

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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Case 3-2009: A 9-Month-Old Boy with Seizures

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PRESENTATION OF CASE

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Dr. Bronwen C. Carroll (Pediatrics): A 9-month-old boy was admitted to this hospital because of a generalized seizure and a bulging fontanelle.

The patient was reportedly well until 3 days before admission, when nasal congestion developed, and he was thought to have a low-grade fever. On the day of admission, two episodes of watery diarrhea occurred. His mother noted that his skin felt warm and the fontanelle was bulging. He was sleeping when jerking movements of the arms and legs began, lasting approximately 2 minutes, that were associated with fecal incontinence but no vomiting. After the seizure, he was limp, unresponsive, and apparently not breathing. Emergency medical services were called; on arrival, rapid spontaneous respirations were noted. The patient was transported by ambulance to another hospital. En route, generalized tonic-clonic activity occurred, and diazepam was administered per rectum. Seizure activity abated for a few minutes and then recurred. He arrived in the emergency department approximately 40 minutes after the initial onset of seizure activity.

On examination, tonic-clonic movements were present. The temperature was 39.9°C, the blood pressure 116/52 mm Hg, the pulse 160 to 170 beats per minute, the respiratory rate 60 to 80 breaths per minute, and the oxygen saturation more than 95% while he was receiving 100% inspired oxygen by means of a nonrebreather mask. The patient was intermittently responsive to pain. The anterior fontanelle was large and bulging but not tense. The pupils were 2 mm in diameter and constricted slightly on exposure to illumination. There was conjugate gaze, and intermittently the eyes deviated to the left. There was green-liquid stool in the diaper. An analysis of arterial blood revealed a pH of 7.37, a partial pressure of carbon dioxide of 29 mm Hg (reference range, 35 to 45), a partial pressure of oxygen of 164 mm Hg (reference range, 70 to 95), and a bicarbonate level of 16 mmol per liter (reference range, 22 to 27). Urinalysis revealed a pH of 5.0, a urobilinogen level of 0.2 Ehrlich unit per deciliter, and rare white cells; the urine was positive for ketones (+), protein (+), and bacteria (3+) and was otherwise normal. Other laboratory-test results are shown in Tables 1 and 2. Lorazepam, fosphenytoin, and additional diazepam were administered; tonic-clonic movements continued, with grunting and chest retractions. Fentanyl and rocuronium were administered, the trachea was intubated, and then ceftriaxone was administered. A bolus of normal saline with

Table 1. Results of Hematologic and Coagulation Laboratory Tests.*

Variable	Reference Range, Infants†	Day of Admission to Other Hospital	On Admission to This Hospital
Hematocrit (%)	33.0–39.0	30.6	28.9
Hemoglobin (g/dl)	10.5–13.5	9.8	9.5
White-cell count (per mm ³)	6000–17,500	11,090	7,000
Differential count (%)			
Neutrophils	17–49	40.0 (ref 20.0–50.0)	81
Lymphocytes	67–77	18.0 (ref 42.0–76.0)	5
Monocytes	4–11	7.0 (ref 3.0–7.0)	1
Basophils	0–3	1.0 (ref 0.0–1.0)	0
Band forms	0–10	34.0 (ref 0.0–7.0)	13
Reticulocyte count (%)	0.5–2.5		0.7
Red-cell morphology		1+ anisocytes, few schistocytes, 2+ microcytes, 1+ hypochromatocytes, 1+ burr cells, few polychromatocytes	2+ anisocytes, 2+ hypochromatocytes, 3+ microcytes
Platelets (per mm ³)	150,000–450,000	321,000	223,000
Mean corpuscular volume (μm ³)	70–86	59.9	61
Mean corpuscular hemoglobin (pg/red cell)	23.0–31.0	19.2	20.0
Mean corpuscular hemoglobin concentration (g/dl)	30.0–36.0	32.0	32.7
Red-cell distribution width (%)	11.5–16.0	21.5	19.3
Activated partial-thromboplastin time (sec)	22.1–34.0		86.3; 40.9 after heparinase
Prothrombin time (sec)	10.3–13.2		17.2; 15.8 after heparinase
International normalized ratio			1.6; 1.4 after heparinase
Fibrinogen (mg/dl)	150–400		299
ABO blood type			O-positive, negative antibody screen
Hemoglobin (%)			
A	>96.0		58.1
A2	1.8–3.5		4.3
F	<2.0		2.8
S	0.0		34.8
D-Dimer (ng/ml)	<500		2,083
Erythrocyte sedimentation rate (mm/hr)	0–17		19

