Vitamin D Deficiency in Early Infancy[1]

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ABSTRACT We analyzed the characteristics of young infants diagnosed with vitamin D deficiency in early infancy at 2 medical centers in Turkey. In this retrospective, cross-sectional study, the clinical, biochemical, and radiographic findings of infants who were diagnosed with vitamin D deficiency at <3 mo of age between May 2001 and May 2003 were reviewed. A total of 42 infants (27 boys and 15 girls) were diagnosed with vitamin D deficiency in the first 3 mo of life during this 2-y period. The age of infants at diagnosis was 60 ± 19 d (range 32–112 d). The majority (78.7%) presented with seizures. No skeletal deformities were detected clinically, and radiological findings were subtle. All infants had low serum calcium levels but serum phosphorous levels varied. Eight infants (19.0%) had low, 19 (45.3%) had normal, and 15 (35.7%) had elevated serum phosphorous levels. Serum 25-hydroxyvitamin D levels in those measured (29 infants and 15 mothers) were <37.5 nmol/L. Most infants (83%) were exclusively breast-fed without supplemental vitamin D, and none of the mothers were supplemented with vitamin D during pregnancy. All mothers had limited sunlight exposure and 33 of 42 mothers (78.6%) wore concealing clothing. The majority of young infants diagnosed with vitamin D deficiency present with seizures, have low dietary vitamin D intake, and mothers with poor vitamin D reserves. Evaluation of vitamin D status should be included into the workup of hypocalcemia in early infancy. Prevention of deficiency by supplementing pregnant women and infants who are exclusively breast-fed is essential. J. Nutr. 135: 279–282, 2005.

KEY WORDS: • *vitamin D deficiency* • *vitamin D* • *hypocalcemia*

Vitamin D deficiency and/or nutritional rickets remains prevalent in developing regions of the world and ranks among the 5 most common diseases in children. In Turkey, nutritional rickets was detected in 6% of children < 3 y old who were brought to an outpatient clinic for various reasons (1). The prevalence of nutritional rickets in developed countries also appears to be rising (2–7). Several lifestyle and environmental factors including inadequate exposure to sunlight, an increase in breast-feeding among women with dark skin, and a decrease in the number of physicians routinely prescribing vitamin D supplements for breast-fed infants are likely to be responsible for the high prevalence of vitamin D deficiency in developing countries as well as its resurgence in developed countries (8,9). Not only do these children often produce inadequate amounts of vitamin D, but many begin life with small stores as a result of maternal vitamin D deficiency.

Classically, nutritional rickets presents after 6 mo of age. In 2 recent reports with relatively large patient populations, the mean age at diagnosis was 14.6 and 20.2 mo and the youngest patients were 5 and 4 mo old, respectively (2,7). In our clinics, we recently observed an increase in the number of the patients with nutritional rickets who present in the first few months of life. Although there have been sporadic case reports of congenital rickets, the characteristics of early-onset rickets are not well described. Here, we report our experience with 42 children presenting with vitamin D deficiency in the first 3 mo of life and characterize their clinical, biochemical, and radiological features.

SUBJECTS AND METHODS

The medical records of all patients in whom a diagnosis of vitamin D deficiency and/or nutritional rickets was made at the pediatric endocrinology clinics of Ataturk University and Kocaeli University in Turkey between May 2001 and May 2003 were reviewed. The diagnosis of vitamin D deficiency and/or nutritional rickets was made on the bases of clinical features, radiological findings, and biochemical features including low serum Ca concentration, elevated alkaline phosphatase (ALP)[3] activity, and/or a low 25-hydroxyvitamin D [25(OH)D] level. Radiographic and laboratory abnormalities resolved completely in response to vitamin D therapy.

Information obtained from the patient's record included age at diagnosis, infant feeding history, history of vitamin D supplementation, supplemental food intake, and history of vitamin D supplementation of the mother during pregnancy, type of maternal clothing,

[1] Presented in poster form at the 43rd annual meeting of the European Society for Paediatric Endocrinology, 10–13 September, 2004, Basel, Switzerland (Hatun, S., Ozkan, B., Orbak, Z., Doneray, H., Cizmecioglu, F., Toprak, D. & Calikoglu, A. S. Vitamin D deficiency in early infancy).

