A 10-Year-Old Girl with Nontraumatic Loss of Central Incisors

Anthony Feghali, MD; and Amin J. Barakat, MD, FAAP

A 10-year-old white girl presented at age 12 months with a nontraumatic loss of her left and right lower central incisors. She was born by normal vaginal delivery to a 31-year-old healthy mother. Her birth weight was 3,600 g, and her neonatal course was complicated by hyperbilirubinemia and a small midmuscular ventricular septal defect that resolved spontaneously. There was no history of bone fractures or renal disease. Family history was unremarkable; specifically, there was no history of hypophosphatasia.

Physical examination at age 1 year revealed a healthy, well-nourished infant with a weight of 19.16 kg (25th percentile), length of 74.2 cm (25th percentile), and head circumference of 45 cm (25th percentile). She had a patent anterior fontanel and a prominent occiput. Oral examination revealed four teeth in the lower jaw and eight teeth in the upper jaw. The lower left and right central incisors were missing. Skeletal examination was normal with no widening of the growth plate and no rachitic rosary. The rest of her examination was normal and she had normal development. The patient walked at age 12 months and had a proficient vocabulary at 36 months of age. Pubertal staging was Tanner I.

A full laboratory workup showed calcium of 10.5 mg/dL, an elevated phosphorus of 6.8 mg/dL, magnesium of 2.3 mg/dL, 1,25-dihydroxyvitamin D of 82 pg/mL, parathryroid hormone of 1.4 pmol/L, and a low alkaline phosphatase of 47 U/L (normal, 145 to 320 U/L). A complete blood count showed mild iron deficiency (iron of 23 mg/dL), hematocrit of 32.8%, hemoglobin of 11.2 g/dL, and a white blood cell count of 7,600 with normal differential and platelet count. Further exams were performed by a pediatric endocrinologist shortly after her initial pediatric visit: urinary phosphoethanolamine was 859 mmol/L creatinine (normal, 108 to 533), and pyridoxal X-rays of the skull, chest, and upper and lower extremities were all normal with no evidence of metabolic bone disease. Dental X-rays showed a slightly widened pulp cavity. Genetic studies were not performed.

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Disclosure: The authors have no relevant financial relationships to disclose.

doi: 10.3928/00904481-20130222-06

Editor’s note: Each month, this department features a discussion of an unusual diagnosis in genetics, radiology, or dermatology. A description and images are presented, followed by the diagnosis and an explanation of how the diagnosis was determined. As always, your comments are welcome via email at Pediatrics@Healio.com.

For diagnosis, see page 104
Diagnosis: Odontohypophosphatasia

Given the history of early deciduous tooth loss, significant decrease in alkaline phosphatase, elevated phosphoethanolamine and pyridoxal phosphate, and normal skeletal X-rays, the diagnosis of odontohypophosphatasia was made. The patient continued to develop in healthy manner, and no treatment was needed.

**DISCUSSION**

The patient has a history of early deciduous tooth loss with significantly decreased alkaline phosphatase and an elevated phosphoethanolamine and pyridoxal phosphate with normal skeletal X-rays, satisfying the diagnosis of odontohypophosphatasia. Hypophosphatasia is a rare inherited disorder characterized by defective bone and tooth mineralization and deficiency of serum and bone alkaline phosphatase activity. Severe hypophosphatasia occurs in about 1 of every 100,000 individuals, but the incidence of moderate forms of the disease are probably much higher.1

Hypophosphatasia is caused by mutations in the liver, bone, and kidney alkaline phosphatase gene (ALPL; OMIM# 171760) encoding the tissue nonspecific alkaline phosphatase (TNSLAP) activity.1-3 TNSLAP normally hydrolyzes inorganic pyrophosphate (PPI) and pyridoxal 5’-phosphate (PLP). When TNSLAP is low, PPI can accumulate extracellularly and inhibit the formation of hydroxyapatite, therefore preventing bone mineralization and sometimes producing rickets and osteomalacia.2 The TNSALP gene is localized on chromosome 1p36.1 and consists of 12 exons distributed over 50 kb.4,5 More than 127 distinct mutations have been described in the TNSALP gene.

The clinical symptoms of hypophosphatasia can vary greatly, and range from stillbirth with no mineralization of bone, to early teeth loss mainly involving the anterior deciduous teeth. There are six different clinical forms of the disease based on the clinical picture and age of diagnosis (see Table 1).1 These include the perinatal (lethal), perinatal (benign), infantile, childhood, and adult forms, as well as odontohypophosphatasia.

