parametric Mann Whitney test. Statistical significance of qualitative variables was determined by chi square test or Fischer exact test. Spearman rank correlation was calculated to find the strength of relationship between various quantitative variables. $P \leq 0.05$ was taken as level of statistical significance.

Results

A total of 480 infants presented with seizures in pediatric emergency during the study period (January 2011 to December 2011), out of which 60 were taken as cases fulfilling inclusion criteria. 60 healthy term neonates or infants were taken as controls. None of them received calcium or vitamin D supplementation.

Baseline data comparison of cases and controls is shown in Table 1. It shows the mean age, mean weight and mean length of cases were 6.11, 5.89 and 62.72 respectively. The mean age, mean weight and mean length of controls were 5.9, 6.18 and 62.70 respectively. Statistically there was no significant difference in mean age, weight and length between the two groups (p value- not significant). Among cases, 33/60 children and among controls, 35/60 were of age between 6-12 months and rest were below 6 months. There was no significant difference between two groups in relation to age (p=0.713). In both groups, males were predominant (55% and 60% of cases and controls respectively). The feeding pattern among cases and controls of 0-6month age group showed that most of the infants in cases and controls were exclusively breast fed (29/35 and 24/28 in cases and controls respectively). There was a seasonal variation in the presentation of seizures as more cases presented in winter (55% or 33/60) but it was not statistically significant. We also compared adequacy of sunlight exposure in cases and controls. Majority of the cases i.e. infants with hypocalcemic seizures had inadequate exposure to sunlight (44/60 or 73.3%) as compared to controls (31/60 or 41.7%) which was statistically significant (p<0.05).

Parameter	Cases Mean ± SD	Controls Mean ± SD	P Value
Sample Size	60	60	-
Age(months)	6.11 ± 3.80	5.9 ± 3.43	0.753
Sex- male Female	33 27	36 24	0.580
Weight(kg)	5.897 ± 2.18	6.18 ± 2.03	0.455
Length(cm)	62.72 ± 6.63	62.70 ± 6.34	0.990
Weight/age	1	1	-
Length/age	1	1	-

Table 1: Comparison of baseline parameters

Table 2 shows comparison of various biochemical parameters in cases and controls. Mean level of 25(OH)vitamin D in cases and controls was 28.79 and 47.62 respectively, which was significantly low in cases as compared to controls (p<0.05). Also, there was significant difference in the mean Serum Alkaline Phosphatase (S.ALP) levels between cases and controls (p<0.05). However there was no significant difference in serum phosphorus levels between two groups (p=0.361). On comparing vitamin D status in cases and controls, vitamin D deficiency (<50 nmol/l) was seen in 88.3% (53/60) cases and 68.3% (41/60) controls. This difference was statistically significant (p<0.05). In both groups, serum alkaline phosphatase levels was found to be

elevated in most of the children, 44/60(73.3%) cases and 39/60(65%) controls.

We also studied severity of vitamin D deficiency in cases and controls. 31.7% (19/60) of the cases were severely deficient in vitamin D whereas amongst controls, out of total vitamin D deficient children, only 16.7% cases were severely deficient ($p<0.05$). Among cases, both mild and severe deficiency was seen in 31.7% cases (19/60 in each), so the severity of vitamin D deficiency did not have any relation to the occurrence of seizures.

	Cases Mean ± SD	Controls Mean ± SD	P Value
Sample size	60	60	-
S. Calcium (mg/dl)	6.98 ± 0.96	8.86 ± 1.15	<0.05
S.Phosphorus (mg/dl)	5.06 ± 1.74	4.73 ± 1.39	0.361
S.Alp (IU/L)	660.13 ± 352.05	440.72 ± 222.62	<0.05
S.Vitamin D(nmol/l)	28.79 ± 33.85	47.62 ± 46.16	<0.05

Table 2: Comparison of biochemical parameter

Among all hypocalcemic infants with seizures, 41.7% (25/60) showed wrist widening and out of these, 25% (15/60) had evidence of rickets on X ray wrist.

Relation was studied between 25hydroxy vitamin D, serum calcium and serum ALP levels using spearman rank correlation (Tables 3 and 4). No significant relation was seen between 25 hydroxy vitamin D and serum calcium in both cases ($r=0.198$, $p=0.13$) and controls ($r=0.445$, $p=0.06$). However, a significant inverse relation between 25(OH)D and S.ALP among controls ($r = -0.615$, $p<0.05$) and cases ($r = -0.213$, $p<0.05$) was noticed.

	S. vitamin D	S. calcium	S. ALP
S. vitamin D	r=1	r=0.445, p=.000	r= -0.615, p<0.05
S. calcium	r=0.445, p=.000	r=1	r=-0.252, p=0.052

Table 3: Relation of various parameters among cases

Correlation coefficient

	S. vitamin D	S. calcium	S. ALP
S.vitamin D	r=1	r=0.445, p=.000	r= -0.615, p<0.05
S.calcium	r=0.445, p=.000	r=1	r=-0.252, p=0.052

Table 4: Relation of various parameters among controls

Discussion

There has been increasing global interest regarding the role vitamin D in health and disease. Vitamin D deficiency continues to be a public health problem, prevalent in many Asian countries. In our study, vitamin D levels and other associated factors were studied in infants with hypocalcemic seizures.