* Ref denotes reference range.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital for newborns and infants are derived from a combination of published normal ranges and internal data for these age groups.

calcium gluconate was given intravenously. Seizure activity ceased. A chest radiograph revealed opacification in the right upper lobe, thought to represent atelectasis. Specimens of blood and stool were cultured. The patient was transferred to this hospital by helicopter. En route, calcium gluconate, fentanyl, and lorazepam were administered, and a nasogastric tube was inserted. No

seizure activity was observed. The patient arrived approximately 3 hours after the onset of seizures.

The patient was born at 36 weeks of gestation; his parents had immigrated to the United States from East Africa 2 years earlier. At birth, the weight (3515 g), length (50.5 cm), and head circumference (35.5 cm) were at the 50th percentile; at 6 months, the weight (7.6 kg) and length

Table 2. Results of Serum Chemical Laboratory Tests.*

Variable	Reference Range, Infants†	Day of Admission to Other Hospital	On Admission to This Hospital
Glucose (mg/dl)	70–110	217	268
Sodium (mmol/liter)	135–145	133	136
Potassium (mmol/liter)	3.4–4.8	3.9	3.3
Chloride (mmol/liter)	98–106	106	105
Carbon dioxide (mmol/liter)	22.0–27.0	16 (ref 20–28)	17.4
Urea nitrogen (mg/dl)	5–20	10	10
Creatinine (mg/dl)	0.3–1.0	0.4	0.4
Total bilirubin (mg/dl)	0.0–1.0		0.2
Direct bilirubin (mg/dl)	0.0–0.4		0.1
Total protein (g/dl)	6.0–8.3		6.2
Albumin (g/dl)	3.3–5.0		3.9
Globulin (g/dl)	2.6–4.1		2.3
Phosphorus (mg/dl)	4.5–6.7	3.3	3.0
Magnesium (mg/dl)	1.7–2.4	2.3	2.3
Calcium (mg/dl)	8.5–10.5	6.2 (ref 8.8–10.8)	6.2
Calcium, ionized (mmol/liter)	1.14–1.30	0.86	0.94
Alkaline phosphatase (U/liter)	15–350		970
Aspartate aminotransferase (U/liter)	9–80		63
Alanine aminotransferase (U/liter)	10–55		13
Lactic acid (mmol/liter)	0.5–2.2	2.1 (ref 0.5–2.0)	1.1
Lipase (U/dl)	1.3–6.0		1.7
Amylase (U/liter)	3–100		89
Ammonia (μ mol/liter)	12–48		18

* Ref denotes reference range. To convert the values for glucose to millimoles per liter, multiply by 0.0555. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for phosphorus to millimoles per liter, multiply by 0.323. To convert the values for magnesium to millimoles per liter, multiply by 0.4114. To convert the values for calcium to millimoles per liter, multiply by 0.25. To convert the values for ammonia to micrograms per deciliter, divide by 0.587.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital for newborns and infants are derived from a combination of published normal ranges and internal data for these age groups.

(66 cm) remained at the 50th percentile. Results of newborn screening tests were normal, except for the presence of hemoglobins F, A, and S, consistent with sickle cell trait. The patient had met developmental milestones, including crawling, pulling himself to stand, speaking “mama,” and demonstrating adequate pincer grasp for his age. He was reported to have been exclusively breast-fed, with no vitamin supplementation, until approximately 3 weeks before admission, when breast-feeding was discontinued and milk-based formula reconstituted with water and rice cereal were begun. There was no recent trauma, unusual ingestion, travel, exposure to animals, or

contact with sick persons. Liquid multivitamins had been prescribed; he had no allergies to medications. The child had attended well-child visits and received routine immunizations. He lived with his parents and four siblings and was cared for at home by his mother. There was no family history of seizures or other known hereditary disorders.

