PERSPECTIVE

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Hypophosphatasia: Enzyme Replacement Therapy Brings New Opportunities and New Challenges

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ABSTRACT

Hypophosphatasia (HPP) is caused by loss-of-function mutation(s) of the gene that encodes the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP). Autosomal inheritance (dominant or recessive) from among more than 300 predominantly missense defects of TNSALP (ALPL) explains HPP's broad-ranging severity, the greatest of all skeletal diseases. In health, TNSALP is linked to cell surfaces and richly expressed in the skeleton and developing teeth. In HPP,TNSALP substrates accumulate extracellularly, including inorganic pyrophosphate (PPi), an inhibitor of mineralization. The PPi excess can cause tooth loss, rickets or osteomalacia, calcific arthropathies, and perhaps muscle weakness. Severely affected infants may seize from insufficient hydrolysis of pyridoxal 5′-phosphate (PLP), the major extracellular vitamin B_6. Now, significant successes are documented for newborns, infants, and children severely affected by HPP given asfotase alfa, a hydroxyapatite-targeted recombinant TNSALP. Since fall 2015, this biologic is approved by regulatory agencies multinationally typically for pediatric-onset HPP. Safe and effective treatment is now possible for this last rickets to have a medical therapy, but a number of challenges involving diagnosis, understanding prognosis, and providing this treatment are reviewed herein. © 2017 American Society for Bone and Mineral Research.

KEY WORDS: ALKALINE PHOSPHATASE; CALCIFICATION; CHONDROCALCINOSIS; HYDROXYAPATITE; HYPERCALCEMIA; INBORN-ERROR-OF-METABOLISM; INORGANIC PYROPHOSPHATE; MATRIX VESICLE; MINERALIZATION; OSTEOMALACIA; RICKETS; VITAMIN B_6

Introduction

In fall 2015, our field achieved a milestone in the management of rickets and osteomalacia. Among the disorders that feature generalized impairment of hard tissue mineralization and its consequences,[1] the final entity lacking a medical treatment acquired one sanctioned internationally by regulatory agencies. The holdout was hypophosphatasia (HPP), the inborn-error-of-metabolism identified in 1948[2] and caused by loss-of-function mutation(s) of the TNSALP (ALPL) gene that encodes the "tissue-nonspecific" isoenzyme of alkaline phosphatase (TNSALP).[3,4] The therapy is asfotase alfa (AA), a recombinant bone-targeted ALP now typically approved for pediatric-onset HPP.[5–7] This advance ended hopelessness for many HPP patients and offers physicians important successes in treating an orphan disease. However, as I will discuss, a number of challenges call for further progress and an especially thorough understanding of HPP, particularly its wide-ranging severity.[3,4] Reviews concerning HPP,[3,4,8] including comprehensive reports from testing this biologic in pediatric patients,[5–7] have been published recently.

Background

TNSALP (liver/bone/kidney ALP) is found on cell surfaces, richly in the skeleton and developing teeth.[8] In HPP, deficient TNSALP phosphohydrolase activity leads to extracellular accumulation of its natural substrates,[3,4] including inorganic pyrophosphate (PPi),[9] a potent inhibitor of hydroxyapatite (HA) crystal formation and propagation.[10] Mineralization that should occur, including after rupture of matrix vesicles (MVs) containing nascent HA crystals, is instead blocked by the superabundance of extracellular PPi (ePPi).[11] Consequently, patients suffer dental disease and a distinctive rickets or osteomalacia.[5,6] In severely affected neonates and infants, insufficient dephosphorylation of pyridoxal 5′-phosphate (PLP), the major circulating form of vitamin B_6, can compromise neurotransmitter synthesis in the brain and cause epilepsy.[12] Reports now totaling several hundred HPP patients have delineated the disorder's key clinical and biochemical features and its radiographic and histopathological findings in the skeleton. The genetic basis is established, and its pathophysiology is largely understood.[3,4,8] The extraordinarily broad expressivity of HPP is known to span at one extreme death in utero due to an unmineralized skeleton, and at the other extreme dental complications or arthropathy without bone disease presenting in middle age or later.[3,4,13] I see HPP's range of severity as greatest among all skeletal diseases.[3] Life-threatening HPP reflects autosomal recessive inheritance[14,15] and occurs in ~1 per 100,000 and 300,000 births in Canada[16] and in Europe,[17] respectively. For Mennonites in Manitoba, Canada, ~1 in 25

