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Vitamin D–Deficient Rickets in a Child With Cow's Milk Allergy

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This article describes the case of a 16-month-old Hispanic male toddler with cow's milk allergy living in northern California who was admitted to a children's hospital for weight loss and markedly elevated levels of serum alkaline phosphatase and parathyroid hormone. At a routine outpatient well-child visit, his mother expressed concern about a decrease in his appetite and activity level. A detailed diet history revealed that breast milk was his primary source of nutrition during his first year of life and he had not been given supplemental vitamins. With attempts to introduce cow's milk formula, he had developed a rash and swelling around the mouth. Shortly after his first birthday, his mother weaned him from breast milk and introduced unfortified rice milk as a palatable milk substitute. Upon admission he was pale and lethargic; his laboratory studies were remarkable for

elevated serum alkaline phosphatase and parathyroid hormone and low levels of phosphorus, 25-hydroxy-vitamin D, and ferritin. Lower extremity radiographic studies were consistent with rickets. After 5 weeks of therapy with vitamin D₃ and iron, his serum 25-hydroxy-vitamin D level normalized. Within 12 weeks following therapy, the child demonstrated significant clinical improvement, with resolution of growth failure and bone reossification. His activity level had returned to normal. This case emphasizes the importance of adequate vitamin D intake for children with special attention to those who might have nutrition deficiencies attributable to milk allergy. (*Nutr Clin Pract.* 2010;25:394-398)

Keywords: vitamin D; rickets; milk hypersensitivity

Nutrition-related rickets has been increasingly reported in the United States and other Western countries.¹⁻⁷ Most case reports are of infants who have been exclusively breastfed and have dark skin pigmentation. Milk allergy poses an additional risk factor for developing rickets.¹ In 2008, the American Academy of Pediatrics published new guidelines for vitamin D, recommending a minimum daily intake of 400 international units (IU) of vitamin D per day for all infants and children, including adolescents.² Our case demonstrates a common food allergy leading to inadequate intake of dietary sources of vitamin D in a light-skinned toddler in California. Cow's milk allergy is one of the most common allergies in infancy, with a prevalence of 1.9%-3.2%.³ The potential for nutrition deficiencies exists when parents substitute traditional cow's milk products with milk alternatives that are not adequately fortified with vitamin D and calcium. The problem may be exacerbated in children

who have been previously breastfed without receiving supplemental vitamin D. Lack of sun exposure, dark skin pigmentation, and the use of sunscreen may also compromise vitamin D status. Recognition of the importance of vitamin D for the normal development and growth of bones dates back to the 1600s, when Frances Glisson described the clinical and anatomical features of vitamin D–deficiency rickets.⁴ Until recently it was thought that vitamin D–deficiency rickets had been nearly eradicated in the United States, but reported cases in the literature have increased.⁸⁻¹¹ Even though there has been an increased awareness of the need for vitamin D in our diets, and fortification of milk products is standard in the United States, many milk substitutes do not meet the recommended daily allowances of vitamin D and calcium for growing children. Careful examination of a child's diet during regular pediatric visits is warranted to ensure adequate intake of vitamin D and prevention of rickets.

Case Report

A 16-month-old Hispanic male presented to our primary care clinic for a routine well-child visit in March 2009. Developmentally, he was attaining milestones and had

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Table 1. Results of Serum Chemical Laboratory Tests

Laboratory Variable	Reference Range for Children	Day of Admission	5 Wk After Treatment	10 Wk After Treatment
Phosphorus, mg/dL	4.0-6.0	3.2	5.6	6.5
Calcium, mg/dL	8.5-10.5	8.9	9.0	9.5
Alkaline phosphatase, units/L	<350	4,487	361	226
25-Hydroxy-vitamin D, ng/mL	10-55	3.5	27	—
Parathyroid hormone, pg/mL	10-80	193	54	—

started to walk at 10 months of age. Dietary history revealed that he was breastfed until 12 months of age. When he was 4 months old, pureed vegetables, pureed fruits, chicken broth, and soups were introduced. At 5 months, a cow's milk-based formula was introduced which, according to the parents, was not tolerated because of vomiting, diarrhea, urticaria, and swelling around the mouth. The mother discontinued the formula and continued breastfeeding until he was 12 months old. At 6 months of age, cereal was introduced. On several occasions during the first year of life he was offered milk-containing products such as cheese, yogurt, and ice cream; on each exposure, he developed a rash and swelling around his mouth. Therefore, the mother chose to discontinue all cow's milk products. At his 13-month well-child visit, the mother had been advised to try fortified soy milk as a substitute for cow's milk; because the patient refused to drink soy milk, the mother tried rice milk as an alternative. The mother was unaware of the nutrition content of the rice milk, which lacked both vitamin D and calcium. Medical history was remarkable for 6 episodes of upper respiratory tract infections, 2 episodes of oral thrush, a prolonged bronchiolitis exacerbation, and eczema in the first year of life. At his 16-month visit, the mother expressed concerns that the patient had been falling frequently, seemed to have a lack of energy, and was showing increased weakness since his previous well-child visit at age 13 months.