On examination, the patient was sedated, unresponsive, and intubated. The temperature was 37.6°C, the blood pressure 113/58 mm Hg, the pulse 123 beats per minute, the respiratory rate 20 breaths per minute, the length 71 cm (50th percentile), the estimated weight 8 kg (10th per-

centile), and the head circumference 48 cm (97th percentile). There was frontal bossing with no dysmorphic features; the fontanelles were wide open and full. There was a reducible umbilical hernia; the remainder of the examination was normal. An analysis of arterial blood revealed a pH of 7.29, a partial pressure of oxygen of 156 mm Hg, and a partial pressure of carbon dioxide of 36 mm Hg while the patient was breathing 40% inspired oxygen; other test results are shown in Table 1. A central venous catheter was placed in the right femoral vein. Electrocardiography revealed sinus tachycardia but was otherwise normal. A chest radiograph revealed atelectasis of the right upper lobe and perihilar interstitial opacities.

Vancomycin, dexamethasone, acyclovir, ceftriaxone, calcium gluconate, fosphenytoin, midazolam, fentanyl, and ranitidine were administered, and a feeding tube was placed. A radiograph of the abdomen revealed mildly distended loops of small bowel, a gas-containing nondilated colon, and no evidence of bowel obstruction or masses. Computed tomography (CT) of the brain was normal.

Additional diagnostic tests were performed.

DIFFERENTIAL DIAGNOSIS

Dr. Michael F. Holick: May we see the imaging studies?

Dr. Ruth Lim: A chest radiograph (Fig. 1A) revealed opacification of the right upper lobe, which could represent atelectasis or aspiration in the context of a seizure. Mild perihilar interstitial opacities could be the result of low lung volumes or mild inflammation of the airways. An abdominal radiograph revealed loops of bowel that were distended with gas, without evidence of bowel obstruction or mass. CT of the head showed no evidence of hydrocephalus, intracranial hemorrhage, mass lesion, or increased intracranial pressure; a three-dimensional CT surface reconstruction of the skull (Fig. 1B) revealed an enlarged anterior fontanelle and frontal bossing (Fig. 1C, arrow).

Dr. Holick: This 9-month-old breast-fed infant presented with a seizure after a few days of nasal congestion, diarrhea, and possible fever. Examination showed a bulging fontanelle and frontal bossing, and the results of laboratory tests showed hypocalcemia, hypophosphatemia, and an elevated alkaline phosphatase level. To arrive at a diag-