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individuals carries a *TNSALP* founder mutation, and ~1 in 2500 newborns manifests perinatal HPP.[18] Two *TNSALP* founder mutations underlie severe HPP in the Japanese.[19] In the United States, white ancestry seems disproportionately predominant for HPP,[14,20] and two prevalent *TNSALP* missense defects explain relatively many occurrences from autosomal dominant inheritance.[21,22] *TNSALP* mutation analysis has suggested "moderately" severe HPP affects 1 in 6370 Europeans.[17] HPP carrier prevalence in the United States and in Europe (E Mornet, personal communication) might be 1 per 250 to 300 people.

HPP Nosology

Beginning in 1957,[16] a clinical nosology for HPP evolved that helps organize its remarkable range of severity that is largely explained by autosomal recessive or autosomal dominant transmission from among at least 310 mutations (typically missense) scattered throughout *TNSALP* (*ALPL*).[15] This nosology emphasizes whether only dental manifestations are present, or patient age when skeletal or other significant complications have emerged.[3,4] Now, seven major forms of HPP guide recurrence risk prediction, prognostication, and research.[23–25] Dental issues alone denote "odonto" HPP, the mildest and likely most common HPP. Then, ranked by increasing severity with younger age at presentation and perhaps diminishing prevalence, clinicians can encounter "adult" HPP, "mild childhood" HPP, "severe childhood" HPP, "infantile" HPP, and "perinatal" HPP.[3,4] Finally, "benign prenatal" HPP refers to the newborn with skeletal abnormalities in utero or at birth from HPP that improve spontaneously during late pregnancy and ex utero.[23] I refer to the many people who harbor one *TNSALP* mutation yet have good health as "carriers" of HPP (see Challenges). These principal forms of HPP are described briefly below.

Odonto HPP refers to dental complications of HPP at any age but without other physical or radiographic signs of the disease. Painless premature (ie, age <5 years) loss of one or more deciduous teeth with root intact (Fig. 1) reflects the exquisite sensitivity of the primary dentition to TNSALP deficiency. Inadequately mineralized cementum compromises tooth root anchorage to the periodontal ligament. Skeletal radiographs (Fig. 2*A*) and bone biopsy show no abnormalities, and health is otherwise good (Supplemental Video S1).

Adult HPP typically presents in middle age,[26–28] yet some patients recount early shedding of deciduous teeth or past rickets.[3,4] Loss of secondary dentition seems common.[26] Then, recurrent metatarsal stress fractures beginning in adult life eventually fail to heal.[26–28] Subsequently, hip or thigh pain may indicate femoral pseudofractures,[29] a radiographic hallmark of osteomalacia resembling the prodromal lesion of atypical subtrochanteric femoral fractures associated with bone antiresorptive treatment (Fig. 3).[30] Excessive ePPi can also cause calcium pyrophosphate dihydrate crystal deposition (chondrocalcinosis) and PPi arthropathy including pseudogout.[31,32] Seemingly paradoxical in HPP, calcific periarthritis is deposition of HA near joints[13] and syndesmophytes can cause ankylosing spinal hyperostosis (Forestier disease).[31] Recurrent fracturing, skeletal and joint pain, and muscle weakness sometimes become debilitating.[33]

Childhood HPP presents during growth after age 6 months. Premature exfoliation of one or more primary teeth is nearly inevitable,[14,20] and sometimes all are lost early.[14] Health is generally good in mild childhood HPP (Supplemental Video S2), with only subtle bone changes disclosed radiographically (Fig. 2*B*). In contrast, severe childhood HPP substantially compromises health (Supplemental Video S3) and skeletal pain and muscle weakness can be significant. These patients can have a misshapen skull, bowed legs or knock knees, and enlarged "joints" from metaphyseal flaring. Muscle weakness helps explain their delayed walking and waddling gait.[6,34] Craniosynostosis can raise intracranial pressure and damage the brain. Radiographs of major long bones reveal characteristic "tongues" of lucency projecting from growth plates into metaphyses where there is patchy osteosclerosis and osteopenia (Fig. 2*C*).[3–6] Physes can be wide and irregular and metaphyses flared. Dental pulp chambers and root canals may be large and resemble "shell teeth." Nevertheless, HPP in children is typically a stable condition.[25] In young adult life, musculoskeletal symptoms sometimes improve or resolve, perhaps from growth plate fusion and/or diminished need for TNSALP. Permanent teeth fare well at first, but dental and skeletal problems may reemerge.

