PERSPECTIVE

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Hypophosphatasia in Adults: Clinical Assessment and Treatment Considerations

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ABSTRACT

Hypophosphatasia (HPP) is a rare inherited disorder of bone affecting approximately 500 to 600 known individuals in the United States. HPP is the result of mutations involving the gene for tissue nonspecific alkaline phosphatase. Five clinical types of HPP are recognized. The clinical presentation of HPP varies from devastating prenatal intrauterine disease to mild manifestations in adulthood. In adults, main clinical involvement includes early loss of primary or secondary teeth, osteoporosis, bone pain, chondrocalcinosis, and fractures. Treatment for HPP is limited. Asfotase alfa is a subcutaneously administered synthetic human alkaline phosphatase that is approved for treatment of patients, including adults, with perinatal/infantile- and juvenile-onset HPP. However, guidelines for the treatment of adults with HPP are not available. This discussion addresses diagnostic and treatment considerations for adults with HPP. © 2017 American Society for Bone and Mineral Research.

KEY WORDS: HYPOPHOSPHATASIA; OSTEOPOROSIS; ALKALINE PHOSPHATASE; OSTEOMALACIA; ASFOTASE ALFA

Introduction

Hypophosphatasia (HPP) is a rare disorder affecting mineralization in bone and teeth.[1] To date, approximately 500 to 600 individuals have been recognized in the United States; additional affected individuals may be unrecognized or misdiagnosed. Treatment is now available for HPP in infants and children.[1] However, less has been written about the diagnosis and treatment of HPP in adults. In addressing these issues, we offer an overview of what is currently known of HPP in adults. Our aim is to promote discussion and further study of the management of adults with HPP until the medical evidence and clinical experience are sufficient to allow the development of evidence-based clinical practice guidelines.

HPP is the result of mutations involving the gene ALPL on chromosome 1, which encodes for tissue nonspecific alkaline phosphatase (TNSALP), an ecto-enzyme bound to membrane inositol-phosphate on the outer surface of osteoblasts reported in standard laboratory test metabolic panels as total serum alkaline phosphatase.[2] This enzyme dephosphorylates several substrates, including inorganic pyrophosphate (PPi), an inhibitor of bone mineralization produced by osteoblasts and chondrocytes. The accumulation of PPi when TNSALP is deficient impairs tissue calcium/phosphate formation of hydroxyapatite, leading to the accumulation of unmineralized osteoid, a feature of rickets and osteomalacia.

Background

There are five major clinical types of HPP (Table 1). The disorder is more severe and may be lethal when expressed in utero or perinatal in infants. Certain infants with the perinatal phenotype may follow a more benign course for reasons unexplained. However, when symptoms first occur at older ages, as in childhood or in adults, the expression of the disease, although variable, tends to be less severe. Inherited as either an autosomal recessive or autosomal dominant trait, HPP is characterized by marked variability in clinical expression, even within affected families. There is no defined treatment for adults with HPP. Teriparatide has been used with variable success.[3] Recombinant human alkaline phosphatase (asfotase alfa) was approved by the US Food and Drug Administration (FDA) in October 2015 for treatment in adults where evidence of the disease was present in childhood (Strensiq; Alexion Pharmaceutical, New Haven, CT, USA).[4] We discuss here the clinical findings in adults with HPP that would suggest consideration of treatment with asfotase alfa, understanding that there are no current data regarding effectiveness or optimal treatment regimen in adult HPP.

The hallmark of HPP is a low age- and sex-adjusted total serum alkaline phosphatase (ALP). ALP levels decrease from high levels during childhood to adult levels of 40 U/L to 117 IU/L at the age of 13 to 14 years in females and 15 to 17 in males.[5] Some drugs (eg, glucocorticoids, fibrates, estrogen) and multiple systemic illnesses (eg, zinc and magnesium deficiency, celiac disease,

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Table 1. Clinical Types of Hypophosphatasia

Perinatal	In utero and at birth
Infantile	<6 months
Childhood/juvenile	>6 months to >18 years
Adult	>18 years
Odontohypophosphatasia (dental only)	Any age

malnutrition, multiple myeloma) may also decrease ALP levels; these must be considered when interpreting a serum level less than 40 U/L. However, as emphasized by Maman and colleagues and as we have confirmed in our review of patient records, low ALP is often not recognized by physicians as a matter of clinical concern.[6]

