Bone Reports 5 (2016) 228–232

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

Case series: Odontohypophosphatasia or missed diagnosis of childhood/adult-onset hypophosphatasia? – Call for a long-term follow-up of premature loss of primary teeth

Mari Mori [a], Stephanie L. DeArmey [a], Thomas J. Weber [b], Priya S. Kishnani [a,*]

[a] Department of Pediatrics, Division of Medical Genetics, Duke University Medical Center, Durham, NC, USA
[b] Department of Medicine, Duke University Medical Center, Durham, NC, USA

ARTICLE INFO

Article history:
Received 27 June 2016
Accepted 25 August 2016
Available online 26 August 2016

Keywords:
Hypophosphatasia
Odontohypophosphatasia
Premature tooth loss
Metabolic bone disease
Tissue-nonspecific alkaline phosphatase

ABSTRACT

Introduction: Hypophosphatasia, a metabolic bone disease caused by a tissue-nonspecific alkaline phosphatase deficiency, leads to undermineralization of bone and/or teeth, impaired vitamin B6 metabolism, and a spectrum of disease presentation. At the mild end of the spectrum, it presents as pathologic fractures in later adulthood. Patients with isolated dental manifestations, typically presenting as premature loss of primary teeth, are classified as having odontohypophosphatasia (odontoHPP). A subset of patients diagnosed with odontoHPP in childhood can later develop extra-dental manifestations that constitute childhood- or adult-onset hypophosphatasia.
Case reports: methods/results: Retrospective data related to onset, detailed clinical course, and method of diagnosis were collected as part of a natural history of adult patients with hypophosphatasia.
Of 9 initial patients, all had low serum alkaline phosphatase levels for their age and gender at adult presentation (Table 2). The majority (8/9) demonstrated childhood dental signs of hypophosphatasia as the initial clinical manifestation: premature loss of primary teeth (7/9), absent primary teeth (1/9), and delayed loss of primary teeth (1/9). Despite childhood dental presentation and/or other signs/symptoms, diagnosis of hypophosphatasia was delayed 20–54 years (median = 46) since the primary tooth problems and 8–45 years (median = 27) since the first fracture or onset of a major adult tooth problem.
Conclusion: Patients with primary tooth loss in childhood were often diagnosed with hypophosphatasia later in life. Pediatric patients classified as having odontoHPP under present practice can manifest significant disease burden later in life.

1. Introduction

Hypophosphatasia (HPP) is a heritable metabolic bone disease characterized by defective bone mineralization and complications (Hofmann et al., 2013) due to deficiency of tissue-nonspecific alkaline phosphatase (TNSALP), 1 of the 3 alkaline phosphatase isoforms (Hofmann et al., 2013; Whyte, 2012; Rockman-Greenberg, 2013). At least 300 distinct mutations of the TNSALP gene (*ALPL*; Genbank accession number NG_008940.1) have been identified to cause HPP in different populations from various ethnic backgrounds, in either autosomal dominant or autosomal recessive fashion (Mornet, 2015). The TNSALP deficiency is also reflected in a low serum total alkaline phosphatase (ALP) level. Serum ALP measurement is readily available in most clinical settings and is a sensitive screening test for HPP in the setting of clinical history consistent with the disease. As physiological ALP is normally higher in childhood, it is critical that an age- and gender-specific reference range is used for its interpretation (Mornet and Nunes, 2016). Other conditions that can cause low ALP include hypothyroidism, multiple myeloma, Cushing's syndrome, profound anemia, and vitamin D intoxication (Whyte, 2013). These conditions can be differentiated by clinical history and additional laboratory tests. TNSALP deficiency also leads to elevated concentrations of some substrates in urine and plasma, which can be used as diagnostic markers. These biomarkers include inorganic pyrophosphate (PPi) (Buchet et al., 2013), pyridoxal-5′-phosphate (PLP), the predominant circulating form of vitamin B6 (Coburn and Whyte, 1988), and phosphoethanolamine. Elevated extracellular levels of PPi inhibit bone mineralization by blocking hydroxyapatite crystal growth (Millán and Plotkin, 2012). In severe cases, PLP cannot sufficiently be dephosphorylated to pyridoxal by TNSALP in order to cross the blood-brain barrier and function as a cofactor in neurotransmitter biosynthesis, which may cause vitamin B6-responsive seizures (Baumgartner-Sigl et al., 2007; Buchet et al., 2013; Waymire et al.,