Among hypocalcemic seizure patients (cases) of 0-6months age, 82% were exclusively breast fed, 11.5% were on mixed feeding and 5.7% were on animal/toned milk. Out of total, in 41.7% cases complementary feeding was started soon after 6 months. These results were comparable Manzoor Ali Khan et al. study [10] and Ahmed et al. study [2].

Our study reported a marginally higher incidence of hypocalcemic seizure during winter season (55% of cases presented during nov-feb.). Whereas, Ahmed et al. reported [2] that 70% cases were seen in winter months.

Inadequate sunlight exposure was an important contributing factor for development of vitamin D deficiency rickets which in turn is a common cause of hypocalcemia in children. Our study highlighted that majority of the cases (73.3%) had a history of limited sunlight exposure than controls (51% controls reported to have inadequate sun exposure). This difference is statistically significant ($p<0.05$). This was consistent with Manzoor Ali Khan et al. [10] study which reported that 68% of children with hypocalcemic fits had poor sun exposure. It was also comparable with other studies of Mivako et al. [11] and Erfan et al. [12] (Figure 1).

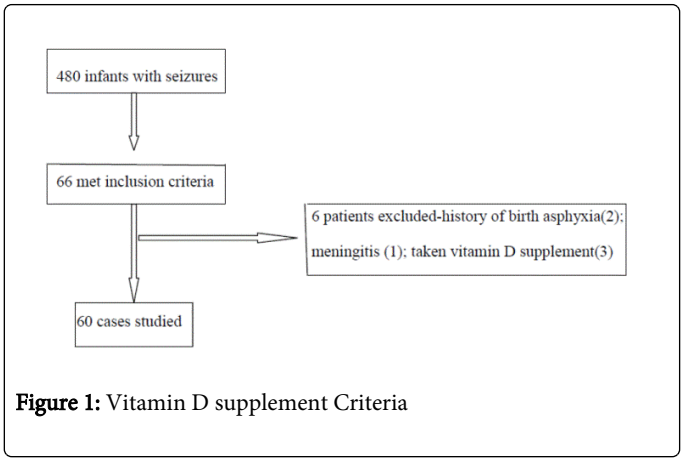

Figure 1: Vitamin D supplement Criteria

Bio-chemical parameters included in present study were serum calcium, serum phosphorus, serum ALP and most importantly serum 25 (OH)D. Mean serum 25 (OH)D was very low among cases (mean 28.79 ± 33.85) than controls (mean 47.62 ± 46.16) and this difference is highly significant ($P=0.008$). This means that hypocalcemic seizures were very likely to be associated with low serum vitamin D levels (<50 nmol/litre). Most of the infants with hypocalcemic fits (88.3%) were reported to have low serum vitamin D levels. Thus vitamin D deficiency appears to be a major risk factor for hypocalcemic seizures. These results were comparable to Mehrorta et al. study [13] that studied 60 hypocalcemic seizure infants along with their mothers and demonstrated high prevalence of hypovitaminosis D in these infants (90%) and their mothers (85%). However, vitamin D deficiency was also found to be prevalent in our control population (68.3% had low serum vitamin D levels). This was comparable to some studies on Indian infants [14] which reported vitamin D deficiency in 66.7% of healthy breast fed term infants at 3 months of age. The reason for this high prevalence of hypovitaminosis D in India may be related to decrease cutaneous synthesis owing to higher skin pigmentation and lower duration, as well as less surface area exposed to sun. This is due to greater coverage of body and lesser participation in outdoor activities. Intake of vitamin D is also inadequate as food items in India are not fortified and there is no policy of routine vitamin D supplementation in pregnant or lactating women and infants. Indian

diet is low in calcium and high in phytates which may contribute by causing secondary hyperparathyroidism [15].

In the present study, vitamin D deficiency was further classified based on concentration of serum 25(OH)D. Deficiency is found to be symptomatic in form of hypocalcemic seizures but the severity of deficiency does not have any relation with the occurrence of seizures in hypocalcemic infants.

Our study reported that low vitamin D levels were associated with increased serum ALP levels (>341 IU/litre). Another novel observation was a significant inverse relation between 25(OH)D and S.ALP in cases ($r=-0.213$, $p<0.05$) as well as controls ($r=-0.615$, $p<0.05$) which was comparable to Jain et al. [14]. It can be concluded that elevated S.ALP is a marker of vitamin D deficiency if liver pathology is excluded. However, Mehrotra et al. [13] found no significant correlation between vitamin D, calcium or ALP in study infants with hypocalcemic seizures.

To conclude, vitamin D deficiency is an important etiological factor for hypocalcemic seizures in infancy. Sunlight exposure for <30 minutes/week is a leading risk factor for development of vitamin D deficiency among infants. Elevated serum ALP can be a surrogate marker of vitamin D deficiency provided other causes of raised S.ALP are excluded. So, vitamin D supplementation can be considered as an adjuvant therapy in the management of hypocalcemic seizures along with use of intravenous and oral calcium.

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