There is great heterogeneity of clinical expression in adults with HPP. Adults may be essentially asymptomatic, have nonspecific symptoms such as joint pain or loss of secondary teeth, and have low bone mineral density (BMD). A history of childhood symptoms and early loss of primary teeth may have been forgotten. Joint pain and restricted motion are common in HPP as a consequence of chondrocalcinosis. HPP may be associated with deposition of hydroxyapatite crystals in rotator cuff, elbow, and Achilles tendons. Some patients are disabled with recurrent poorly healing fractures. Berkseth and colleagues reported the clinical findings of 22 adults with HPP diagnosed from 1976 through 2008 at the Mayo Clinic (Rochester, MN, USA).[7] In this cohort, the median minimum serum ALP was 43% below normal limit. Most of the patients (68%) were symptomatic at presentation, and 41% had musculoskeletal pain. A history of fracture was present in 54%, with 36% having multiple fractures. Chondrocalcinosis was found radiologically in 27%; 14% had pyrophosphate arthropathy. Atypical femur fractures have been reported in a patient with HPP who was treated with alendronate, suggesting that HPP may be a risk factor for this rare type of fracture, especially in the setting of treatment with a bisphosphonate.[8] In a retrospective case–control study of 10 individuals with atypical femur fractures previously treated with bisphosphonates and 13 patients on bisphosphonates without such fractures, there was no biochemical or genetic evidence implicating hypophosphatasia as a risk factor these fractures;[9] none of the patients in this study had a diagnosis of HPP.

The impact of HPP on patients' quality of life was examined by Weber and colleagues in a group of 125 patients by means of advocacy groups and survey questions concerning medical history, mobility, and health-related quality of life.[10] Similar to the report of Beckseth and colleagues,[7] 95% of patients listed pain as a major complaint, 86% of patients had fractures, and 26% reported more than 10 fractures; 62% had muscle weakness, and 52% reported unusual gait. Sixty percent reported use of assistive devices for mobility; 74% of patients had undergone orthopedic/dental surgical procedures.

Diagnosis of HPP in Adults

Adults with HPP may come to clinical attention by finding low-serum ALP on routine laboratory testing or during the course of evaluation for osteoporosis or fractures. If low-serum ALP is confirmed on repeat testing and other causes of low ALP are eliminated, elevation of serum pyridoxal-5′-phosphate (vitamin B6) and/or elevation of urinary of phosphoethanolamine (PEA) support the diagnosis. Only one of these biomarkers may be elevated in some patients with HPP. The finding of a mutation in the ALPL gene provides additional level of confirmation, but is not a requirement for the clinical diagnosis of HPP.

Treatment of HPP in Adults

Treatment with teriparatide in an effort to increase osteoblast production of ALP has been reported to date in a total of 10 adult patients. However, the effects of treatment on BMD have been variable. Teriparatide reportedly improved pain, mobility, and fracture repair in two sisters with HPP ages 56 and 64 years.[11] Comacho and colleagues treated two women, ages 53 and 68 years, with HPP.[12] Serum ALP increased in one patient while receiving teriparatide, but BMD remained unchanged; no new fractures were sustained. Serum ALP increased transiently in the second patient. Femoral neck BMD increased significantly during the first cycle, declined significantly afterwards, and was regained during a second course of teriparatide. However, a fracture occurred shortly after treatment was discontinued. Teriparatide treatment failed to heal a humerus fracture with pseudoarthrosis in a 43-year-old woman with HPP.[13]

A recent publication reports the treatment of 8 adult patients with HPP with a monoclonal anti-sclerostin antibody (BPS804) in a phase IIA escalating-dose trial.[14] Treatment for 29 weeks increased bone formation markers as well as a transient decrease in the bone resorption marker C-telopeptide. Lumbar spine BMD showed a mean increase of 3.9% at end of the study.

After the FDA approval of asfotase alfa, it has been used to treat infants, children, and some adults with HPP.[15,16] At this time, there are no guidelines for selecting adult patients for treatment, for evaluating the results of treatment, or determining the optimal duration of treatment. Because treatment with asfotase alfa is likely to be expanded as more patients are diagnosed, we present suggestions for the evaluation of patients with regard to indications for starting treatment and assessment of treatment response. The question of how long treatment should be continued must await the evaluation of clinical trials.

Care should be taken to avoid some medications commonly used in the treatment of osteoporosis that might be harmful in patients with HPP. Treatment with bisphosphonates and possibly denosumab may have adverse effects in adults with HPP. Any potent antiresorptive agent might lower serum ALP, which is already low in patients with HPP. Excessive vitamin D intake may aggravate the occurrence of hypercalcemia and hypercalciuria.