* Corresponding author at: BOX 103856 DUMC, GSRB 1, 4th Floor, Room 4010, 905 S. LaSalle Street, Durham, NC 27710, USA.
E-mail addresses: mari.mori@duke.edu (M. Mori), stephanie.dearmey@duke.edu (S.L. DeArmey), thomas.weber2@duke.edu (T.J. Weber), priya.kishnani@duke.edu (P.S. Kishnani).

http://dx.doi.org/10.1016/j.bonr.2016.08.004

1995). Sequelae of HPP may include muscle weakness, abnormal gait, deformity of bones, osteomalacia, premature loss of teeth, and dental caries, as well as failure to thrive, craniosynostosis, seizures, nephrocalcinosis, and respiratory compromise due to rachitic chest in severe forms (Rockman-Greenberg, 2013).

HPP shows considerable expressive variability, with highest mortality risk in patients with onset of signs or symptoms *in utero* or during infancy, and non-lethal disease burden in patients with later disease manifestation (Rockman-Greenberg, 2013; Whyte et al., 1979; Whyte et al., 1982). HPP has been historically classified according to the presence/absence of bone disease and the age of first appearance of clinical manifestation(s): perinatal (onset *in utero* and generally lethal), infantile (onset prior to 6 months of age and associated with approximately 50% mortality due to respiratory failure), childhood (onset from 6 months to 18 years inclusive), or adult (onset after 18 years of age) (Rockman-Greenberg, 2013; Whyte, 2013; Mornet and Nunes, 2016). However, substantial clinical overlap among the identified phenotypes can occur (Hofmann et al., 2013). Odontohypophosphatasia (odontoHPP) is characterized by isolated dental symptoms in the absence of skeletal abnormalities (Rockman-Greenberg, 2013; Whyte, 2013). Diagnosis of odontoHPP is made when dental disease is the only physical manifestation accompanying the biochemical characteristics of HPP. Therefore, additional diagnostic radiological studies and bone biopsies, if needed, should be done to rule out evidence of rickets or osteomalacia (Millán and Plotkin, 2012; Whyte et al., 2015). The dental abnormalities frequently observed include abnormal formation of cementum, enamel, increased pulp spaces, and premature loss of fully rooted primary teeth before the age of 5 years and often adult teeth (Beck et al., 2009; Hartsfield, 1994).

Adult-onset HPP is typically diagnosed upon the presentation of skeletal symptoms in middle age. Frequently, however, these patients recollect unusual early childhood tooth loss (Whyte, 2013) or their parents' accounts of it, or have a childhood history of fractures or chronic muscle pain. When dental symptoms appear early in life in the absence of skeletal disease, a diagnosis of odontoHPP may seem appropriate at the time, but a subset of affected patients may later develop signs of childhood/adult-onset HPP. These patients and their families require appropriate education and periodic follow-up for bone and other secondary complications. In light of the recent approval of enzyme replacement therapy with recombinant human TNSALP, this population may potentially benefit from early diagnosis and early treatment.