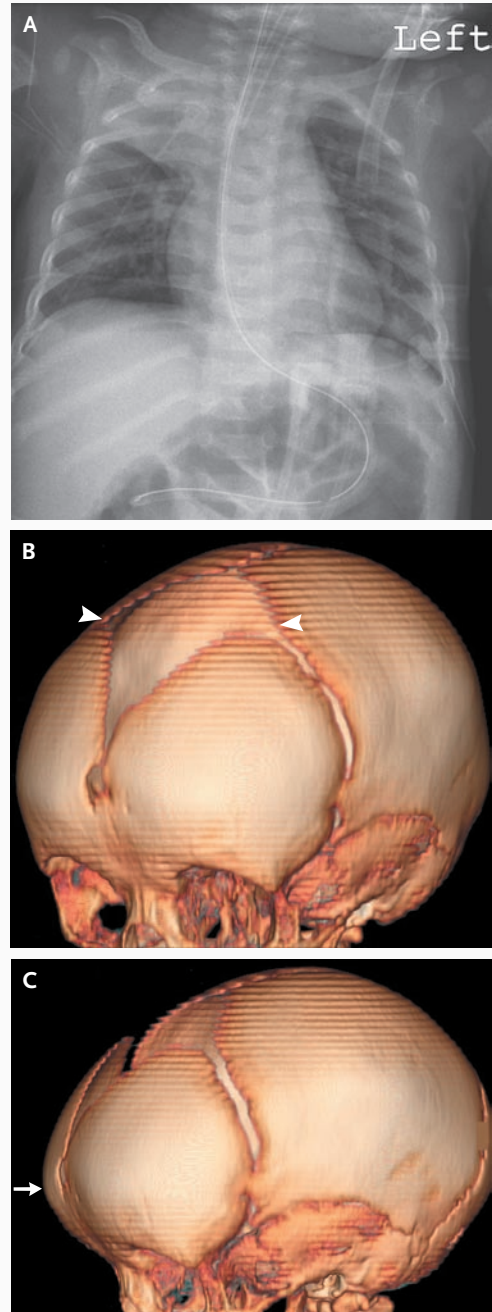


Figure 1. Imaging Studies Performed on Admission.

An anteroposterior chest radiograph (Panel A) shows atelectasis of the right upper lobe and mild perihilar interstitial opacities. The opacities could be due to volume loss with crowding of normal structures, or they could represent mild inflammation of the airways. A CT scan with three-dimensional CT surface reconstruction of the skull (Panel B) shows an enlarged anterior fontanelle, 5.4 cm in width (arrowheads), and frontal bossing (Panel C, arrow).

nosis, we need to consider the causes of seizures and the consequences of breast-feeding without vitamin supplementation.

SEIZURES

The immediate concern regarding this child with seizures is infectious meningitis or encephalitis or both. Other considerations include tumor, bleeding in the brain, toxins, pyridoxine dependency, and phenylketonuria, among others. A child with seizures should also be evaluated for the presence of metabolic disturbances, such as hypoglycemia, hyponatremia, hypoxia, and hypocalcemia.

HYPOCALCEMIA

This child had marked hypocalcemia, which could have caused his seizure. Clinical signs of hypocalcemia, including fatigue, anxiety, and muscle cramps, may be subtle and not appreciated until tetany, seizures, or laryngeal spasms occur. Hypocalcemia has numerous causes. Since the child was normal at birth and met milestones in growth and muscle function, genetic causes such as the DiGeorge syndrome are unlikely. Acute, severe illness with sepsis, pancreatitis, osteopetrosis, or tumor metastases can cause hypocalcemia but is unlikely in this case. Rickets and the hungry bone syndrome (rapid mineralization of unmineralized osteoid that is “hungry” for calcium hydroxyapatite) are rare causes of hypocalcemia that merit consideration.

BULGING FONTANELLE AND CRANIAL BOSSING

The differential diagnosis of a bulging fontanelle is extensive and includes increased intracranial pressure from a variety of causes, such as intracranial infection.¹ However, widened fontanelles and a thin skull that is soft and parchmentlike (craniotabes) are early manifestations (in the third and fourth months) of rickets.² This child also had frontal cranial bossing (thickening of the vault), which is due to new bone formation derived almost entirely from the periosteum, on the outer surface of the skull; it also has many causes, including achondroplasia, Hurler’s syndrome, congenital syphilis, and rickets.³

NUTRITIONAL DEFICIENCIES

This child received breast milk as his primary source of nutrition for almost 9 months. This can

Table 3. Rickets.

Clinical signs

Restlessness and irritability
Head sweating
Skeletal signs (enlargement of costochondral junctions at 6 to 9 months of age)
Frontal bossing (head appears somewhat square)
Fontanelles wide open
Osseous borders soft (craniotabes)
Teething delayed
Muscles flabby
Upper respiratory tract infections
Anemia (von Jaksch–Luzet syndrome)

Differential diagnosis

Congenital syphilis
Infantile scurvy
Chondrodystrophy
Renal disease
Vitamin D deficiency
Vitamin D–resistance syndromes
Hypophosphatemia
 Autosomal dominant rickets
 X-linked
Calcium deficiency
Fluorosis

result in several nutritional deficiencies, such as deficiencies in iron and the fat-soluble vitamins A, D, and K.⁴

The mother is of African descent, and the presence of dark skin puts her at risk for vitamin D deficiency, and thus increases the breast-fed child’s risk of vitamin D deficiency. Vitamin D deficiency manifesting as rickets is resurgent in the United States in recent years, particularly in infants who are solely breast-fed.^{5,6} There is essentially no vitamin D in human breast milk (approximately 25 IU per liter).⁷ This child’s mother would have needed to ingest at least 2000 to 4000 IU of vitamin D per day in order to transfer enough of the vitamin in her milk to satisfy the infant’s requirement.^{7,8}