In the lethal perinatal form, patients show severely impaired mineralization in utero and develop skin-covered osteochondral spurs on the forearms and legs. Affected patients rarely survive past the neonatal period due to respiratory complications. Patients with the benign perinatal form manifest with skeletal defects such as shortened limbs and bowed legs. In the infantile form, patients usually appear normal at birth, but around age 6 months they develop rachitic deformities of the chest and premature craniosynostosis.6 Furthermore, hypercalcemia is noted, which explains the clinical findings of poor feeding, irritability, and

**TABLE.**

<table>
<thead>
<tr>
<th>Clinical Form</th>
<th>Mode of Inheritance</th>
<th>Bone Symptoms</th>
<th>Dental Symptoms</th>
<th>Clinical Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal, lethal</td>
<td>AR</td>
<td>Hypomineralization, osteochondral spurs</td>
<td>n/a</td>
<td>Radiographs, ultrasound</td>
</tr>
<tr>
<td>Perinatal, benign</td>
<td>AD</td>
<td>Bowing of long bones, craniosynostosis, hypomineralization, rachitic ribs, hypercalciuria</td>
<td>n/a</td>
<td>Ultrasound, clinical</td>
</tr>
<tr>
<td>Infantile</td>
<td>AR</td>
<td>Short stature, skeletal deformity, waddling gait, bone fractures/pain</td>
<td>Premature loss of deciduous teeth</td>
<td>Radiographs, clinical AP, PEA, PLP</td>
</tr>
<tr>
<td>Childhood</td>
<td>AR, AD (rare)</td>
<td>Premature loss of deciduous teeth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>AR/AD</td>
<td>Stress fractures of metatarsal/tibia, osteoarthritis</td>
<td>+/- Premature loss of deciduous teeth</td>
<td></td>
</tr>
<tr>
<td>Odontohypophosphatasia</td>
<td>AR/AD</td>
<td>Loss of alveolar bone</td>
<td>Exfoliation of incisors, reduced thickness of dentin, enlarged pulp chambers of teeth, dental caries</td>
<td>Clinical, AP, PEA, PLP</td>
</tr>
</tbody>
</table>

AD = autosomal dominant; AP = alkaline phosphatase; AR = autosomal recessive; n/a = not applicable; PEA = urinary phosphoethanolamine; PLP = pyridoxal 5’-phosphate.

Source: Mornet E1
constipation, which can eventually cause renal damage. In addition, patients can have early loss of deciduous teeth that needs to be distinguished from odonto-
hyrophosphatasia.

The childhood form of the disease presents with skeletal deformities such as short stature, a waddling gait, and history of bone fractures. Premature loss of teeth can also be seen, usually beginning with the incisors. The adult form is seen in middle-aged adults. It usually presents with foot pain that is due to stress fractures of the metatarsals or tibia. A detailed history may reveal early loss of deciduous teeth. Our patient had odonto hypophosphatasia, which represents the most benign form of the disease. This form of the disease is characterized by premature exfoliation of primary teeth, usually the central incisors, with no associated skeletal abnormalities. Dental X-rays in these patients show reduced alveolar bone, and enlarged root canals and pulp chambers.

In order to make the diagnosis of hypophosphatasia, both clinical and laboratory findings must be satisfied. Important but not pathognomonic markers are reduction in alkaline phosphatase activity and increased urinary phosphoethanolamine level. In general, the more severe the disease, the lower the serum AP activity. A more sensitive marker is an increase in blood pyridoxal 5’-phosphate.

The most definitive means of diagnosing hypophosphatasia is genetic testing for mutations in the TNAP gene. Our patient has a moderate form of the disease.

Inheritance of odonto hypophosphatasia may be autosomal recessive or dominant. There is no definitive cure for this disease at the present time, and treatment is symptomatic. The mainstay of treatment of more severe forms of hypophosphatasia is nonsteroidal anti-inflammatory drugs to prevent pain; there is hope of developing a definitive treatment of the disease with enzyme replacement.

Patients with odonto hypophosphatasia have a normal lifespan.

CONCLUSION

Odonto hypophosphatasia is the most benign form of hypophosphatasia, which is a rare inherited disorder characterized by defective bone and tooth mineralization and deficiency of serum and bone alkaline phosphatase activity. It is characterized by premature exfoliation of primary teeth, mainly the central incisors, with no associated skeletal abnormalities. Dental X-rays reveal reduced alveolar bone, and enlarged root canals and pulp chambers. Odonto hypophosphatasia usually presents in a subtle manner and can be easily missed. Treatment is not required and affected children grow normally and have a normal lifespan. The diagnosis should be suspected in infants with early nontraumatic loss of deciduous teeth.

REFERENCES