Physical examination revealed an inactive, pale toddler who appeared weak and had eczematous skin lesions. His weight was 9.8 kg (8th percentile) (Figure 1), length was 77.5 cm (17th percentile), and head circumference was 48 cm (66th percentile). Although his growth parameters appeared in the normal range for age, he was noted to have a weight loss of 0.5 kg and a deceleration in his height velocity. Weight had fallen off on the growth chart since his last well-child visit at 13 months of age, when his weight was 10.3 kg (38th percentile) (Figure 1). Clinical features of rickets present on examination were genu varum and mild frontal bossing. Laboratory studies revealed a markedly elevated serum alkaline phosphatase level of 4487 units/L, a low phosphorus level of 3.2 mg/dL, a normal calcium level of 8.9 mg/dL, a hemoglobin level of 10.9, a hematocrit level of 34.2, and a low ferritin level of 3 ng/mL (Table 1). The 25-hydroxy-vitamin D level was low

at 3.5 ng/mL and the parathyroid hormone level was markedly elevated at 193 pg/mL (Table 2). Anteroposterior radiographs of the knees revealed findings consistent with early signs of rickets including widening and irregularity of the metaphyses of the distal femur and proximal tibia (Figure 2). Radiologic evaluation of the chest revealed mild hyperinflation of the lungs and peribronchial cuffing, consistent with bronchiolitis.

The patient was prescribed 1000 IU/d of cholecalciferol per day, 1 mL/d of a multivitamin solution, and 60 mg/d of ferrous sulfate. It was recommended that his rice beverage be changed to an enriched formulation of rice milk (Rice Dream, The Hain Celestial Group Inc, Boulder, CO) containing vitamin D and calcium. He was subsequently referred to a pediatric allergist to evaluate the history of cow's milk allergy. Skin prick tests were positive for cow's milk and histamine but negative for soy and saline control. The mother was advised to avoid all products that contained cow's milk because the prick test confirmed a true allergy to cow's milk. One week after starting vitamin D treatment, the child was already showing signs of improvement. According to his mother, he did not seem weak anymore and was more physically active. After 5 weeks of treatment, his alkaline phosphatase and parathyroid hormone levels were greatly reduced, and the levels of phosphorus and 25-hydroxy-vitamin D were back to normal (Table 2). His ferritin level was normalizing (Table 1). Ten weeks after treatment, serum alkaline phosphatase and parathyroid levels were normal. Follow-up radiographic studies after 3 months of treatment showed significant improvement with increased ossification, especially of the knees and ankles (Figure 2). These findings were consistent with resolving rickets following therapeutic doses of vitamin D and nutrition supplementation.

Discussion

Rickets has been reported increasingly in the United States, with the main cause being vitamin D deficiency.¹² Not all vitamin D-deficiency cases have the classic features on presentation. It is known that vitamin D production in the skin can be limited by dark skin pigmentation, season, latitude, limited time spent outdoors, and the use

