Hypocalcemia in Nonwhite Breast-Fed Infants

Vitamin D Deficiency Revisited

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Introduction

Vitamin D deficiency is an unusual but potentially dangerous condition in infants and children. Characterized by a complex derangement of calcium and phosphorus homeostasis, it often results in poor linear growth, defective mineralization of cartilage, and bone and skeletal deformities. In many cases the serum calcium concentration is normal or only slightly diminished at the time of initial evaluation. However, in some children vitamin D deficiency is recognized because of symptomatic hypocalcemia.

Although vitamin D deficiency was once quite common in the United States, it has been nearly eliminated since the introduction of vitamin D-fortified milk and dietary vitamin D supplements.1 As human breast milk contains very small amounts of vitamin D and vitamin D metabolites,2,4 oral vitamin D supplements have been recommended for breast-feeding babies. More recently, several studies of white infants have suggested that vitamin D supplementation may not be necessary if nursing mothers have adequate levels of vitamin D.5,7 Over a one-year period from April 1989 to March 1990, we evaluated five nonwhite breast-fed infants who had hypocalcemia due to vitamin D deficiency. We present their histories as a reminder that nonwhite breast-feeding infants are at particular risk for vitamin D deficiency and to emphasize the importance of ensuring that all breast-feeding infants receive adequate vitamin D.

Case Histories

The clinical presentations of the five subjects are summarized in Table 1. All subjects were solely breast-fed without vitamin D supplementation. None of them had a history of gastrointestinal or renal disease. The nutritional status of the mothers was normal except for the mother of patient 2. She had a history of poor nutrition during pregnancy and demonstrated biochemical evidence of vitamin D deficiency, characterized by a subnormal serum concentration of 25-hydroxyvitamin D (7 ng/mL), at the time of her son’s evaluation.

In three of the children (patients 1, 2, and 3), grand mal seizures were the initial clinical manifestation of hypocalcemia. Patient 5 came to medical attention because of fever and dehydration. Patient 4 had a one-day history of fever, cough, and vomiting and died of cardiorespiratory arrest despite attempted resuscitation. Radiographic studies in the emergency room showed pulmonary edema, cardiomegaly, and ascites, indicating the possibility of an underlying cardiomyopathy. No autopsy was performed. Hence, we were not able to determine the cause(s) of death in this infant.

Physical signs of rickets were variable in the five patients. Patient 1 had frontal bossing, widening of the wrist, tibial torsion, and rachitic rosary. Patient 2 had frontal bossing and craniotabes. Patients 3 and 4 had widening of the wrist. By contrast, patient 5 had craniotabes, rachitic rosary, widening of the wrist and ankle, tibial torsion, and hip rotation.
Patients 1 to 3 had evidence of mild rickets in radiographs of long bones. Patients 1 and 2 had ulnar cupping and mild osteopenia. Patient 3 had widening and flaring of the metaphysis in the distal radius and ulna in addition to the findings observed in patients 1 and 2. By contrast, patients 4 and 5 had radiographic evidence of severe osseous deformities. Patient 4 had striking cupping and flaring of the metaphysis in the radius and ulna, with coarse trabecular architecture, cortical tunneling, and subperiosteal new bone formation. There was also increased curvature of the neck of each radius. In addition, there was marked widening of the epiphyseal plates in the hips and knees. Patient 5 had metaphyseal cupping, splaying, fraying, and osteopenia.

