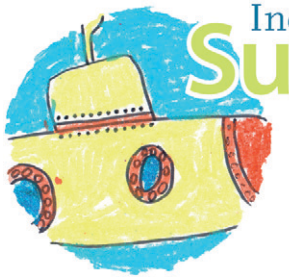

Index of Suspicion

1 Growth Failure and Abnormal Radiographs in a 3-year-old Girl

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EDITOR'S NOTE

We invite readers to contribute Index of Suspicion cases at: Submit and Track My Manuscript.

AUTHOR DISCLOSURE Drs Ramakrishnan, Fuchs, and Singhal have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 3-year-old African American girl is being evaluated for a history of failure to thrive and concern for neglect. She was born at term and was small for gestational age. Her growth records are unavailable, but growth velocity was reportedly normal until age 2 years. Four months ago, her pediatrician referred her to a gastroenterologist for ongoing poor weight and height gain, but she was not seen due to social barriers. The patient typically eats 3 regular meals and drinks 24 oz of chocolate milk per day. Her mother reports that her daughter has unusual dietary preferences, such as craving coffee and soda. She states that the girl has constipation, but she has no vomiting, diarrhea, abdominal pain, bone pain or fractures, hematuria, or edema. She denies recurrent infections or hospitalizations. Motor and cognitive development are normal. Her tuberculin skin test result was negative 1 year ago. The mother has been previously incarcerated, and in the emergency department, the mother is agitated and her speech is slurred, with some incoherent speech.

The patient's height and weight are below the 5th percentile and head circumference is at the 10th percentile. Her vital signs are normal. The only finding of note on physical examination is frontal bossing with minimal subcutaneous fat. The alert, thin child has normal heart and lung sounds and no organomegaly or signs of trauma. She displays age-appropriate gross motor skills and speech.

Complete blood cell count and comprehensive metabolic panel show normal renal function, elevated serum calcium (10.0 mg/dL [2.5 mmol/L]), and low phosphorus (2.5 mg/dL [0.81 mmol/L]). Further evaluation, including laboratory and imaging studies, confirms the diagnosis.

DISCUSSION

Despite normal findings on the respiratory examination, clinicians obtained a chest radiograph (CXR) to evaluate for pulmonary tuberculosis due to the mother's history of incarceration. The child's CXR revealed costochondral changes consistent with rachitic rosary without lymphadenopathy or parenchymal changes (Fig 1). Additional radiographs demonstrated metaphyseal flaring and widening of various long bones with overall lucency of the bone, suggesting a generalized demineralizing disorder (Fig 2). Although social challenges in the

family suggested neglect or malnourishment as the cause, the patient surpassed calorie count goals on her own while hospitalized.

Endocrinology evaluation included normal serum parathyroid hormone (PTH) and 25-hydroxyvitamin D values along with excess phosphorus in her urine, suggesting a diagnosis of familial hypophosphatemic rickets. She was discharged on vitamin D and potassium phosphate supplementation, but the family admitted to poor compliance due to insurance issues and the difficulty in giving the phosphate supplementation 4 times per day. The girl was seen by a geneticist specializing in skeletal dysplasia, who recommended genetic testing for X-linked and autosomal dominant hypophosphatemia (*PHEX* and *FGF-23* genes, respectively), but the family declined. The girl continues to be evaluated every 3 months by a pediatric endocrinologist, but her skeletal abnormalities and phosphorus values have not improved due to the family's inability to adhere to the potassium phosphate regimen.

The Condition

Rickets is a failure of normal mineralization of growing bone that should be included in the differential diagnosis of children presenting with failure to thrive and orthopedic abnormalities, such as leg bowing, osteopenia, or frequent fractures. Although vitamin D–deficient rickets is at the forefront of clinicians' minds, other diagnostic possibilities include familial hypophosphatemic rickets, hereditary hypophosphatemic rickets with hypercalcuria, vitamin D–dependent rickets, renal osteodystrophy, and medication-induced rickets. In fact, renal phosphate-wasting disorders are estimated to be the most common causes of rickets in North America. Because rickets is not a reportable disease, few data document the epidemiologic likelihood of its various types. Fewer than one-third of rickets cases in the United States are estimated to result from nutritional deficiencies. When present, nutritional rickets typically affects darker-complected children, exclusively breastfed infants not receiving vitamin D supplementation, or those with diets deficient in calcium.

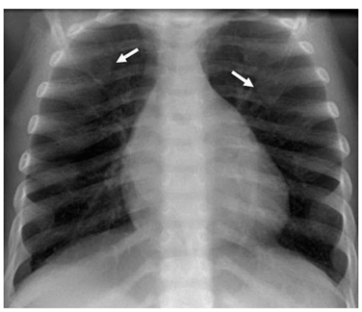

Figure 1. Chest radiograph demonstrates prominent metaphyseal widening at the costochondral junction anteriorly, also known as "rachitic rosary" (white arrows).