Considerations Related to the Treatment of Adults with HPP

The recent interest in treating adults with HPP occurs at a time when the clinical indications for initiating treatment are not defined, in part because this is a rare disorder with which most physicians have no or limited experience. Because there is a paucity of data and little guidance from the FDA for identifying adult HPP patients for treatment with asfotase alfa, we suggest that one or more of the following criteria, when felt to be

secondary to HPP, be present before treatment is considered. Although these are suggested as potential clinical indications for treatment, we suggest that the extent of disability should also be a major factor guiding the decision to treat. The fundamental principles for treating adults with HPP are that the goals of treatment should be identified before starting treatment and that objective baseline and follow-up assessments are made to monitor for treatment effect and attainment of the treatment goals. The patient may assist in setting individualized treatment goals.

We suggest that treatment of adults with HPP be considered when there is a history of childhood involvement (before age 18 years), such as early loss of primary or secondary teeth, craniosynostosis, gait disturbance, developmental delays, skeletal deformity, bone pain or fractures, or when there is no documentation of childhood symptoms, and one or more of the following is present, determined to be clinically significant and attributable to HPP:

1. Musculoskeletal pain requiring prescription pain medications, especially chronic opioids
2. Disabling polyarthropathy or chondrocalcinosis
3. Major low-trauma fracture (eg, spine, hip, humerus, pelvis) attributable to HPP
4. Delayed or incomplete fracture healing or fracture non-union
5. Repeated episodes of orthopedic surgery for complications of HPP, especially for non-union and delayed union fractures
6. Disabling functional impairment (eg, mobility, gait, activities of daily living) assessed by validated measures
7. Low BMD by dual-energy X-ray absorptiometry (DXA): *T*-score ≤ -2.5 in postmenopausal women and men age 50 years and older, or *Z*-score ≤ -2.0 in younger adult women and men in patients with fractures
8. Radiological evidence of nephrocalcinosis </NL>

Some of these clinical manifestations of HPP have a more robust association with disease severity than others and any of them may be present and not attributable to HPP. Treatment decisions should be individualized according to all available clinical information, including patient preference. The list is not intended to be all-inclusive. Assessment of outcomes for patients selected for treatment according to these criteria or others requires validation in clinical trials. The optimal dose of asfotase alfa, dose adjustments, duration of therapy, and possible cycling of dosing in adults with HPP are unknown. Adverse effects of long-term therapy have not been defined.

Safety Assessments

The most common adverse reactions ($\geq$10%) are injection site reactions, lipodystrophy, ectopic calcifications, and hypersensitivity reactions. Lipodystrophy, including lipoatrophy and lipohypertrophy, may occur, with localized reactions during several months of treatment. Ectopic calcifications of the eyes and kidneys can be assessed with baseline and follow-up ophthalmologic examinations and renal ultrasounds. Serum ALP measurements on treatment may be greatly elevated but do not appear to have harmful effects.

Considerations for Efficacy and Safety Assessments at Baseline and 6- to 12-Month Intervals (According to Clinical Circumstances)

1. Musculoskeletal-focused physical exam, including bone tenderness, gait speed, mobility, and joint range of motion
2. Imaging for joint chondrocalcinosis
3. Renal ultrasound for nephrocalcinosis and renal stones
4. Ophthalmoscopic evaluation for ectopic calcification of the eye including the cornea and conjunctiva
5. Annual DXA BMD testing
6. Quality-of-life questionnaire (eg, The Oswestry Disability Index, SF-36/12, or SF-36v2 health surveys)
7. Assessment of pain severity and use of pain medication
8. Improvement in activities of daily living</NL>
9. The decision to continue treatment should be reassessed at 6- to 12-month intervals with appropriate consideration of the balance of benefits and risks, achievement of treatment goals, or likelihood of achieving the goals.

Summary

These suggestions are intended to provide information relative to the management of adults with HPP. Unlike data available after treatment of children with severe HPP, the benefits and risks of treatment in adults remain to be determined. Given the high cost of treatment and uncertainties of the treatment effects in adults with HPP, the use of asfotase alfa should be reserved for severely affected patients with well-documented disease. To facilitate the collection of data, we recommend that physicians treating adults with HPP enroll them in the Hypophosphatasia Registry sponsored by Alexion Pharmaceuticals (HPPRegistry.com). We also highly recommend clinical investigation of adult treatment indications, outcomes of treatment, and strategies to monitor treatment effect. The suggestions in this report are preliminary and may serve as an aid to physicians treating this potentially devastating disease until evidence-based clinical practice guidelines can be developed.

Disclosures

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