Berkseth and colleagues (Berkseth et al., 2013) performed a retrospective medical record review of 22 adults with HPP. However, the study was limited due to its method of medical record review. It is possible that a childhood dental history was under-recognized. Here, we describe our experience with the first 9 patients in our HPP natural history study who were diagnosed with HPP in adulthood. The majority had dental manifestations in childhood, such as premature tooth loss, persistent primary teeth, or absent primary teeth, and later developed chronic muscle/joint pain and recurrent pathological fractures. Most of these patients remained undiagnosed despite evaluation by multiple specialists. Our study illustrates the importance of HPP as a differential diagnosis in patients with primary tooth problems in the setting of low serum total ALP for age and gender, as well as their long-term follow-up.

2. Case reports: methods and results

We collected retrospective clinical data related to the onset of HPP in our patients, its detailed clinical course, and method of HPP diagnosis through patient interview and medical record review. Biochemical analytical assessments were conducted by Covance Inc., 8211 SciCor Drive, Indianapolis, IN 46214, USA. PLP analysis was performed at either ARUP, 500 Chipeta Way, Salt Lake City, UT 84108, USA or Biotrial Bioanalytical Services, Inc., 3885 boul. Industriel, Laval, Quebec, Canada, H7L 4S3. Gene mutation analysis was conducted by Connective Tissue Gene Tests (CTGT), 6580 Snowdrift Road, Suite 300, Allentown, PA 18106, USA.

2.1. Compliance with ethical guidelines

Our natural history study was approved by the Duke University Health System Institutional Review Board under protocol Pro00024134 and is registered in ClinicalTrials.gov (NCT02237625). The authors obtained patient consent to report their clinical data. Retrospective medical histories obtained at enrollment are reported here.

2.2. Case report findings

2.2.1. Case 1

This patient was a 35-year-old man who required extraction of primary teeth because they would not spontaneously exfoliate and developed an inability to sit on the ground, due to discomfort in childhood; chronic back and foot pain; and shattering of a molar tooth at age 25. Dentists reported his teeth were translucent with microfractures. He was diagnosed with HPP based on low ALP level, clinical history, and a heterozygous mutation in *ALPL*.

2.2.2. Case 2

This 71-year-old woman had developed a total of 21 fractures starting at age 26, and at age 53 was diagnosed with HPP by a rheumatologist. She had experienced loss of adult teeth and a tooth abscess requiring root canal surgery.

2.2.3. Case 3

This is a 32-year-old man who lost all of his primary teeth soon after their eruption, was noted to have bowed tibia in childhood, and was diagnosed with childhood HPP at age 3 based on this history and low ALP. He later developed repeated stress fractures of the third metatarsals after intense military training. He lost an adult maxillary incisor tooth after biting into a piece of meat and hitting bone unexpectedly. His dental bridge required support by multiple contiguous teeth due to loose anchoring of the adjacent tooth.

2.2.4. Case 4

The patient was a 58-year-old woman who had premature primary tooth loss at age 3. Starting at age 14, she had experienced a total of 7 fractures and delayed healing of the fractured bones, as well as progressive musculoskeletal pain in her late 40s.

2.2.5. Case 5

This is a 62-year-old woman who lost all her front primary teeth at age 13 months, and developed 7 fractures starting at age 8. A bone scan at age 55 showed marked degenerative changes in both hands and both feet, as well as abnormal radiotracer uptake in the mid-left third metatarsal suggestive of a stress fracture.

2.2.6. Case 6

This 63-year-old woman is the sister of Case 7. She had premature loss of primary teeth at age 3, developed chronic joint pains in her teens, lost an adult tooth at age 18, and experienced her first fracture at age 19 after a fall. She had a total of 9 fractures throughout her life, which took longer than expected to heal. An endocrinologist diagnosed her with HPP at age 57.

2.2.7. Case 7

This is a 50-year-old woman who had missing teeth and premature primary tooth loss, developed chronic joint pain and required orthopedic shoes in childhood, and developed 19 fractures starting at age 18. She was evaluated by an endocrinologist for osteoporosis refractory to medical therapy and multiple fractures, and radioiodine ablation was performed due to suspected hyperthyroidism as an underlying cause.