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ARAŞTIRMA / RESEARCH

Characteristics of vitamin D deficiency in early infancy

Erken bebeklik döneminde D vitamini eksikliğinin özellikleri

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Abstract

Purpose: Vitamin D deficiency is a health problem in developing countries. This study aims to investigate the characteristics of children with vitamin D deficiency in early infancy.

Materials and Methods: Hundred and forty infants with vitamin D deficiency (mean age:3.5 ± 1.7 [0-6] months) and a control group of 200 healthy infants (mean age: 3.4 ± 1.7 [0-6] months) were included in the study. Serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone (PTH), and 25-hydroxyvitamin D (25(OH)D) levels were measured in the patient, control groups, and the mothers of the patients. In 38 patients, radiological findings were evaluated with knee and wrist radiographs. Thacher Rickets Severity Scoring (RSS) system was used for radiological evaluation of rickets severity.

Results: The most common (42%) complaints were respiratory symptoms, including cough, respiratory distress, and wheezing. The most common finding of physical examination was the rachitic rosary. Serum calcium (Ca++), alkaline phosphatase (ALP), 25(OH) vitamin D, and parathormone (PTH) levels were significantly different in the patient and the control groups. The mean Thacher radiological score of 38 patients was 3.1 ± 2.1 (0-8) points. The mother's dressing style of covering up the whole body, i.e., veiling, increased the infant's risk of vitamin D deficiency by 17.5 times.

Conclusion: Subtle clinical, laboratory, and radiological findings of vitamin D deficiency are detected in early infancy. Vitamin D deficiency should be considered primarily in infants with hypocalcemia whose mothers are less frequently exposed to sunlight due to geographical conditions and their preferred or imposed lifestyle.

Keywords:. Vitamin D deficiency, infant, maternal-fetal relationships, secondary hyperparathyroidism, thacher radiological score

Öz

Amaç: D vitamini eksikliği gelişmekte olan ülkelerde sağlık sorunu olmaya devam etmektedir. Bu çalışma erken bebeklik döneminde D vitamini eksikliği olan çocukların özelliklerini araştırmaktadır.

Gereç ve Yöntem: Çalışmaya, yaş ortalaması 3,5±1,7 (0-6) ay ve D vitamini eksikliği olan 140 infant ve kontrol grubu olarak yaş ortalaması 3,4±1,7 (0-6) olan 200 sağlıklı bebek alındı. Hasta ve kontrol grupları ile hastaların annelerinin serum kalsiyum, fosfor, alkalen fosfataz, paratiroid hormon ve 25 hidroksivitamin D düzeyleri ölçüldü. 38 hastada radyolojik bulgular diz ve el bileği grafileri ile değerlendirildi. Raşitizm şiddetinin radyolojik değerlendirilmesinde Thacher skoru kullanıldı..

Bulgular: En sık görülen şikayetler (%42) öksürük, solunum sıkıntısı, hırıltılı solunum gibi solunum yolu semptomları idi. Fizik muayenede en sık rastlanan bulgu raşitik rozary idi. Hasta ile kontrol grubu arasında serum kalsiyum (Ca), alkalen fosfataz (ALP), 25 (OH) D vitamini ve parathormon (PTH) değerleri arasında anlamlı fark vardı. Thacher radyolojik skoru incelenen 38 olgunun ortalama skoru 3,1±2,1 (0-8) puan idi.; Annenin tüm vücudunu kapatacak şekilde giyinmesinin, bebekte D vitamini eksikliği riskini 17,5 kat artırdığı görüldü.

Sonuç: Erken süt çocukluğu dönemindeki D vitamin eksikliğinin klinik, laboratuvar ve radyolojik bulguları silik olmaktadır. Yaşanan coğrafya ve yaşam tarzı nedeniyle güneş ışığına az maruz kalan annelerin çocuklarında hipokalsemi var ise öncelikle D vitamini eksikliği düşünülmelidir.