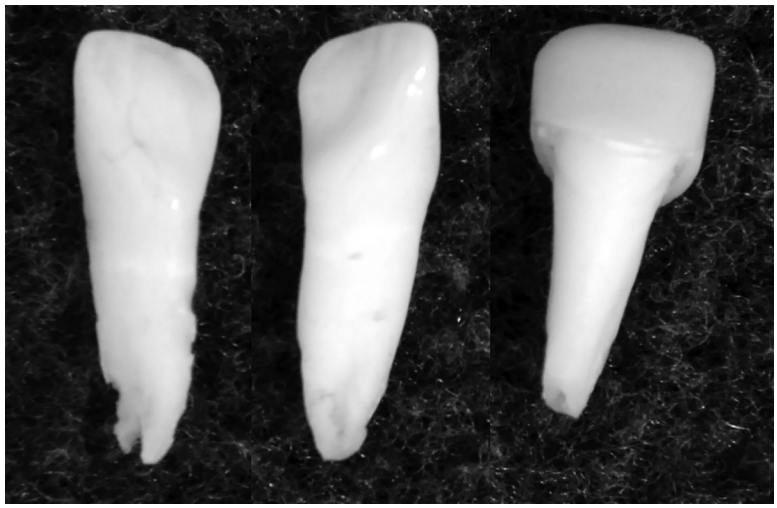

Fig. 1. HPP tooth loss: These deciduous incisors were shed prematurely with root intact, a hallmark of pediatric HPP.

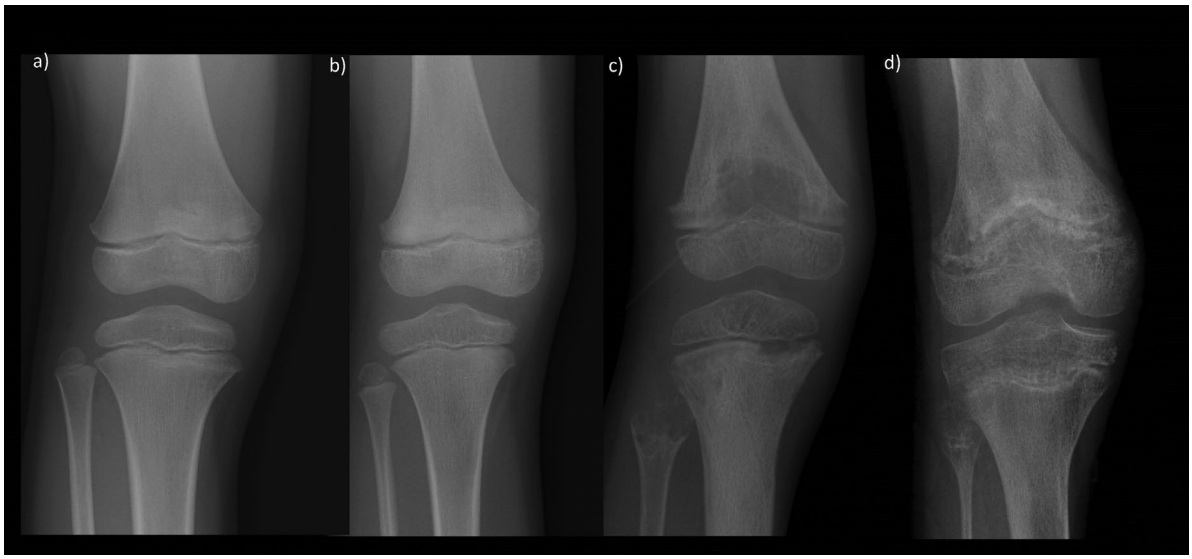

Fig. 2. Radiographic severity of HPP in children: Anteroposterior view of the right knee of the patients shown in the videos. Note no abnormalities in odonto HPP (*A*), subtle changes observed here best in the head of the fibula in mild childhood HPP (*B*), characteristic "tongues of radioluency" and metaphyseal changes in severe childhood HPP (*C*), and especially marked findings in the survivor of infantile HPP (*D*).