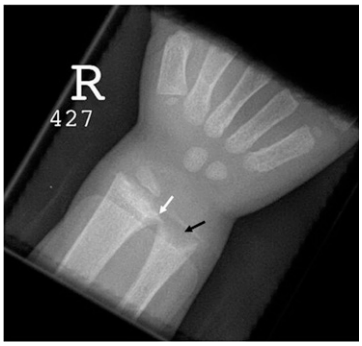

Figure 2. Wrist radiograph shows metaphyseal flaring at the distal end of both the radius and ulna (white arrow) as well as significant cupping of the distal ulnar metaphysis (black arrow).

Familial hypophosphatemic rickets or X-linked hypophosphatemic rickets (XLH) is caused by a mutation of the phosphate-regulating gene (*PHEX*) on the X chromosome (Xp22.1), leading to renal proximal tubule wasting of phosphorus. The mechanism is not yet completely understood but is believed to be related to an increase of fibroblast growth factor 23 (FGF-23), a potent regulator of a renal proximal tubule sodium-potassium cotransporter, causing phosphaturia. This results in hypophosphatemia with inappropriately normal concentrations of calcitriol. An autosomal dominant form of hypophosphatemic rickets is much rarer than XLH and is caused by mutation in *FGF23*. The clinical and biochemical features are similar to those of XLH.

Diagnosis

Although clinical findings can raise the suspicion of rickets, diagnostic testing is required to determine the exact cause and recommended management. A child's gestational age, dietary intake of vitamin D and calcium, and sunlight exposure should be noted. XLH rickets typically presents in the first 2 years after birth, and the clinical presentation involves short stature, lower extremity deformities that include genu varum, bone pain and tenderness, frontal bossing of the skull, and dental abscesses. Barriers to access to health care may be responsible for delayed diagnosis in this 3-year-old patient. Although some patients may display hypotonia and delayed walking, muscle weakness is not a predominant feature; affected patients typically have normal strength. Among the long-term complications of untreated disease are skeletal deformities, particularly abnormal lower extremity growth, which may require surgical correction.

TABLE. **Typical Laboratory Findings With the Various Types of Rickets**

TYPE OF RICKETS	CALCIUM VALUE	PHOSPHATE VALUE	PARATHYROID HORMONE VALUE	ALKALINE PHOSPHATASE VALUE	25-HYDROXYVITAMIN D VALUE
Vitamin D-deficient	Normal/low	Normal/low	Increased	Increased	Low
Vitamin D-dependent	Low	Low	Increased	Increased	Normal
Hypophosphatemic (includes X-linked hypophosphatemic)	Normal/low	Low	Normal	Increased	
Renal osteodystrophy	Normal/low	Increased	Increased	Increased	Normal

Laboratory features of XLH rickets include hypophosphatemia and increased alkaline phosphatase. Serum concentrations of calcitriol, calcidiol, calcium, and PTH are within normal ranges, although they are inappropriate given the hypophosphatemia (Table).

Radiologic evidence of XLH rickets includes osteopenia, fraying, widening, and cupping of the metaphyseal ends of rapidly growing long bones (radius, ulna, distal femur, and tibia) and beading of the costochondral junctions, known as rachitic rosary.

Treatment

The treatment of XLH rickets is supplementation with oral phosphorus to replete losses due to renal wasting in conjunction with calcitriol to supplement the inappropriately normal concentrations of vitamin D. A single high dose of vitamin D is not recommended due to concern for vitamin D intoxication and renal damage related to hypercalcinosis. Rather, a low dose of vitamin D (typically 1,000 IU) is coupled with oral phosphorus and titrated based on frequent assessment of serum calcium, phosphate, calcitriol, and renal function. As with any chronic disease, compliance with maintenance therapy is a major challenge. Treatment is generally continued until alkaline phosphatase values normalize. Biochemical changes following appropriate nutritional supplementation are evidenced by a rise in serum phosphorus within the first week of treatment. Treating active rickets improves mineralization, thereby promoting bone growth, correcting leg deformities, and improving dentition. Typically, after 2 years of treatment, growth velocity is restored, although 25% to 40% of patients with XLH rickets show linear growth delay despite optimal treatment and have a final height more than 2 standard deviations below normal.

Lessons for the Clinician

- Rickets is a failure of normal mineralization of growing bone that should be included in the differential diagnosis of children presenting with failure to thrive and orthopedic abnormalities such as frontal bossing or leg bowing.
- X-linked hypophosphatemic rickets is caused by renal proximal tubule wasting of phosphorus, with inappropriately normal vitamin D concentrations. Treatment involves oral supplementation of phosphorus and calcitriol until alkaline phosphatase values normalize.
- The physician should be aware of his/her own biases about the social circumstances of patients and their families that may influence the diagnostic reasoning process.

Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/37/8/348.

Parent Resources from the AAP at HealthyChildren.org

Case 1: Growth Failure and Abnormal Radiographs in a 3-Year-Old Girl

- https://www.healthychildren.org/English/healthy-living/nutrition/Pages/Vitamin-D-Deficiency-and-Rickets.aspx
- Spanish: https://www.healthychildren.org/spanish/healthy-living/nutrition/paginas/vitamin-d-deficiency-and-rickets.aspx

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