Anahtar kelimeler: Vitamin D eksikliği, bebek, maternal-fetal ilişkiler, sekonder hiperparatiroidizm, thacher radyolojik skoru

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INTRODUCTION

Vitamin D deficiency/insufficiency is a global health problem affecting more than one billion children and adults worldwide[1]. Vitamin D is essential for the active absorption of calcium and skeletal health. Inadequate vitamin D in infants leads to poor bone mineralization and, as a result, an increased risk of rickets[2]. Inadequate vitamin D intake in women of childbearing age, veiling, lifestyle, insufficient exposure to sunlight, and maternal vitamin D deficiency are the major risk factors for vitamin D deficiency in early infancy. Clinical and biochemical manifestations of vitamin D deficiency in early infancy may differ from those of classical rickets. Vitamin D deficiency in early infancy is usually characterized by severe hypocalcemic symptoms, including seizures, so it may be overlooked[3]. The hypocalcemic stage of the disease lasts longer, mostly in infants aged 2-9 months, probably due to insufficient PTH stimulation[4].

All guidelines agree that serum levels of 25-hydroxyvitamin D (25-OHD) <25 nmol/l (10 ng/ml) should be avoided at all ages[5]. Children with limited sun exposure should take vitamin D supplements. Regardless of the mother's vitamin D status, there is a significant positive relationship between afternoon sunlight exposure and vitamin D levels of the infants [6]. The association between rickets and latitude may be reflected in the risk of infants being exposed to insufficient sunlight, which does not allow adequate vitamin D biosynthesis in northernmost latitudes where solar radiation is less intense. The northeastern part of Turkey also has risky geographical conditions in this respect.

Vitamin D deficiency/insufficiency is more common in infants than pregnant/breastfeeding mothers. Low maternal 25(OH)D levels during pregnancy are significant risk factors for infant vitamin D deficiency. Although most breastfeeding mothers have normal vitamin D levels, breastfed infants may still be deficient in vitamin D[7].

Clinical, biochemical, and radiological findings of vitamin D deficiency in newborns indicate that they are less adaptable to this condition than older infants[8]. Most young infants diagnosed with vitamin D deficiency present with seizures, low dietary vitamin D intake, and their mothers' poor vitamin D reserves[3]. Evaluation of vitamin D status should be included in the workup of hypocalcemia in early infancy.

It has been observed that the characteristics of vitamin D deficiency in early infancy are different compared to other childhood periods, and there is little relevant data in the literature about this period. In this study, we aimed to examine the clinical and laboratory features and radiological findings of 0-6 month-old infants with vitamin D deficiency and determine the factors contributing to early diagnosis.

MATERIALS AND METHODS

This study was conducted prospectively between January 2004 and December 2005 in the city of Erzurum in northeast Turkey. One hundred and forty infants aged 0-6 months diagnosed with vitamin D deficiency (<25 nmol/L) and two hundred age-matched healthy infants with normal 25 hydroxyvitamin D (>25 nmol/L) levels (control group) were included in the study[9]. The local Ethics Committee approved this study of the Atatürk University Faculty of Medicine (April 02, 2004, 49; 71). Informed consent was obtained from the families of the children.

Sample

Atatürk University Faculty of Medicine, where the study was conducted, is a third-level health institution and receives referrals from the surrounding ten provinces. File reliability is ensured only by entering the attending physician's password into the system within the scope of the confidentiality of personal information. The researcher obtained the information relevant to the study from the mothers, and the attendant nurses collected the blood samples for biochemical analysis. A radiologist and the investigator performed the radiological evaluation. A total of two hours of sunlight exposure per week for a room was accepted as sufficient.

Inclusion and exclusion criteria from the study: The information of all children admitted to the hospital during the study period, and patients whose 25 (OH) D levels were measured was reviewed. All infants aged 0-6 months who met the inclusion criteria were enrolled in the study. Patients with chronic kidney disease, malabsorption, family history of rickets, preterm birth, or long-term use of anticonvulsants were excluded.

Biochemical tests

Serum levels of calcium, phosphorus, alkaline phosphatase, parathyroid hormone, and 25-hydroxyvitamin D levels of the patient and the control groups and mothers of the patients were measured. Serum 25 (OH) D levels were measured after 2 hours of incubation at room temperature using DPC Gamma-C12 Gamma Counter (DPC Cirrus Inc., a subsidiary of Diagnostic Products Corporation Los Angeles, CA 90045 USA) and BioSource 25OH-Vit.D3-Ria-CT kits (BioSource Europe SA Rue de I'Industrie, 8, B-1400 Nivelles, Belgium).

