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Secondary Prevention of Vitamin D-Deficiency Rickets

Jean T. Spence, MD, and Janet R. Serwint, MD

ABSTRACT. Reports of vitamin D-deficiency rickets and its associated morbidity continue among inadequately supplemented, dark-skinned breastfed infants. Despite the new vitamin D dietary guidelines, there remain significant numbers of unsupplemented breastfed infants. Here we report a case of subclinical vitamin D-deficiency rickets. This patient had biochemical and radiographic but not clinical evidence for rickets. We propose a new step of screening high-risk infants for subclinical rickets using wrist films paired with 25-hydroxyvitamin D levels. *Pediatrics* 2004;113:e70–e72. URL: <http://www.pediatrics.org/cgi/content/full/113/1/e70>; vitamin D deficiency, rickets, breastfeeding, subclinical, prevention.

ABBREVIATION. AAP, American Academy of Pediatrics.

Universal vitamin D supplementation for exclusively or predominately breastfed infants remains an area of controversy in the United States. The 1998 American Academy of Pediatrics (AAP) *Pediatric Nutrition Handbook* states that “dark-skinned infants will need a vitamin D supplement particularly if they are exposed to minimum amounts of sunlight.”¹ The literature describes multiple cases of dark-skinned breastfed infants who have developed rickets.^{2–7} The AAP and National Academy of Sciences now recommend a minimum daily intake of 200 IU of vitamin D.⁸ Here we present a 9-month-old breastfed African American patient who had not received the appropriate supplementation. Clinically, he had no signs of rickets, but laboratory and radiographic findings were diagnostic for vitamin D-deficiency rickets. Thus, we propose a new step of screening high-risk infants for subclinical rickets.

CASE REPORT

A 9-month-old African American male presented to an urban clinic for routine well-child care in March 2002. He was born in June and was exclusively breastfed until 6 months, when cereal, fruits, and vegetables were introduced. By 9 months, he was breastfeeding on demand and eating infant cereal, fruits, vegetables, and table foods but had received no vitamin or iron supplementation nor any infant formula. His mother reported no concerns. His development was normal for his age (could stand

holding on, sit unassisted, demonstrated thumb-finger grasp, and said mama, dada nonspecifically).

His examination was entirely normal with no skeletal abnormalities detected. His height was 70 cm (25th percentile for age), weight was 8.5 kg (25th percentile), and head circumference was 44.5 cm (10–25th percentile). He had been tracking consistently along the 25th percentile for the above parameters since birth.

A few weeks earlier, he had been seen for an urgent care visit. As part of his evaluation for fever without a source, a complete blood count was obtained and was remarkable for hemoglobin = 9.4 g/dL, hematocrit = 28%, mean corpuscular volume = 59 fL, and red cell distribution width = 17%, but no intervention was initiated. At the current health maintenance visit, his primary care provider was concerned about iron deficiency and possible vitamin D deficiency because this breastfed infant had not received iron or vitamin D supplementation. An alkaline phosphatase level was sent as a screening test and was markedly elevated at 1154 IU/L. This prompted a complete evaluation for rickets, which included the following: calcium = 9.7 mg/dL (reference range: 8.4–10.5); phosphate = 4.2 mg/dL (reference range: 3.2–6.3); parathyroid hormone = 187 pg/mL (reference range: 10–65); 25-hydroxyvitamin D level = 18 ng/mL (a level of <20 ng/mL is considered a deficient status); and 1,25-dihydroxyvitamin D level = 50 pg/mL (reference range: 27–71). Radiographs of the left wrist and left knee demonstrated definitive changes of rickets with metaphyseal flaring, irregularity, and widening of the physis without evidence of fracture.

Treatment was initiated with 50 mg of elemental calcium per kilogram per day and 4000 IU of ergocalciferol per day. After 3 months of treatment, his laboratory values normalized. His iron-deficiency anemia was treated with 3.5 mg/kg per day of elemental iron. After 3 months of iron therapy, his laboratory results included: hemoglobin = 11.7 g/dL, hematocrit = 34%, mean corpuscular volume = 70 fL, and red cell distribution width = 15%. Radiographs obtained at a clinic visit 3 months after the completion of treatment had normalized.

DISCUSSION

Rickets can cause significant morbidity including delays in growth and motor development, failure to thrive, short stature, skeletal deformities such as tibial bowing and splaying of the anterior ribs, tetany, seizures, and enamel defects.⁹ Reports in the medical literature focus on primary and tertiary prevention, but little is mentioned regarding secondary prevention. Primary prevention includes informing the public about the need for vitamin D supplementation of breastfed infants. Certainly this is the optimal mode of prevention, and the new AAP guideline that supports universal supplementation will facilitate this. Unfortunately, there exist breastfed infants who did not receive the appropriate supplementation and may not receive it in the future because of provider or parental barriers, making secondary and tertiary prevention crucial. Secondary prevention includes detecting and treating subclinical rickets before it progresses to clinical rickets. Tertiary prevention involves treating children with clinical rickets to prevent complications such as hypocalcemia and seizures.¹⁰

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Our case represents an opportunity for secondary prevention. Although the new AAP guideline should increase vitamin D supplementation rates, the clinician will continue to be confronted with cases in which the child did not receive adequate supplementation because of a lack of awareness on the part of the primary care provider or noncompliance on the part of the family. Our case makes the argument that simply initiating vitamin D supplementation in an unsupplemented breastfed infant without signs or symptoms of clinical rickets is inadequate, because subclinical rickets may already be present. Treatment doses of vitamin D for rickets are substantially higher than supplemental doses. We suggest that initiating vitamin D supplementation of our patient at the time of diagnosis would represent insufficient therapy, and we postulate that he would have subsequently presented with clinical rickets. There is a paucity of data in the literature concerning the development and progression of subclinical rickets. Prior case reports detail incidental diagnoses of rickets but not purposeful screening for subclinical rickets.