Table 2 shows the initial laboratory evaluation in the five patients. Serum concentrations of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were determined by SmithKline Beecham (Philadelphia, PA). Serum concentrations of intact parathyroid hormone (PTH) were determined by immunoradiometric assay (Allegro Intact PTH Irma Kit, Nichols Institute, San Juan Capistrano, CA). Four patients had subnormal concentrations of serum calcium, whereas patient 5 had a borderline level. The serum concentration of

### Table 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (months)</th>
<th>Chief problem</th>
<th>Month</th>
<th>Race</th>
<th>Height percentile</th>
<th>Weight percentile</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>Seizure</td>
<td>April</td>
<td>Black</td>
<td>50th</td>
<td>50th</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>Seizure</td>
<td>May</td>
<td>Black</td>
<td>50th</td>
<td>75th</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>Seizure</td>
<td>February</td>
<td>Black</td>
<td>50th</td>
<td>50th</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>Respiratory arrest</td>
<td>February</td>
<td>South Indian (Asian)</td>
<td>ND</td>
<td>25th</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>Fever / dehydration</td>
<td>February</td>
<td>Black</td>
<td>3rd</td>
<td>5th</td>
</tr>
</tbody>
</table>

ND = Not done

### Table 2

<table>
<thead>
<tr>
<th>Subject</th>
<th>Ca (mmol/L)</th>
<th>PO₄ (mmol/L)</th>
<th>Mg (mmol/L)</th>
<th>Alk phos (µkat/L)</th>
<th>PTH (pg/mL)</th>
<th>25(OH) vit D (nmol/L)</th>
<th>1,25(OH)₂ vit D (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.62</td>
<td>1.0</td>
<td>0.70</td>
<td>15.1</td>
<td>193</td>
<td>&lt;10</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>1.37</td>
<td>2.0</td>
<td>0.74</td>
<td>14.4</td>
<td>398</td>
<td>10</td>
<td>140</td>
</tr>
<tr>
<td>3</td>
<td>1.12</td>
<td>1.9</td>
<td>0.62</td>
<td>7.8</td>
<td>60</td>
<td>10</td>
<td>140</td>
</tr>
<tr>
<td>4</td>
<td>1.12</td>
<td>2.4</td>
<td>0.58</td>
<td>12.8</td>
<td>941</td>
<td>10</td>
<td>25</td>
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<tr>
<td>5</td>
<td>2.04</td>
<td>0.9</td>
<td>—</td>
<td>50.0</td>
<td>783</td>
<td>&lt;5</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

Normal values: Ca 2.10–2.70 mmol/L, PO₄ 1.0–1.5 mmol/L, Mg 0.7–1.0 mmol/L, Alk phos 1.0–2.5 µkat/L, PTH 30–60 pg/mL, 25(OH) vit D 30–125 nmol/L, 1,25(OH)₂ vit D 50–150 pmol/L.

Alk phos = alkaline phosphatase; PTH = Parathyroid hormone.
ionized calcium corresponded to the total calcium concentration in all patients (data not shown). Serum concentrations of 25-hydroxyvitamin D were subnormal in all subjects. Serum concentrations of alkaline phosphatase and PTH were markedly elevated in four patients but borderline in patient 3. Serum concentrations of 1,25-dihydroxyvitamin D were normal in three patients (1, 2, and 3).

Hypocalcemia was treated with intravenous calcium gluconate in patients 1, 2, and 3. Patients 1, 2, 3, and 5 received a short course of oral calcium lactate and were treated with daily oral vitamin D for three to four weeks (ergocalciferol; total dose = 250,000 to 300,000 units). Table 3 demonstrates normalization of serum calcium and phosphate one month after treatment. Levels of PTH, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D showed appropriate responses to therapy.

Discussion

The requirement for vitamin D supplementation for breast-feeding infants during the first year of life remains a topic of considerable interest and controversy. The 1980 report by the American Academy of Pediatrics on vitamin and mineral supplements states that vitamin D supplementation may be necessary for the breast-fed infant if the mother’s vitamin D nutrition has been inadequate or if the infant does not benefit from adequate ultraviolet light exposure. Nutritional rickets has been well-documented in nonwhite infants who are exclusively breast-fed. Several risk factors for vitamin D deficiency were present in the infants described in this report. First, all infants received only breast milk, which is considered a poor source of vitamin D. Second, the infants that we evaluated were dark-skinned. Nonwhite infants are at particular risk because their dark skin reduces the ability of ultraviolet light to radiate sterols into vitamin D.