The signs and symptoms of early vitamin D deficiency are often missed (Table 3). Restlessness and irritability are common and nonspecific, but sweating on the head is a distinctive feature. Vitamin D deficiency causes secondary hyperparathyroidism, resulting in removal of calcium from the skeleton to maintain a normal serum calcium level. It also causes hypophosphatemia

due to loss of phosphorus in the urine, which leads to decreased mineralization of bone. This child has skeletal abnormalities, including craniotabes, frontal bossing, and wide-open fontanelles. Other skeletal signs of osteomalacia do not begin to appear until 6 to 9 months of age. Vitamin D deficiency also disturbs maturation of chondrocytes, resulting in widened epiphyseal plates of the long bones and the costochondral junctions. When a child with vitamin D deficiency begins to stand, gravity leads to bowing of the legs. Teething is delayed, and muscle weakness may occur. This child had a respiratory infection; children with rickets have more frequent upper respiratory tract infections than do normal children.⁹ He had anemia; children with severe vitamin D deficiency and secondary hyperparathyroidism can have anemia due to fibrosis of the marrow space (the von Jaksch–Luzet syndrome). Compensatory extramedullary production of red cells in the liver and spleen may cause hepatosplenomegaly, which he did not have.

There is also very little iron in breast milk, and this child had anemia. In one study, children between 6 and 24 months of age who were solely breast-fed for 6 months had an incidence of iron deficiency anemia that was three to five times as great as the incidence among children who were not solely breast-fed.⁴ Although iron is more bioavailable in human breast milk than in fortified formula, the amount of iron is very low (35 to 40 μg per deciliter).

This child also had hyperchloremic acidosis with glycosuria. Primary and secondary hyperparathyroidism cause a decrease in bicarbonate reabsorption in the kidneys, which can lead to hyperchloremic acidosis, glycosuria, and aminoaciduria — a condition known as Fanconi's syndrome.⁹ Although renal tubular acidosis, type II, cannot be ruled out, the more likely cause for the metabolic acidosis is secondary hyperparathyroidism associated with vitamin D deficiency. Hyperglycemia was probably caused by stress, and the presence of ketones in the urine was probably a result of the seizure activity, as well as carpopedal spasms, which may have occurred for weeks before his admission to the hospital.

RICKETS

Vitamin D–deficiency rickets is the most likely cause of the infant's presenting symptoms and abnormal biochemical studies. However, there are several syndromes that need consideration in the

differential diagnosis of this child with severe hypocalcemia and skeletal evidence of rickets.

Pseudo–vitamin D–deficiency rickets is caused by a mutation in the gene for renal 25-hydroxyvitamin D-1 α -hydroxylase, leading to reduced levels of 1,25-dihydroxyvitamin D. Vitamin D-resistant rickets, caused by a mutation of the vitamin D receptor, leads to markedly elevated levels of 1,25-dihydroxyvitamin D; children may have alopecia totalis, which was not observed in this child. Children with vitamin D–dependent rickets type III have an excess production of heterologous nuclear binding protein that prevents 1,25-dihydroxyvitamin D from interacting with its vitamin D receptor. They also have elevated levels of 1,25-dihydroxyvitamin D. Thus, measurement of the serum 1,25-dihydroxyvitamin D level would be helpful in ruling out these causes.⁸

Acquired and inherited disorders of phosphate metabolism are known as hypophosphatemic rickets or osteomalacia and include autosomal dominant and X-linked inherited hypophosphatemic rickets and oncogenic osteomalacia due to the overproduction of fibroblast growth factor 23 and phosphatonins by a tumor. Patients have normal serum calcium levels but markedly low serum phosphorus levels. This child's serum phosphorus level was low, but not as low as would be expected for hypophosphatemic rickets, and he had a low serum calcium level. Increased production of fibroblast growth factor 23 and phosphatonins inhibits renal production of 1,25-dihydroxyvitamin D, and as a result, the 1,25-dihydroxyvitamin D levels are low or undetectable, which helps in making the diagnosis.⁸

RICKETS AND HYPOCALCEMIA

Why did severe hypocalcemia develop in this child? Possible causes include the upper respiratory tract infection and diarrhea, but a more likely cause is the recent addition of milk-based formula and treatment with a multivitamin that presumably contained vitamin D. The milk-based formula contains high levels of phosphate, which could result in a normal calcium-phosphate product, and, together with the addition of vitamin D, could result in the hungry bone syndrome, producing hypocalcemia.

