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

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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.,

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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.

She continued to experience fractures after the ablation. A diagnosis of HPP was made by another endocrinologist based on a low ALP value and was genetically confirmed with compound heterozygous mutations of *ALPL*.

2.2.8. Case 8

This is a 60-year-old woman who had premature primary tooth loss at age 3. While her first fracture occurred at age 12 in her collar bone, she had a relatively healthy adult life until age 42 when she started to have more fractures, went on to develop approximately 25 of them, and also suffered from chronic joint pain. A whole-body scan at age 55, after her menopause, showed evidence of numerous fractures at various healing stages, including fractures of both femurs, both feet, the right ulna, and the left wrist. The diagnosis was made by an endocrinologist based on her clinical history and low ALP.

2.2.9. Case 9

This is a 59-year-old woman who lost her primary teeth at ages 3 to 4 years and was subsequently diagnosed with HPP based on history and low ALP by a dentist. She had clubfoot deformity in infancy and experienced 6 fractures starting at age 6 years. A right knee MRI at age 41 showed findings of chondromalacia, with thinning of the articular cartilage over both femoral condyles.

2.3. Summary of cases

Nine adults with HPP are described (7 women, 2 men), with ages ranging from 33 to 70 years; the median age at HPP diagnosis was 41 years (range, 3–57 years). Summaries of key patient characteristics, including *ALPL* genotypes, are provided in Table 1. Eight out of 9 patients had demonstrated dental manifestations of the disease in childhood; 7 experienced premature loss of primary teeth at ages ranging from 8 months to 4 years (Cases 3–9); 1 had persistence of primary teeth requiring extraction (Case 1; estimated 8 years of age at teeth removal); and 1 had absence of some primary teeth (Case 7). Despite the childhood dental presentation with or without pathological fractures, as well as evaluation by multiple specialists, the delay in diagnosis of HPP following childhood dental problems ranged from 20 years (Case 4) to 54 years (Case 6), with a median of 46 years in the affected patients (Cases 1, 4–8) (not shown in Table 1). The diagnosis of HPP was also delayed since the first fracture or onset of major adult tooth problems in 7 patients (Cases 1, 2, 4, 5, 6, 7 and 8), ranging from 8 years (Case 1 estimate) to 45 years (Case 5), with a median of 27 years; only 2 patients (Cases 3 and 9) were diagnosed with HPP shortly after tooth loss. All 9 patients had complaints of chronic muscle/joint pain affecting their quality of life, either since childhood or young adulthood. Eight patients had recurrent pathological fractures, ranging in number from 2 to 25 fractures, with a median of 8 fractures to date. Five patients experienced bone fractures during childhood (Cases 3, 4, 5, 8, and 9) at ages 17, 14, 8, 12, and 6 years, respectively. The remaining 4 did not report bone fractures during childhood, but 2 showed other symptoms that might be considered suggestive of HPP, such as chronic joint pain and foot deformity (Cases 1 and 7). Four patients (Cases 6–9) were compound heterozygotes for *ALPL* gene mutations. Chemistry values for 25-hydroxy vitamin D (25-OH vitD), calcium, parathyroid hormone, and phosphorus were generally within the reference ranges, with few exceptions (*e.g.*, elevated 25-OH vitD in Case 2). PLP was elevated in all patients. All reviewed cases had low serum ALP levels, near or below the lower limit of the adult reference range (Table 2).