For the measurement of serum parathyroid hormone levels, two milliliters of blood without hemolysis were obtained after 7:00 AM and placed in an iced tube with EDTA. The plasma portion was separated from the blood cells and delivered to the laboratory in an ice tube. The original kits were used to measure serum PTH levels using the two-way chemiluminescence (immunometric assay) method. The assay was conducted using the Immulite 2000 brand hormone analyzer (Diagnostic Products Corporation Los Angeles, CA 90045 USA). Icteric or heavily contaminated samples were not included in the analysis. Lipemic samples were pretreated in lipoclear tubes, and intact PTH was measured after separating the lipid content from plasma.

Radiological evaluation

Radiological findings were evaluated in 38 patients using knee and wrist X-rays. Thacher radiographic scoring system was used for radiological evaluation of rickets severity[10]. The Thacher RSS scores were estimated based on the wrist and knee X-ray findings. A 10-point scale scores from zero (normal) to 10 points (severe) are set to assess the degree of metaphyseal fraying and cupping and the proportion of the growth plate affected. Both the researcher and an experienced radiologist determined radiological scores.

Statistical analysis

Power analysis was calculated using the post- hoc analysis method and G power 3.1.9.7 package. The study sample size was 140 patients, the margin of error was 0.05, and the power of the study was 1.00 percent. The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 15.0. Since all parameters were not normally distributed, median (IQR) values were reported. Therefore, non-parametric tests were applied to the study data. Differences between numerical value groups were investigated using the Mann-Whitney U test and the correlation between parameters using the Spearman correlation test. These tests determined the U value and Spearman correlation coefficient (r_s). In the statistical evaluation of the differences between categorical values, the chi-square values (χ^2) were compared using the chi-square test, and the absolute values with less than five cases were compared with the Fisher exact chi-square test. The correlations between parameters were investigated using the Spearman correlation analysis. Binary logistic regression analysis was performed to determine the risk factors for vitamin D deficiency. All the obtained results were evaluated at the significance level of $p < 0.05$ at a 95% confidence interval.

Binary logistic regression analysis was performed to determine the risk factors for vitamin D deficiency. Parameters that are thought to have an effect on vitamin D deficiency (gestational week of the infants at birth, the season when 25(OH)D was administered, the living place of the study participants, whether or not their rooms have gotten enough sunlight, or they received vitamin D replacements, or their mothers gave birth frequently, presence of comorbidities, mother's clothing style, and a history of seizure) were included in the regression model, and backward LR elimination method was applied.

RESULTS

Three hundred and forty infants, including 97 (69.3%) male, and 43 (30.7%) female patients with vitamin D deficiency and a control group of 200 healthy infants, were included in the study. The median weight (5100 [2350-9000] g), median height (58 [43-75] cm), and median head circumference (39 [32-56] cm) of the patients were as indicated. Although the height and head circumferences were comparable ($p = 0.271$ and $p = 0.055$) between groups, there was a significant difference between the study and the control groups regarding body weight ($p = 0.01$).

The most common complaints of the patients at admission were respiratory symptoms such as cough, respiratory distress, wheezing (42%), and gastrointestinal symptoms (36%). 18.6% of the patients were born in January, the month with the

highest delivery rate. In addition, 41.4% of hospital admissions occurred in the spring. In the control group, hospital admissions happened most frequently in the winter months with a rate of 36% which significantly differed from the patient group (χ^2 =12.539, p = 0.006).

The majority (57.9%) of the patients lived in the countryside, and 42.1% of them in the city. There was no statistically significant difference between the groups in this regard (χ^2= 1.340, p = 0.247).

Eighty-five (60.7%) patients lived in rooms with sufficient exposure to sunlight. This rate was higher (71%) in the control group (χ^2 = 3.926, p = 0.048).

There was no statistically significant difference between the study and the control groups regarding rates of exposure of infants to sunlight (p = 0.372), while exposure rates differed significantly for mothers of both groups (p<0.001). The median exposure time to sunlight was longer for mothers in the control group. The median length of exposure to sunlight was 1 hour per week in infants with vitamin D deficiency and 10 hours per week in their mothers.