SUMMARY

This 9-month-old, breast-fed child's frontal bossing and craniotabes, hypocalcemia, hypophosphatemia, elevated alkaline phosphatase level,

metabolic acidosis, and seizure are all consistent with rickets caused by vitamin D deficiency. I expect that the diagnostic test was the measurement of serum 25-hydroxyvitamin D, parathyroid hormone, and 1,25-dihydroxyvitamin D levels. There may have been radiologic signs of rickets, in addition to the frontal bossing, but these signs may not be apparent in a patient at 9 months of age.

Immediate treatment may require a total of 200,000 to 600,000 IU of vitamin D₂ (ergocalciferol) or vitamin D₃ (cholecalciferol) either orally or parenterally. Other treatments that have been reported to be effective are 1700 to 4000 IU of vitamin D per day for 10 weeks or 2000 to 4000 IU per day for 3 to 6 months. Infantile vitamin D intoxication is essentially unknown, unless there is either intentional or inadvertent vitamin D poisoning. For prevention of various manifestations of vitamin D deficiency, which include not only rickets but also increased frequency of respiratory illnesses,¹⁰ diabetes mellitus,¹¹ and wheezing illnesses,¹² the American Academy of Pediatrics has changed its recommendation from 200 IU of vitamin D to 400 IU daily in drops or tablets from birth through adolescence, which is in line with the recommendation of the Canadian Pediatric Society.¹³⁻¹⁶

Dr. Eric S. Rosenberg (Pathology): Dr. Sherry, what was your clinical impression?

Dr. Nicole A. Sherry (Pediatric Endocrinology): For many of the reasons that Dr. Holick discussed, we also thought that vitamin D deficiency was the most likely diagnosis. We also considered hypoparathyroidism, a relatively common cause of hypocalcemia in this age group. However, in hypoparathyroidism, the phosphate level is usually normal to slightly elevated, whereas in vitamin D deficiency the serum phosphate level is low because of the phosphaturic effect of parathyroid hormone.

CLINICAL DIAGNOSES

Rickets due to vitamin D deficiency.
Iron-deficiency anemia.

DR. MICHAEL F. HOLICK'S DIAGNOSES

Rickets due to vitamin D deficiency.
Iron-deficiency anemia.

PATHOLOGICAL DISCUSSION

Dr. Anand S. Dighe: The diagnostic test was a measurement of the serum 25-hydroxyvitamin D level, which was low, at 16 ng per milliliter ("desirable" reference range, >32). Although 25-hydroxyvitamin D is largely inactive, its levels correlate with clinical markers of the action of vitamin D, such as enhanced intestinal absorption of calcium, enhanced bone density, and the avoidance of secondary hyperparathyroidism. The parathyroid hormone level, measured at a time when the patient was hypocalcemic, was elevated (264 pg per milliliter; reference range, 10 to 60), demonstrating that the patient's calcium-parathyroid axis was functioning appropriately (Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

The 1,25-dihydroxyvitamin D level, measured at a time when the patient was hypocalcemic, was elevated at 98 pg per milliliter. The half-life of 1,25-dihydroxyvitamin D is short (4 to 6 hours) and the level may be reduced, normal, or elevated in cases of vitamin D deficiency, depending on the activity of the 1 α -hydroxylase that converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which in turn depends on the current blood concentrations of calcium, phosphate, and parathyroid hormone. In this patient with elevated parathyroid hormone activity, the 1 α -hydroxylase was activated, resulting in elevated levels of 1,25-dihydroxyvitamin D, despite clinically significant vitamin D deficiency. This case points out that measuring the active form of vitamin D (1,25-dihydroxyvitamin D) lacks utility in the routine evaluation of suspected vitamin D deficiency. Testing for this form of vitamin D should be reserved for patients with suspected genetic rickets and for more complex presentations.