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[3] Abbreviations used: ALP, alkaline phosphatase; 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone.

0022-3166/05 $8.00
Manuscript received 31 July 2004. Initial review completed 26 August 2004. Revision accepted 17 November 2004.

TABLE 1

Demographic characteristics of infants with nutritional rickets

Age of presentation,[1] *d*	60 ± 19 (32–112)
Gender (M:F), *n*	27:15
Exclusively breast-fed, *n*	37
Limited sunlight exposure,[2] *n*	23
Vitamin D supplemented, *n*	
Infants	0
Mothers	0
Maternal covered dress, *n*	33
Season of diagnosis	
Winter	10
Spring	19
Summer	4
Fall	9

[1] Mean ± SD (range), $n = 42$.
[2] $n = 23$ because sun exposure history was not available for the others.

clinical, biochemical, and radiographic findings, and maternal vitamin D status at the time of diagnosis and follow-up studies.

Serum 25(OH)D was measured using RIA according to the manufacturer's protocol (Biosource-Europe). This assay measures 25-hydroxycholecalciferol levels and has 84% cross-reactivity with 1,25 dihydroxycholecalciferol and 0.6% with 25-hydroxyergocalciferol. Intra- and interassay CVs were 7, and 7.7% respectively. Because 1,25 dihydroxycholecalciferol concentrations are 0.001 times the concentration of 25OH-cholecalciferol, and because vitamin D supplementation in Turkey is exclusively in the form of cholecalciferol, these cross-reactions were considered to be negligible. A 25(OH)D level < 37.5 nmol/L was considered to indicate vitamin D deficiency. Serum Ca, P, and ALP were measured using a Beckman CX-9 autoanalyzer. The serum PTH level was measured using the intact-PTH electrochemiluminescence immunoassay (Roche Intact PTH). The assay was conducted using a Roche Modular E 170®. The intra-and interassay CVs were 2.8 and 3.4%, respectively. The normal range for PTH is 1.47–7.58 pmol/L, and the lower detection limit of the assay was 0.127 pmol/L.

The statistical analysis of the study was conducted using SPSS 11.0. Continuous variables were presented as means ± SD (range). Pearson correlation analysis was performed on biochemical markers of rickets. Differences with $P < 0.05$ were considered significant.

The study was reviewed and approved by the institutional review board.

RESULTS

A total of 42 infants (27 boys and 17 girls) < 3 mo old and diagnosed with vitamin D deficiency and/or nutritional rickets were included in the analysis (Table 1). Their age was 60 ± 19 d (32–112 d). Most cases were diagnosed in winter and spring (69.0%). Thirty-five (83%) infants were exclusively breast-fed; 3 infants (7%) received additional cow's milk and 3 infants (7%) were fed cow's milk exclusively. Cow's milk and other dairy products are not enriched with vitamin D in Turkey. With the exception of 1 infant who received some formula, no affected infants were fed formula as a main source of nutrition or as a supplement. None of the infants were supplemented with vitamin D. Sunlight exposure was very limited for the 23 infants for whom a history of sun exposure was available. None of the 42 mothers were supplemented with vitamin D during pregnancy; 33 mothers (78.6%) wore clothes that concealed them from head to toe for religious reasons.

The most common presenting symptom was seizure; 33 infants (78.7%) presented with seizures, whereas the remaining nine (21.3%) were diagnosed with vitamin D deficiency and/or nutritional rickets as an incidental finding during other medical workups. Of note, 7 were hospitalized for severe respiratory symptoms. All of the infants had very subtle skeletal deformities including a minimal rachitic rosary and enlargement of the wrists. All but 2 infants had normal stature (length > 5th percentile), whereas 7 infants had inadequate weight gain (weight < 5th percentile). In radiological evaluation using wrist X-ray, all had mild metaphyseal irregularities and osteopenia. Because the radiologists were aware of the diagnosis, these comments should be interpreted cautiously.