Frequent delivery rates were defined as giving birth at intervals of less than two years which were comparable between both groups (χ^2= 0.909, p = 0.340). In addition, there was no difference between the study and control groups regarding breastfeeding (p = 0.746).

Based on the anamnesis of the patients, 98.6% of the mothers breastfed their children, and 5.7 % of them used vitamin D supplements. In addition, 93.6% of the mothers did not receive vitamin D supplementation during pregnancy. The seizure was the presenting symptom in 41.4% of the infants (Figure 1).

The most common physical examination findings were rachitic rosary (62.1%), craniotabes (49%), occipital alopecia (31.4%), and wrist enlargement (27.1%).

Serum phosphorus (P) levels were comparable in the study and control groups. However, there was a statistically significant intergroup difference in Ca^{++}, ALP, 25 (OH) D, and PTH values. In the study group, serum Ca^{++} and 25 (OH) D levels were lower; however, ALP and PTH levels were higher compared to the control group (Table 1). Infant 25(OH) D levels were correlated with maternal 25(OH) D levels (rs=0.360, p=0.000) (Figure 2).

In the radiological evaluation of wrist and knee X-rays, metaphyseal fraying was detected in 35%, cupping in 25.7%, and metaphyseal widening in 15.7% of the patients. The mean radiological score of 38 infants was 3.1 ± 2.1 (0–8) points. While mean radiological scores of the infants younger (1.7 ± 1.3 [0-4.5] pts) and older (4.3 ± 1. 9 [1–8]) pts) than three months were also estimated (Figure 3). Thacher scores were not correlated with serum P levels (r_s=-0.180, p=0.280).

Head-to-toe covered dressing style (i.e., veiling) of the mothers (covering hair, face, hands, arms, and legs), sweating history, and hospital admissions in summer months increased the risk of vitamin D deficiency by 17.5 times (p=0.01), 9.3 times (p<0.001), and 6.4 times (p< 0.001), respectively. The other risk factors were the partially covered dressing style of the mothers (covering hair, arms, and legs without face and hands) (p = 0.01), other comorbidities (p = 0.01), history of seizures (p = 0.012), and hospital admissions in winter months (p = 0.028). The results of logistic regression analyses are summarized in Table 2.

Table 1. Serum Ca, P, ALP, 25 (OH) D, and PTH levels of the study and control groups.

Parameters	Study Group (n = 140) Median (IQR:25-75)	Control Group (n = 200) Median (IQR: 25-75)	P
Ca^{++} (mg/dL)	7.0 (5.5–8.5)	9.3 (8.6-9.9)	**0.000**
P (mg/dL)	4.6 (3.7–5.7)	5.1 (4.1-5.8)	0.05
ALP (U/L)	899 (101–4267)	495 (292-813)	**0.000**
25(OH)D (nmol/L)	10.6 (0–25)	91.8 (59–178)	**0.000**
PTH (pg/mL)	197 (12–1940)	36 (20–85)	**0.000**

Ca: Calcium, ALP: Alkaline Phosphatase, 25(OH) D: 25 (OH) Vitamin D, PTH: Parathormone, IQR: Interquartile Range

Table 2. Multivariate logistic regression model of vitamin D deficiency.

Variables	P	Odds Ratio	Confidence Interval (95.0%) Lower	Upper
Mother's dressing style, covered from head-to-foot	.001	17.503	3.028	101.177
Sweating history	.000	9.283	4.718	18.266
Diagnosis in the summer season	.000	6.363	2.741	14.770
Mother's dressing style, partially covered	.001	4.458	1.804	11.021
Additional disease (non-rickets, comorbidity)	.001	2.798	1.496	5.232
Seizure	.012	2.204	1.193	4.072
Diagnosis in the winter season	.028	2.093	1.082	4.050
The mother's dressing style, Uncovered		1		
Diagnosis in the spring season		1		
Without vitamin D supplementation	.000	.149	.055	.405