Infantile HPP presents postnatally before age 6 months.[3,4] Often there is acquired poor feeding, failure to thrive, weakness, and delayed motor milestones accompanying signs of rickets.[5] Cranial sutures may be functionally closed, or after infancy undergo bony fusion, elevating intracranial pressure. Hypercalcemia and hypercalciuria from blocked mineral entry into the skeleton can cause nephrocalcinosis, sometimes with renal compromise.[5] The radiographic skeletal features are pathognomonic (Fig. 2*D*).[5,35] Death from pneumonia is predicted if worsening bone disease causes rib fractures with thoracic deformity and instability or if pyridoxine-dependent seizures occur.[7,12] Mortality has been estimated to be 50% during infancy.[3,4]Survivors can have significant debility (Suppemental video S4).

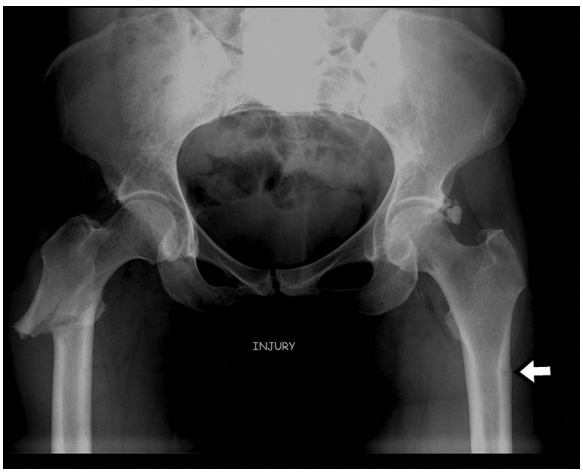

Fig. 3. Adult HPP: This 36-year-old woman has a subtrochanteric fracture of her right femur matched by a prodromal pseudofracture[30] in her left femur (arrow).

Perinatal HPP, the most sinister HPP, almost invariably kills in utero or soon after birth.[7,36] Caput membraneceum and short and deformed limbs reflect profound skeletal hypomineralization. Calvarial bones can feel mineralized only centrally. Pyridoxine-dependent seizures, unexplained fever, irritability, myelophthisic anemia, and intracranial hemorrhage may occur.[37] Sometimes the lungs are deemed hypoplastic.[38] Several or nearly all bones can appear completely unmineralized, contributing to the pathognomonic radiographic findings (Fig. 4).[5]

Benign prenatal HPP signifies relatively mild skeletal abnormalities in utero, usually detected by sonography or revealed at birth, that improve spontaneously in late pregnancy and/or ex utero and then range broadly in severity from odonto to infantile HPP. Typically, the mother harbors a *TNSALP* defect,[23] perhaps further deleterious to the HPP fetus.

Pathogenesis

Nearly all rickets/osteomalacia features hypocalcemia and/or hypophosphatemia.[1] HPP is a striking exception in which TNSALP deficiency instead causes the following three phosphocompounds to accumulate extracellularly: phosphoethanolamine (PEA),[39] PPi,[9,10] and PLP.[40] In health, osteoblasts and hypertrophic chondrocytes richly express the bone isoform of TNSALP,[8] including their MVs that are buds of the plasma membrane.[11] After the MV ruptures, elevated ePPi in HPP adsorbs to the HA crystal, preventing its growth and skeletal mineralization,[10] and sometimes leads to excessive extracellular calcium (Ca) levels.[3–5] In severe HPP, vitamin D levels are unremarkable,[41] and this hypercalcemia can suppress parathyroid hormone (PTH) levels,[5] helping to explain hyperphosphatemia. High ePPi in adults with HPP would also explain chondrocalcinosis, PPi arthropathy, or pseudogout,[13,32,42] and