All infants had low serum calcium levels (<2.2 mmol/L), and 25 had severe hypocalcemia (serum Ca levels <1.5 mmol/L) (**Table 2**). Serum ALP activity was elevated in most cases (78.0%). The typical hypophosphatemia of florid rickets was observed in only 8 infants (19.0%); 19 infants (45.3%) had normal, and surprisingly, 15 (35.7%) had elevated serum P concentrations. All infants had normal renal function. Serum PTH levels were measured in all infants. Secondary hyperparathyroidism was present in 24 infants (57.1%), whereas 18 (42.9%) had normal PTH levels despite low serum calcium levels. There was no correlation between serum P and PTH concentrations ($r = -0.08$, $P = 0.3$). Also, serum Ca and PTH concentrations were not correlated ($r = 0.14$, $P = 0.3$). Serum 25(OH)D levels were measured in 29 infants and in 15 mothers. All had low serum 25(OH)D levels (<37.5 nmol/L). Infant 25(OH)D levels were not correlated with maternal 25(OH)D levels ($r = 0.35$, $P = 0.1$). Infant 25(OH)D levels were correlated with Ca levels ($r = 0.37$, $P = 0.04$) and inversely correlated with P levels ($r = -0.45$, $P = 0.01$).

DISCUSSION

We report a large population of infants with overt clinical and biochemical evidence of vitamin D deficiency and/or nutritional rickets in the first 3 mo of life. Vitamin D deficiency was documented in the majority of patients with low serum 25(OH)D levels. The diagnosis of rickets was confirmed in the others with clinical, radiological, and biochemical findings including hypocalcemia, high ALP, and elevated PTH levels. This large patient population provided us with an opportunity to review the clinical and biochemical signs of

TABLE 2

Serum biochemistry of 42 infants with nutritional rickets

	n	Mean ± SD (range)	Category[1]	n (%)
Ca, *mmol/L*	42	1.45 ± 0.26 (0.86–2.1)	Low	42 (100)
			Normal	0 (0)
P, *mmol/L*	42	1.77 ± 0.57 (0.71–3.0)	Low	8 (19.0)
			High	15 (35.7)
			Normal	19 (45.3)
ALP, *U/L*	42	971 ± 598 (71–394)	High	33 (78.6)
			Normal	9 (21.4)
25(OH)D, *nmol/L*	29	17.5 ± 5 (10–27.5)	<37.5 nmol/L	29 (100)
			>37.5 nmol/L	0 (0)
Maternal 25(OH)D, *nmol/L*	15	19.5 ± 7.5 (7.5–32.5)	<25 nmol/L	15 (100)
			>25 nmol/L	0 (0)
Intact PTH, *pmol/L*	42	16.64 ± 17.48 (4.74–103)	High	28 (66.7)
			Normal	14 (33.3)

[1] Low, normal, and high categories for serum concentrations are relative to the normal range provided by the manufacturer (Abbott Reagent Kit) for Ca (2.2–2.7 mmol/L), P (1.25–2.1 mmol/L), and ALP (145–420 U/L). Serum 25(OH)D < 37.5 nmol/L is considered low (24).

vitamin D deficiency in early infancy and to assess the risk factors for the development of nutritional rickets in young infants.

Vitamin D sources in early infancy consist of transplacental stores, human milk, and cutaneous production via sunlight. Vitamin D and 25(OH)D cross the placenta during the last months of gestation (10) and establish vitamin D stores for the newborn. Maternal vitamin D status is important in determining the amount of vitamin D transported across the placenta during fetal life and therefore, the size of vitamin D reserves at birth. Although maternal and infant serum 25(OH)D concentrations are correlated during the first 8 wk of life (11), infants can no longer meet their vitamin D needs from fetal stores after several weeks. Breast-fed infants rely primarily on cutaneous synthesis to maintain a normal vitamin D status because the amount of vitamin D obtained through human milk is usually insufficient (12–60 U/L) (12,13). Therefore, vitamin D deficiency and/or nutritional rickets in early infancy is expected to be most prevalent in infants with limited sunlight exposure, limited dietary vitamin D intake, and/or mothers with poor vitamin D reserves.