3. Discussion and conclusion

Findings from our case series suggest that patients with an isolated dental manifestation of HPP in childhood may later develop the adult or childhood forms of the disease. Therefore, odontoHPP may well be more appropriately characterized as a disease manifestation of patients with HPP during their childhood rather than as a discrete diagnostic category in cases when premature tooth loss is the primary manifestation. It should be noted that there is a subset of patients with premature tooth loss who do not go on to develop other bone manifestations of HPP and are thus likely true odontoHPP patients, as defined in the literature. Most (8/9) of the patients in this case series showed clear signs of early deficits in dental health during early childhood between ages 8 months and 4 years. The pathology of persistent primary teeth in Case 1 was not made clear and may or may not be due to his HPP. Without additional gross evidence of skeletal abnormalities, the other 8 subjects appeared to have met the dental criteria for odontoHPP until additional bone-related pathologies manifested much later in life. Interestingly, at the initial dental presentation, most of them (6/8) did not receive an odontoHPP or HPP diagnosis. Increased awareness of the early disease presentation of HPP among dental and primary care providers is warranted. More has to be learned to permit distinguishing those patients who have premature loss of primary teeth as the discrete diagnostic category from those where this tooth loss is an initial manifestation of signs and symptoms of HPP. Low total ALP in the setting of a clinical history of dental issues and/or skeletal manifestations is strongly suggestive of HPP.

Our study also demonstrates significant disease burden in these patients with what was thought to be a mild form of HPP, with many of them suffering frequent fractures, chronic pain, restrictive life style, and depression due to chronic pain and fear of sustaining pathological fractures. Eight of the 9 patients did in retrospect manifest non-dental signs/symptoms in childhood such as skeletal deformity and fractures, and all suffered from chronic muscle pain and depression (personal observations). Notably, nearly all (8/9) patients experienced fractures, either starting in childhood between the ages of 6 and 17 years (Cases 3–5, 8, and 9) or in adulthood (≥18 years old) (Cases 2, 6, and 7).

In our series, the diagnosis of HPP was often significantly delayed (median of 46 years since the initial dental presentation and 27 years since the first fracture/major adult tooth problem) despite low ALP levels or a substantial disease burden often starting in childhood. The early diagnosis and appropriate follow-up of these patients, starting from the initial presentation in childhood and continuing into adulthood, is important so that other symptoms of HPP can be identified and treated at their earliest presentation. Bone-targeted enzyme replacement therapy with asfotase alfa (a human recombinant TNSALP fusion protein) has shown promising results in infants and young children (Whyte et al., 2012), and is now approved as therapy in many countries worldwide (currently approved for perinatal/infantile/childhood-onset forms in the United States, Canada, and European Union; and for all categories of HPP in Japan). Clinical trials for adolescent and adult HPP are underway (NCT01163149; NCT00739505). Early diagnosis could offer patients the opportunity to benefit from this therapy as it becomes widely available.

The strength of this study is the post-HPP diagnosis interview process, which facilitated targeted medical history elicitation in regard to skeletal and dental events. The study is limited by its observational case-based nature and the absence of a control group.

Patients with premature primary tooth loss or significant dental abnormalities in the setting of low ALP for age should be evaluated for a diagnosis of HPP. These patients should be followed closely for other manifestations of HPP, including developmental delay, hypotonia, skeletal abnormalities, hypercalcemia, chronic pain/fatigue, and pathological fractures. Patients presenting with apparently isolated dental symptoms should be monitored for the emergence of bone or systemic symptoms during the remainder of childhood and throughout adulthood. Based on our observations, we would propose that the term *odontohypophosphatasia* should be used to describe the dental manifestation(s) of the disease and that its use as a diagnostic category should be reserved until much later in life when extra-dental manifestations have not become evident after long-term follow-up.

Table 1
Key characteristics of 9 adult patients with HPP.