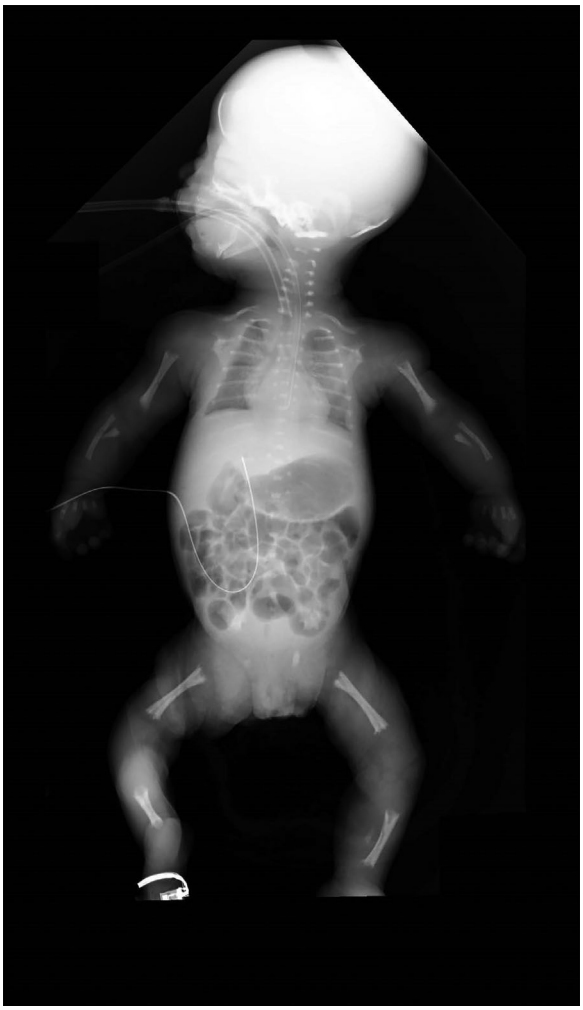

Fig. 4. Perinatal HPP: The pathognomonic constellation of findings includes the poorly mineralized skull and non-apparent bones (fibulas, pubic bones, many vertebrae) with ossified portions of long bones that are short with frayed ends. The ribs are very thin and clavicles small. The radius, ulna, and hand bones are largely inapparent.

in certain tissues could enhance calcium phosphate deposition[43] underlying their calcific periarthritis and perhaps ligament calcification and syndesmophyte formation.[13,31,32] Although eucalcemia and normal serum PTH levels typify childhood and adult HPP, above average (and sometimes frankly elevated) circulating inorganic phosphate (Pi) levels reflect enhanced renal reclamation of Pi.[44,45] Directly, or perhaps by controlling urinary PPi levels,[46,47] TNSALP seems to facilitate kidney excretion of Pi.[46] Vitamin B_6-dependent seizures in HPP signify decreased hydrolysis of PLP to pyridoxal necessary for uptake by the brain and neurotransmitter synthesis.[8,12] The pathogenesis of the muscle weakness in HPP is poorly understood. Notably, however, muscle weakness, rickets/osteomalacia, and hyperphosphatemia from enhanced kidney reabsorption of Pi characterize both HPP and etidronate toxicity.[46] Etidronate, a first-generation bisphosphonate (BP), is a PPi analogue. Perhaps the muscle weakness of HPP is somehow from ePPi toxicity.[44] Derangements of other tissues and organs in HPP can be secondary to the weakness and skeletal disease and (if present) indirectly to any hypercalcemia, hypercalciuria, and hyperphosphatemia. However, circulating ALP seems physiologically unimportant. HPP patients restored briefly to "euphosphat*asemia*" by repeated intravenous (IV) infusions of soluble ALPs have shown no significant clinical or radiographic improvement.[35,48]

Prognosis

Serum ALP and PLP levels both correlate with the severity of HPP[3] but too imprecisely for prognostication (in manuscript). The outcome for perinatal and infantile HPP seems principally to reflect the skeletal disease and muscle weakness, especially their impact on thoracic stability and pulmonary function.[5,7] In 2013, retrospective study of perinatal HPP in Manitoba, Canada, showed rapid and certain fatality.[36] When infantile HPP is first encountered, frequent clinical and radiographic assessments (perhaps monthly) have been crucial for prognostication.[5] In 2016, retrospective study of perinatal and infantile HPP documented 58% mortality within the first year of life if chest deformity, respiratory difficulties, and/or pyridoxine-dependent seizures had manifested before age 6 months.[7] However, after the especially rapid body growth of infancy, perhaps any endogenous TNSALP becomes more effective and rachitic disease sometimes improves significantly. Such patients can achieve normal adult height,[3,4] yet persisting complications seem likely. Childhood HPP is a chronic but generally stable disorder[25] that sometimes improves symptomatically and radiographically after growth plates fuse.[3,4] Nevertheless, complications from osteomalacia can eventually emerge.[33] The likelihood of odonto HPP or mild childhood HPP "reemerging" as adult HPP is not known, but we are exploring this using longitudinal and kindred investigations (unpublished). Adult HPP is a lingering condition that sometimes becomes debilitating.[26,29,33]