Furthermore, four of the infants we evaluated were born in the late summer or early fall and therefore had limited exposure to ultraviolet radiation during the first few months of life. Their age at presentation is also fairly typical of hypocalcemia due to vitamin D deficiency, as it may take four to six months for the stores of vitamin D present at birth to decline to critically low levels. The patient who presented with hypocalcemia at 3 months appeared to have congenital vitamin D deficiency stemming from inadequate maternal nutrition.

By contrast, studies by Greer et al have shown that white breast-fed children who had low serum 25-hydroxyvitamin D concentrations at 12 weeks attained normal levels of 25-hydroxyvitamin D by 6 months without vitamin D supplementation. Roberts et al found normal levels of 25-hydroxyvitamin D in breast-fed children at 16 weeks. More recently, Greer and Marshall documented normal bone mineral content and normal serum levels of PTH, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D in a similar group of white breast-fed infants.

Vitamin D deficiency was documented in our patients on the basis of low serum levels of 25-hydroxyvitamin D, elevated serum levels of alkaline phosphatase and PTH, radiographic evidence of rickets, and a rapid response to vitamin D therapy. Normal concentrations of 1,25-dihydroxyvitamin D were observed in three of our patients.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Ca (mmol/L)</th>
<th>PO₄ (mmol/L)</th>
<th>Alk phos (µkat/L)</th>
<th>PTH (pg/mL)</th>
<th>25 (OH) vit D (nmol/L)</th>
<th>1,25(OH)₂ vit D (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.64</td>
<td>2.50</td>
<td>5.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>2.60</td>
<td>2.10</td>
<td>7.4</td>
<td>59</td>
<td>120</td>
<td>360</td>
</tr>
<tr>
<td>3</td>
<td>2.48</td>
<td>2.20</td>
<td>3.7</td>
<td>14</td>
<td>575</td>
<td>335</td>
</tr>
<tr>
<td>5</td>
<td>2.44</td>
<td>1.75</td>
<td>14.7</td>
<td>22</td>
<td>525</td>
<td>290</td>
</tr>
<tr>
<td>Normal values</td>
<td>2.00-</td>
<td>1.20-</td>
<td>2.5-</td>
<td>10-</td>
<td>25-</td>
<td>50-</td>
</tr>
</tbody>
</table>

Alk phos = alkaline phosphatase; PTH = parathyroid hormone

Table 3
and have, in fact, been well-documented in patients with vitamin D deficiency. The explanation for hypocalcemia despite normal levels of 1,25-dihydroxyvitamin D is unknown.

One infant (patient 3) had an inappropriately low concentration of serum PTH and a minimal elevation of serum alkaline phosphatase. This baby possibly had a combination of vitamin D deficiency and mild hypoparathyroidism. Skeletal films obtained one week after the initiation of therapy showed sclerosis in metaphysial margins compatible with healing rickets. Hanukoglu et al. recently reported a patient with a similar clinical presentation and suggested that the hypoparathyroidism in the patient they studied was due to maternal hyperparathyroidism. The etiology of the transient hypoparathyroidism in our patient is unknown, but serum calcium levels have remained normal for nine months after treatment was discontinued.

In 1980, the American Academy of Pediatrics recommended that "when climatic and social conditions interfere with radiation of vitamin D precursors in the skin, breastfed infants should be supplemented with 400 IU of vitamin D daily." Comparing the risk of vitamin D supplementation and the risk of nutritional rickets, Finberg recommended routine daily supplements of vitamin D for breastfed infants. More recently, the Academy recommended vitamin D supplementation for breast-fed infants "if it is suspected that the mother's vitamin D status is not optimal." Our report emphasizes the importance of vitamin D supplementation in infants at risk for vitamin deficiency. In particular, cases such as these reemphasize the need for vitamin D supplements in nonwhite breast-feeding infants.

**Acknowledgments**

We thank Ms. Kathy Klein for her secretarial assistance.

**REFERENCES**