Additional laboratory studies suggested a global nutritional deficiency. The serum vitamin A level was low at 7 μ g per milliliter (reference range, 11.3 to 64.7). The patient also had a mildly elevated prothrombin time (Table 1) that returned to normal 2 days after the administration of oral vitamin K. He had a microcytic anemia suggestive of iron deficiency (Table 1), with a low mean corpuscular volume, anisocytosis, hypochromia, and an elevated red-cell distribution width. The hemoglobin electrophoresis showed sickle cell trait with a reduced percentage of

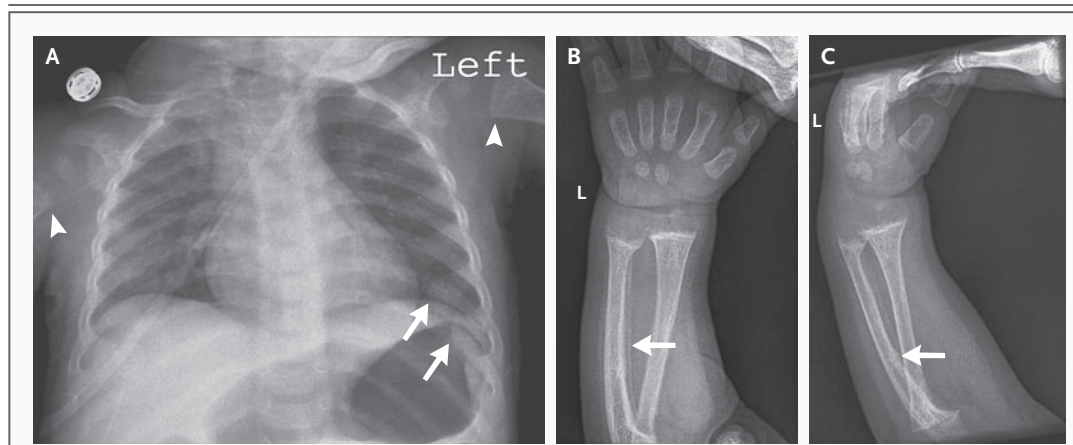


Figure 2. Imaging Studies Performed on Hospital Days 2 and 3.

On an anteroposterior chest radiograph from the second hospital day (Panel A), the lungs show improved aeration with reexpansion of the right upper lobe. There is bulbous enlargement of the lower anterior rib ends (arrows). Subtle findings of demineralization, fraying, and widened physal lucency can be seen at the proximal humeral metaphyses (arrowheads). These bony findings were also present on the initial radiographs (Fig. 1). Anteroposterior (Panel B) and lateral (Panel C) radiographs of the wrist performed the next day show diffuse demineralization, with irregular fraying, flaring, and cupping of the distal radius and ulna and apparent widening of the radial physis. There is bowing and smooth periosteal reaction along the ulna (Panel B, arrow). A transverse lucency with more focal periosteal reaction (Panel C, arrow) is seen in the proximal ulna, a finding consistent with a Looser zone.

hemoglobin S of 34.8% (typically approximately 40% with uncomplicated sickle cell trait), consistent with concomitant iron deficiency, α -thalassemia, or both. The transferrin saturation (calculated as the serum iron level divided by the total iron-binding capacity) was low at 4.9%, confirming the diagnosis of iron deficiency.

The patient also had an absolute lymphopenia and a slightly low globulin level (Table 2). Flow cytometric analysis of blood lymphocytes showed only mild decreases in the number of T cells, and immunoglobulin levels were normal. Although there is no specific explanation for these abnormalities, a variety of vitamins and trace minerals, as well as sufficient calories from protein, are important for optimal functioning of the immune system. The lymphopenia resolved after nutritional needs were met.