Case	Age (y)/gender	Early dental issues	Age of first fracture (y)	Fractures (no.)	Other bone issues	Other disease burden	Genotype[a]	Inheritance	Family history of HPP	Diagnosing specialty	Age at diagnosis (y)
1	35/male	Persistent primary teeth, requiring extraction	No fractures	0	Chronic back pain; bone pain	Chronic fatigue; difficulty sleeping, joint pain	c.335_340dupACCGCC (p.Gly112_Thr113dup2) in exon 5	AD	Sister and niece: c.335_340dupACCGCC (p.Gly112_Thr113dup2). Father and paternal uncle with symptoms without confirmed diagnosis	Unknown	33, due to positive family history
2	70/female	No dental complaints	26	21	Delayed healing of fractures; bone pain	Feeding difficulty	c.1328C > T (p.A443V) in exon 12	AD	Unknown	Rheumatology	53
3	32/male	Loss of all primary teeth starting at 8 months	17	2	–	Unusual gait	c.1133A > T (p.D378V) in exon 10	AD	Asymptomatic 2-year-old son: confirmed familial mutation. Mother, sister, brother, and a maternal aunt with symptoms without diagnosis. Confirmed HPP	Endocrinology	3
4	58/female	Primary tooth loss at age 3 years	14	7	Bone pain; abnormally shaped head; genu valgum	Unusual gait; delayed talking; muscle pain and weakness; joint pain and swelling	c.1133A > T (p.D378V) in exon 10	AD	Niece: prenatally diagnosed HPP. Son of a different niece: confirmed HPP	Endocrinology	23, due to positive family history
5	62/female	Loss of all front primary teeth at 13 months	8	7	Bone pain	Unusual gait	c.1133A > T (p.D378V) in exon 10	AD	Son and granddaughter through the son: confirmed HPP	Unknown	53
6	63/female	Primary tooth loss at age 3 years	19	9	Bone pain	Difficulty eating/swallowing	c.526G > A (p.A176T) in exon 6/c.648 + 1G > A in IVS6	AR	Sister (Case 7): confirmed with HPP	Endocrinology	57
7	50/female	Primary tooth loss before age 2; absent primary teeth	18	19	Bone pain	Unusual gait; joint pain/swelling; long QT; hypokalemia	c.526G > A (p.A176T) in exon 6/c.648 + 1G > A in IVS6	AR	Sister (Case 6): extractions of all of her teeth; metatarsal stress fractures	Endocrinology	41
8	60/female	Primary tooth loss at age 3 years	12	25	Bone pain	Unusual gait; joint hypermobility; joint dislocation/pain; muscle pain/weakness, carpal tunnel surgery, pneumonia	c.571G > A (p.E191K) in exon 6/c.661G > C (p.G221R) in exon 7	AR	Brother: premature tooth loss	Endocrinology	55
9	59/female	Primary tooth loss at 3–4 years	6	6	Club foot; bone pain	Unusual gait; gout	c.571G > A (p.E191K) in exon 6/c.1250A > G (p.N417S) in exon 11	AR	Unknown	Unknown	4

AD, autosomal dominant; AR, autosomal recessive.
[a] Mutations shown are to the *ALPL* gene; Genbank accession number NG_008940.1.

Table 2
Clinical chemistry values in patients with HPP.

Patient ID	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age (y)/M or F	35 M	70 F	32 M	58 F	62 F	63 F	50 F	60 F	59 F
Calcium [8.3–10.6 mg/dL]	9.6	10.2	9.8	10.1	10.3	10.0	9.6	10.4	10.0
Phosphorus [2.2–5.1 mg/dL]	4.4	5	5.1	5.1	4.8	5.5	5.1	5.4	4.5
Alk Phos[a]	17	<18	20	<18	33	24	<18	<18	<18
PTH [11–72 pg/mL]	25	19	nm	31	34	33	42	35	24
25-OH vitD [12–50 ng/mL]	24	67.4	20	47.2	34	37	32.9	31.1	27.6
PLP [5–50 ng/mL]	112	577	163	90.3	249.5	474	508	267	288.8

Alk phos, alkaline phosphatase; F, female; M, male; PTH, parathyroid hormone; 25-OH vitD, 25-hydroxy vitamin D; PLP, pyridoxal-5′-phosphate; nm, not measured; y, years. Values in brackets [] are reference ranges.
[a] Alk phos reference ranges: women, 50–70 y: 35–123 U/L; men, 18–50 y: 31–129 U/L.

Conflict of interest and sources of funding statement

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PSK received travel support and honoraria and is a clinical trial investigator and Registry Chair for Alexion Pharmaceuticals, Inc.

MM and SLD declare no conflicts of interest.

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