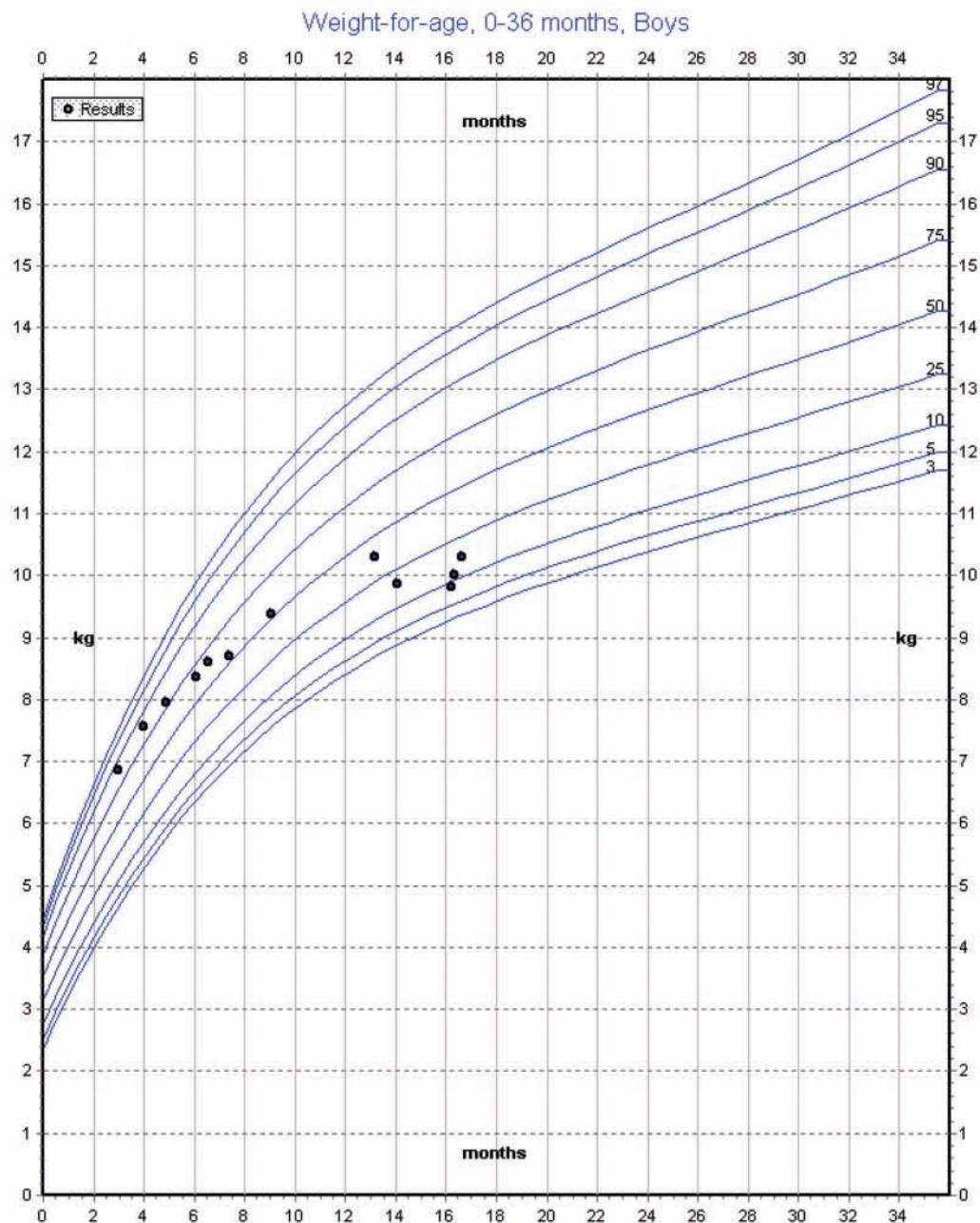


Figure 1. Growth chart illustrating significant growth decline from 13 to 16 months in a child with vitamin D–deficiency rickets.

of sunscreen.^{13,14} Our index case is a Hispanic male living in California who developed rickets despite having lighter skin pigmentation, living in a generally sunny state, and spending a good amount of time outdoors.

In this case, the child had been breastfed for the first year without receiving vitamin D supplementation. Allergy prevented him from taking vitamin D–fortified cow's milk upon weaning. He also had mild iron deficiency. Some data suggest that a child who has iron-deficiency anemia

may be at increased risk for vitamin D deficiency.^{12,13} When the child came to his routine well-child visit, his length and weight were normal but his growth curves were not, thus emphasizing the importance of evaluating growth charts at each visit.

Our case illustrates the risk of using milk alternatives that are not appropriate for growing children. This child was taking a rice beverage that did not contain vitamin D, contained only 2% of the daily recommended intake of calcium,

Table 2. Results of Hematologic and Coagulation Laboratory Tests

Laboratory Variable	Reference Range for Children	Day of Admission	10 Wk After Treatment
White blood cells, K/ μ L	6-17.5	14.8	8.8
Hemoglobin, g/dL	10.5-13.5	10.9	9.9
Hematocrit, %	33.0-39.0	34.2	30.1
Platelet count, K/ μ L	150-400	330	315
Mean corpuscular volume, fL	70-86	70.6	75.1
Red-cell distribution width, %	11.5-14.5	17.6	21.2
Red blood cells, MIL/ μ L	3.7-5.3	4.84	4.01
Mean corpuscular hemoglobin, pg	23-31	22.5	24.8
Mean corpuscular hemoglobin concentration, g/dL	30-36	31.9	33.0
Ferritin level, ng/mL	6-60	3	11
International normalized ratio	1.1	1.1	—
Prothrombin time, s	13.4	13.4	—
Partial thromboplastin time, s	32.7	32.7	—
Slide review		No significant white blood cell abnormalities	—
Morphology		Giant platelets, 1+ microcytosis	—