Our results are, indeed, consistent with these expectations. For women with data available, maternal serum 25(OH)D levels were very low, confirming that maternal vitamin D deficiency is an important risk factor for vitamin D deficiency and/or nutritional rickets in early infancy. Maternal vitamin D deficiency is almost endemic in Turkey. Severe vitamin D deficiency was identified in 46–80% of pregnant women and nursing mothers in different regions of Turkey (14,15). None of the mothers were supplemented with vitamin D during pregnancy and food fortification with vitamin D is not practiced in Turkey. Under these circumstances, exposure to sunlight becomes crucial for vitamin D acquisition. Although it seems odd that sunlight exposure is limited in this geographic setting, cultural practices including traditional clothing (covered dress) for women and limited access to open space for pregnant and nursing women were found to be the primary reasons for inadequate sunlight exposure (14). However, maternal vitamin D deficiency is not unique to developing countries. The prevalence of hypovitaminosis D was found to be as high as 42.4% among African American and 4.2% in Caucasian women of reproductive age in the United States (16). This suggests that nutritional rickets in early infancy may become a more widespread problem in the near future unless strategies to ensure optimal vitamin D status for pregnant women and newborns are developed.

In the current study, infants with vitamin D deficiency and/or nutritional rickets and their mothers had a history of limited exposure to the sunlight. This is not surprising because infants in Turkey are traditionally kept indoors for the first 6 wk of life. In addition, the majority of the cases presented between late fall and early spring, a period of limited sunlight in Turkey.

Dietary vitamin D intake also was inadequate. Although primary care physicians in Turkey encourage vitamin D supplementation of infants beginning at 2 wk of age, no infants were supplemented, most likely because of poor access to health care. The vast majority of the infants were exclusively breast-fed. Although this is desired, it confirms that human milk does not provide sufficient vitamin D for infants in the first months of life, particularly when maternal vitamin D deficiency is present (12,13), and justifies the initiation of vitamin D supplementation in the immediate postnatal period.

The clinical presentation of nutritional rickets is stage dependent and most likely due to the duration of the vitamin D deficiency. Hypocalcemic symptoms determine the clinical spectrum in stage I (17–20). Skeletal deformities become obvious in stage II and worsen in stage III, when hypocalcemic symptoms also occur (2,7). Because the vast majority of our patients presented with hypocalcemic seizures and skeletal deformities were minimal, we believe that our population consisted mainly of patients with stage I nutritional rickets. Although hypocalcaemia in early infancy is commonly associated with functional or organic hypoparathyroidism, vitamin D deficiency and/or nutritional rickets should be considered in the differential diagnosis, and measurement of serum 25(OH)D levels should be included in the workup of hypocalcaemia.

The most recent vitamin D intake guidelines by the American Academy of Pediatrics promote vitamin D supplementation by recommending that all infants, including those who are exclusively breast-fed, have a minimum intake of 5 μg vitamin D/d beginning during the first 2 mo of life (21). Most of our patients had severe hypocalcemic symptoms before they were 2 mo old. We therefore propose that vitamin D supplementation should be started in the first days of life, and not later than age 2 wk.

Strategies should also be developed to prevent maternal vitamin D deficiency. Daily prenatal vitamin supplementation should be promoted, particularly in the 3rd trimester when the majority of placental vitamin D transfer to the fetus occurs. Maternal vitamin D supplementation should continue throughout lactation, preferably longer, particularly for those women who have insufficient sunlight exposure. The current recommended intake for vitamin D during pregnancy and lactation is 5–10 μg/d (22). However, there is evidence that doses $>$ 25 μg vitamin D/d are required to achieve a robust normal concentration of circulating 25(OH)D (23).

In conclusion, vitamin D deficiency and/or nutritional rickets can develop very early in infancy, and is usually characterized by severe hypocalcemic symptoms. Maternal vitamin D deficiency and limited sunlight exposure are the leading risk factors for the development of nutritional rickets in infants. Breast-feeding does not prevent rickets, particularly when the lactating mother is vitamin D deficient. Therefore, all pregnant and lactating mothers should be supplemented. Vitamin D supplementation of all infants should begin during the first days of life; this is particularly critical for infants who are exclusively breast-fed or given unenriched cow's milk.

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