Joiner et al¹⁰ suggest targeted screening of high-risk groups (including unsupplemented African American breastfeeding infants, children who have low intakes of milk and dairy products, and infants who live in northern areas where colder winter weather precludes outdoor activities) with alkaline phosphatase levels to detect asymptomatic affected infants. Elevated alkaline phosphatase levels then would prompt additional investigation for subclinical vitamin D deficiency as in our case. However, 2 studies in children with subclinical rickets demonstrated that alkaline phosphatase levels did not correlate with the presence of metaphyseal changes. In the first study, only 9 of 22 children with radiograph-proven subclinical rickets (defined as loss of the metaphyseal definition of the radius and ulna) had elevated alkaline phosphatase levels.¹¹ Another study of 44 randomly selected infants from South Africa (race unspecified) found that a radiograph of the wrist was the most reliable means of confirming the presence of subclinical rickets.¹² Of the 44 infants, 7 were found to have radiograph changes consistent with rickets; only 2 of those with radiograph changes had elevated alkaline phosphatase levels, whereas all 7 had 25-hydroxyvitamin D levels <12 ng/mL. Although there was striking seasonal variation in the 25-hydroxyvitamin D level, the mean 25-hydroxyvitamin D concentration was significantly lower in those children with radiograph changes at the wrist (8.4 ng/mL) than in those with no radiograph abnormalities (30.6 ng/mL). Thus, Pettifor et al¹² concluded that a radiograph of the wrist is essential to confirm the presence of subclinical rickets, whereas the at-risk infant can be detected by measuring serum 25-hydroxyvitamin D levels.

The osseous changes of rickets can be recognized only after several months of vitamin D deficiency. It is unclear how many unsupplemented breastfed infants have laboratory or radiographic evidence for rickets, because we have not routinely screened them.

In a double-blind, placebo-controlled trial of 46 white infants followed from birth until 6 months of age, Greer and Marshall¹³ found no biochemical or clinical evidence for vitamin D deficiency in the unsupplemented, breastfed group, although their 25-hydroxyvitamin D levels (23.5 ng/mL) were significantly lower than the supplemented group (37 ng/mL). However, all infants in this study were white, and the mothers were given supplemental vitamin D during pregnancy. This study did not address the vitamin D status at 6 months of age for the unsupplemented breastfed infant whose skin is more darkly pigmented. Without adequate sun exposure, these infants produce lower vitamin D levels because of increased skin melanin.⁸ In the study by Peng and Serwint⁶, a 6-month-old, exclusively breastfed, African American girl and a 14-month-old African American girl were diagnosed with rickets by incidental radiograph findings. Other studies have shown that rickets may develop by 4 months of age and have highlighted the need to insure adequate vitamin D intake for dark-skinned infants who are exclusively breastfed.⁷

It is unclear how frequently subclinical rickets in unsupplemented breastfed infants progresses to clinical rickets and its associated morbidity. One patient in the study by Peng and Serwint⁶ presented with bony deformities and was diagnosed with clinical rickets at 30 months of age. This child had been exclusively breastfed for the first 6 months of life without supplementation and then was partially breastfed from 6 to 18 months of age. Infant drops containing 400 IU of vitamin D were prescribed from 6 to 18 months of age, although the level of compliance was not known. This child's progression to clinical rickets raises the question of how long he had subclinical rickets. Routine supplementation of 400 IU of vitamin D (as this child was prescribed beginning at 6 months of age) likely provides an inadequate dose of vitamin D for the child who has already developed subclinical rickets. Although no prospective longitudinal trial has been performed, we hypothesize that patients with subclinical rickets may progress to clinical symptoms and signs of rickets if not treated adequately. We propose that, by diagnosing and treating our patient's subclinical rickets through secondary prevention, we have averted his developing the morbidity associated with symptomatic rickets.

CONCLUSIONS

Given the paucity of data on infants with subclinical vitamin D-deficiency rickets, we support additional research on this topic. The recent guidelines from the AAP appropriately target primary prevention.⁸ Until these guidelines are broadly implemented, practitioners will still be faced with the problem of subclinical rickets. Symptomatic vitamin D-deficiency rickets can develop with failure to thrive, bowing of the legs, hypocalcemia, and seizures because of a lack of supplementation. Our case suggests that it may be prudent for the clinician to screen for subclinical vitamin D-deficiency rickets in inadequately supplemented infants by using wrist

radiographs paired with 25-hydroxyvitamin D levels. This may prevent significant morbidity while we work to improve the effectiveness of our primary prevention strategies with better education to health care providers and families.

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