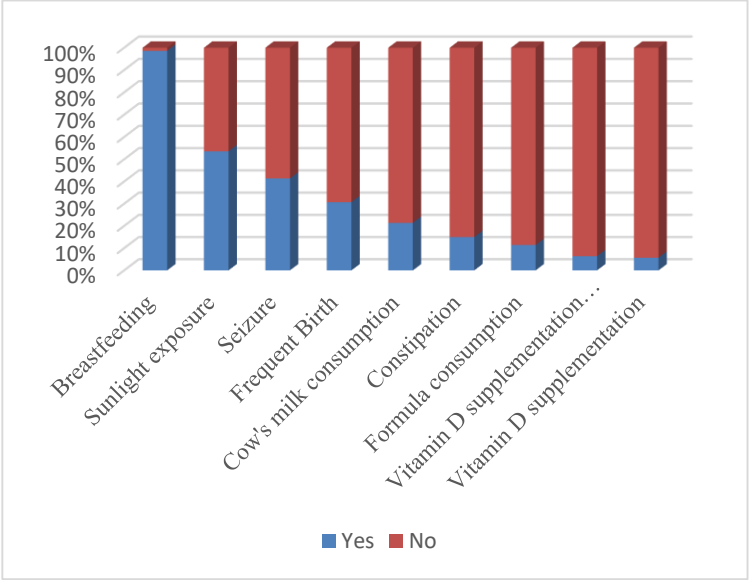

Figure 1. History of the infants with vitamin D deficiency.

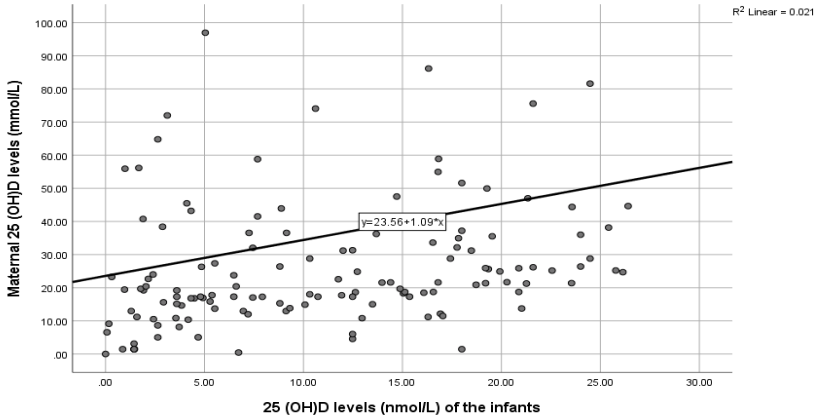

Figure 2. The correlation between the infants' serum 25 (OH) D levels and their mothers.

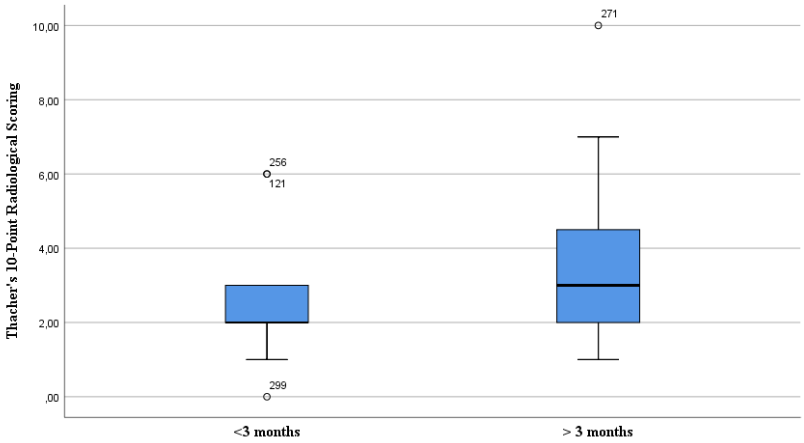

Figure 3. Radiological scores of the infants with vitamin D deficiency

DISCUSSION

The importance of body weight in the determination of vitamin D status is a newer and less well-known finding[11]. Obesity and vitamin D deficiency are one of the most emphasized issues in recent years[12]. Contrary to what is known regarding early infancy, it has been shown that low body weight is more frequently proportional to vitamin D deficiency.