Dr. Lim: A follow-up chest radiograph on the second hospital day (Fig. 2A) showed improved lung aeration. In addition, there was generalized demineralization of bone. Diffuse demineralization, cortical thinning, and trabecular coarsening are characteristic of vitamin D–deficiency rickets. There was physal widening and metaphyseal irregularity of the proximal humeri and

enlarged lower anterior rib ends. This flared, bulbous appearance of the rib ends, resembling a chain of beads (termed “rachitic rosary”), is characteristic of rickets.¹⁷ In retrospect, these abnormalities were present on the initial chest radiograph (Fig. 1A).

Radiographs of the left wrist performed the next day (Fig. 2B and 2C) revealed demineralization with irregular fraying, flaring, and cupping of the distal radius and ulna. There was physal widening, with increased distance between the distal radial epiphysis and the metaphysis. There was mild bowing deformity and smooth periosteal reaction along the ulna. A transverse linear radiolucency (termed “Looser zone”) with more focal periosteal reaction was seen in the proximal ulnar diaphysis.

These are characteristic radiographic manifestations of vitamin D–deficiency rickets that become apparent several weeks after biochemical and histologic changes can be detected. The osseous abnormalities first occur at the rapidly growing ends of long bones. Irregular fraying of the metaphysis causes the end of the bone to become radiolucent and indistinguishable from the adjacent physis, leading to an apparent in-

crease in the distance between the epiphysis and metaphysis, often with flaring and cupping of the metaphyseal ends. Skull findings include frontal bossing, as in this case, and enlargement and delayed closure of the anterior fontanelle.^{1,18}

DISCUSSION OF MANAGEMENT

Dr. Sherry: Calcitriol (the active form of vitamin D), ergocalciferol, and calcium carbonate were administered for 2 weeks, and the serum calcium level returned to normal (Fig. 2 in the Supplementary Appendix). Although calcitriol does not correct the underlying deficiency, the onset of its action is faster than that of ergocalciferol (hours vs. days), and it was used in this case in an attempt to normalize the serum calcium level quickly. The patient also received multivitamin drops, ferrous sulfate, oral sodium phosphate, vitamin E, and vitamin K to correct the other deficiencies. Evaluation by an infectious-disease consultant revealed positive antigen tests for rotavirus in the stool. An analysis of cerebrospinal fluid was normal, except for an elevated glucose level, and cultures and a polymerase-chain-reaction assay were negative for microorganisms; a test for the human immunodeficiency virus was negative. After 2 weeks, the patient was transferred to a children's hospital affiliated with this hospital and was discharged from there 1 week later.

On discharge, a streamlined medication plan, developed at his mother's request to avoid multiple doses of medications throughout the day, included calcium carbonate three times daily and ergocalciferol (50,000 IU orally) weekly. After dis-

charge, the mother did not keep appointments at the endocrine clinic. Ergocalciferol was discontinued after 3 weeks, and oral polyvitamin drops were continued (400 IU of vitamin D per day) by the child's pediatrician. Five months after discharge, the patient's 25-hydroxyvitamin D level was low at 12.7 ng per milliliter. We recommended vitamin D by means of injection, followed by 800 IU daily thereafter, but the patient did not return for follow-up. When we finally saw him again 11 months after admission, he was developing normally, and the 25-hydroxyvitamin D level was 26 ng per milliliter. He was taking only a multivitamin, and we again prescribed ergocalciferol (1600 IU) daily.

Dr. Holick: If one gives vitamin D (D₂ or D₃) to a vitamin D–deficient infant, it will quickly be converted to 1,25-dihydroxyvitamin D (calcitriol). Calcitriol enhances the 25-hydroxyvitamin D-24-hydroxylase (CYP24R) activity and increases degradation of both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, which is why I prefer not to use it.¹⁵

FINAL DIAGNOSES

Rickets due to vitamin D deficiency.

Iron-deficiency anemia.

Severe protein-calorie malnutrition.

Dr. Holick reports receiving consulting fees or serving on the paid advisory boards of Novartis, Bayer, Merck, Procter & Gamble, and Quest Diagnostics; lecture fees from Merck, Procter & Gamble, and Novartis; and grant support from the National Dairy Council and the UV Foundation. No other potential conflict of interest relevant to this article was reported.

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