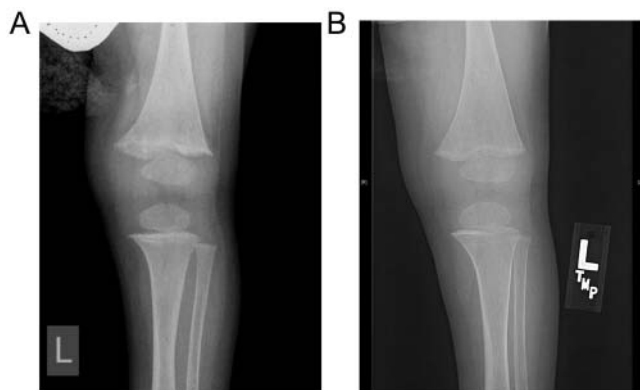


Figure 2. Imaging studies performed on admission and 3 months after vitamin D therapy in a 16-month-old Hispanic male. (A) Anteroposterior radiograph of the left knee showing mild findings of demineralization, fraying, and widening and irregularities of the metaphyses of the distal femur and proximal tibia. The zone of provisional calcification is ill defined. (B) Three months after therapy, marked improvement in the degree of ossification and healing of the knees. There is some mild metaphyseal widening about the left knee that is residuum of the changes due to rickets.

and contained only 1 g of protein per 8 oz (Table 3). In comparison, 8 oz of cow's milk contains 91 IU of vitamin D, 258 mg of calcium, and 7.31 g of protein. Enriched formulations of rice beverages and soy milk are more appropriate than unenriched rice milk because they are fortified with vitamin D and calcium. Pediatric healthcare providers should play a more active role to educate parents that not all products marketed as healthy are appropriate for children

and that parents should pay attention to the vitamin D, calcium, and protein content of these products.

There have been many advances in the understanding of vitamin D function and structure. Vitamin D comes in 2 forms: D₂ ergocalciferol, which is synthesized by plants, and D₃ cholecalciferol, which is synthesized by mammals after exposure to sunlight. Vitamin D₃ can be more than 3 times as effective as vitamin D₂ in raising serum 25-hydroxy-vitamin D concentrations and maintaining those levels for a longer time, and its metabolites have superior affinity for vitamin D-binding proteins in plasma.^{5,15} When 4000 IU of D₂ or D₃ were given to patients for 14 days, those receiving D₃ had blood levels 1.7 times higher than those receiving D₂.¹⁶ Likewise, a single dose of 50,000 IU of vitamin D₃ results in a significantly longer period of adequate blood levels than does the same dose of vitamin D₂.¹⁷ These results suggest that vitamin D₃ may be more potent in humans than the D₂ form.^{5,15,16,17} Vitamin D plays an important role in regulating calcium metabolism, which is essential for proper bone growth and remodeling.⁶ In addition, vitamin D deficiency has been associated with an increased susceptibility to infections and with a number of immune-mediated disorders such as asthma, eczema, type I diabetes, psoriasis, systemic lupus erythematosus, multiple sclerosis, and cancers.^{7,18-20}

In the last decade, several articles in the medical literature have supported a role for vitamin D in the modulation of the immune system and the prevention of infections, autoimmune diseases, and cancer.⁸⁻¹⁰ It is interesting to note that since the introduction of a well-balanced diet for our patient and treatment of his nutrition deficiencies, his eczema has improved and he has experienced fewer episodes of respiratory infections.

Table 3. Comparison of Nutrition Content of Different Milk Formulations

Nutrition Content (8 fl oz)	Whole Cow's Milk ¹	Rice Milk ²	Fortified Rice Milk ²	Fortified Soy Milk ³
Calories	150	120	120	100
Total fat, g	5	2.5	2.5	4
Cholesterol, mg	35	0	0	0
Sodium, mg	125	100	100	135
Total carbohydrates, g	11	24	23	8
Fiber, g	0	0	0	2
Sugars, g	11	11	10	4
Protein, g	8	1	1	7
Vitamin D, %*	25	0	25	25
Calcium, %*	30	2	30	35

*Percent Daily Values are based on a 2,000 calorie diet.

¹Clover Stornetta Farms, California

²Rice Dream, Hain Celestial, North America

³Soy Dream, Hain Celestial, North America

In summary, our case demonstrates that rickets should be considered in breastfeeding infants with failure to thrive and that infants with cow's milk allergy may be at increased risk for vitamin D deficiency. Rickets in children can be prevented with routine health maintenance surveillance and ongoing nutrition education by a multidisciplinary healthcare team including, but not limited to, physicians, dietitians, and nurses. Avoidance of cow's milk and milk products, with provision of alternative food choices, requires careful monitoring. Parents should be advised of nutrition adequacy and proper selection of appropriate foods and the importance of these foods especially during feeding transitions. It is imperative to review dietary history and educate parents about expected growth and development in children and adolescents. Healthcare professionals have a unique opportunity, particularly during health maintenance encounters, to play an integral role in the prevention and resurgence of preventable diseases such as rickets.

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