The most common findings in our study were rachitic rosary (62.1%), craniotabes (49%), occipital alopecia (31.4%), and wrist enlargement (27.1%). The incidence rate of occipital alopecia, one of the rare findings of nutritional rickets, was higher than in other studies. Its underestimation may result from clinicians not paying enough attention to this finding during physical examination. It should be kept in mind that craniotabes, one of the classical findings of rickets, is a physiological characteristic finding in the first three months of life. Therefore, it would not be appropriate to give high-dose vitamin D supplements to infants younger than six months of age whose rickets were diagnosed based on craniotabes' presence. On the other hand, it is challenging to diagnose vitamin D deficiency with clinical findings in early infancy. Our study observed a rachitic rosary in 87 (62.1%) and wrist enlargement in only 38 (27.1%) of 140 infants.

Exposure to sunlight is not recommended for infants in the first six months of life. In our study, most of the infants were born in January (18.6%), October (12.9%), and November (12.1%). Considering the seasonal characteristics of the Erzurum province, it is not surprising that infants born in the mentioned months will not be exposed to sunlight sufficiently and are candidates for vitamin D deficiency. Consistent with the literature, 41.4% of the patients born in the spring were diagnosed with vitamin D deficiency. In addition, there was a statistically significant difference between the study and control groups regarding seasons of hospital admissions.

In the first eight weeks of life, infants' serum 25 (OH) D levels correlate with their mothers, and sunlight becomes more determinant in the following months[13]. Considering the relationship between maternal blood and breast milk vitamin D levels, a significant risk factor for clinical and subclinical vitamin D deficiency in early infancy is maternal vitamin D deficiency. Andiran et al. reported that the most critical risk factors for vitamin D deficiency in the neonatal period were maternal serum vitamin D levels below 25 nmol/L, veiling, being an untrained mother, and low socioeconomic level[14]. The present study has examined the epidemiological, clinical, laboratory, and radiological characteristics of 140 infants with serum 25 (OH) D levels below 25 nmol/L. We detected vitamin D deficiency (<25 nmol/L) in 120 (85.7%) of 140 mothers in the study group. We also observed a moderately significant

positive correlation between the vitamin D levels of the infants and their mothers (Figure 2). This result shows that infants in the 0-6 month age group need vitamin D supplementation from their mothers to prevent deficiency. Since 2011, the Ministry of Health in Turkey has recommended daily vitamin D supplementation of 1200 IU for mothers from the 12th week of pregnancy to the sixth month of delivery to prevent neonatal vitamin D deficiency[15].

Thacher et al. reported a mean radiological score of 4.8±2.7 points in a series of 123 cases aged 34–63 months with a mean 25(OH)D level of 14±6 ng/mL[10]. No studies in the literature have hitherto examined the Thacher radiological score in infants younger than six months of age. In our series, the mean Thacher score of 38 cases was 3.1±2.1 (0–8) points (Figure 3). There was a statistically significant difference between the radiological scores of infants younger and older than three months. The Thacher scoring method in early infancy will contribute to the diagnosis of vitamin D deficiency.

This study was conducted in Erzurum, one of Turkey's coldest and least sunny provinces. Besides the limited sunlight exposure in this geographic area, it is common for women to cover their bodies from the head-to foot for cultural reasons. Thus, the data reflects a locally characteristic feature of dressing and does not represent a tradition valid all over Turkey.

In conclusion, vitamin D deficiency is a public health problem. As emphasized in our study, vitamin D deficiency has a subtle clinical, laboratory, and radiological manifestations in early infancy. In regions where maternal vitamin D deficiency is common, vitamin D deficiency should be considered in infants younger than six months of age presenting with hypocalcemia, and serum 25(OH)D levels should be measured in case of need. In addition, measures should be taken to eliminate risk factors that may cause vitamin D deficiency in early infancy, mainly to prevent maternal vitamin D deficiency. Future studies on vitamin D deficiency in early infancy will also contribute to the literature on this little-known subject. This study was conducted in the years when vitamin D supplementation was not enforced legally, and studies investigating the differences in the rates of vitamin D deficiency/insufficiency in early infancy should be performed after the implementation of this regulation.

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