Diagnosis

HPP has been diagnosed confidently for decades. The hypophosphat*asemia* (low serum ALP) stands out as paradoxical for a rickets or osteomalacia and is expected even in odonto HPP.[14] Premature loss of one or more deciduous teeth with root intact occurs in nearly all affected children (Fig. 1). Pathognomonic radiographic changes characterize pediatric HPP when severe (Figs. 2 and 4). Affected adults,[4] like all HPP patients, share persistent hypophosphatasemia with TNSALP substrate accumulation. This is matched by a medical history, physical examination, and routine laboratory and radiographic studies (Fig. 3) indicating the osteomalacia of HPP. Accordingly, skeletal biopsy or *TNSALP* mutation analysis is typically unnecessary. However, some adults with HPP present only with calcific periarthritis from excess ePPi.[13,32]

In HPP, serum ALP and PLP are expected to be distinctly and persistently subnormal and elevated, respectively. Family investigation for these biochemical findings is often revealing because new mutation of *TNSALP* is rare, and other affected family members and some carriers will show these findings.[49] Blood for ALP assay must be collected correctly; chelation of Mg^{2+} or Zn^{2+} deactivates ALP.[8,46] In health, reference ranges for serum ALP change substantially for the pediatric age groups and become particularly high in puberty that normally occurs earlier for girls than boys.[8] Hence, reference values should be age- and sex-specific. Although the problem is waning, some

laboratories provide only adult normative values, and remarkably some give no lower limit. Hypophosphatasemia can reflect certain drugs (glucocorticoids, chemotherapy, tamoxifen, and perhaps bone antiresorptives), milk–alkali syndrome, vitamin D toxicity,[50] and occurs in some neonates with severe osteogenesis imperfecta[51] and in cleidocranial dysplasia.[52] Conditions that increase serum ALP (eg, third-trimester pregnancy, hepatobiliary disease, major fractures) could theoretically obscure a biochemical diagnosis of HPP,[19] and here quantitation of ALP isoenzymes and TNSALP isoforms might be helpful, although normative values are not precisely defined for all ages. Endogenous accumulation of TNSALP substrates in HPP is best documented by assaying serum PLP,[3,4] ordered from commercial laboratories as "vitamin B_6." Even odonto HPP reliably features this finding.[24,40] Elevated serum PLP is a sensitive, inexpensive, and apparently specific marker for HPP,[5,6,14,40] except that mild increases together with mild reductions in serum ALP can occur in HPP carriers[53] (see Challenges). False-positive serum PLP elevations are avoided if any vitamin B_6 supplementation can stop 1 week before testing.[53] An especially high serum PLP level after oral pyridoxine loading marks carriers as well as patients with HPP.[53] Assaying serum PLP also helps to assess instances of hypophosphatasemia unrelated to HPP, because elevated PLP seems expected only in HPP where all TNSALP isoforms are deficient, including bone and liver TNSALP (personal observation). High blood or urine PEA levels support a diagnosis of HPP,[54] but not consistently or specifically.[55] PEA values are conditioned by age and diet[55] and sometimes are normal in mild HPP.[37] Commercial or "inborn error" laboratories offer relatively costly PEA quantitation during amino acid profiling. PPi is elevated in the blood and urine of most HPP patients and some carriers[43] but currently is assayed only by research facilities.

Skeletal radiographs reveal pathognomonic changes in perinatal, infantile, and severe childhood HPP (see previously).[5,6] MRI helps identify a rare and painful bone marrow edema syndrome occurring in children and adolescents with HPP.[56] Dual-energy X-ray absorptiometry (DXA) may be compromised if there is bony deformity or short stature.[14] However, simple equations can correct DXA bone mineral density (BMD) *Z*-scores for height in prepubertal children, including those with HPP.[57] In adults with HPP, DXA BMD may paradoxically increase, sometimes becoming elevated, as osteomalacia emerges with more osseous tissue (personal observation). Especially then, radiologic evaluation, perhaps with atypical femur fracture assessment[29] by advanced DXA, will be important.

Nondecalcified skeletal histology shows impaired mineralization except in odonto HPP.[26,32,49] The rickets can feature unmineralized cartilage projecting into metaphyses. Characteristics of hyperparathyroidism, typical of most rickets or osteomalacias featuring hypocalcemia, are absent.[49] The cellular sources of skeletal ALP are present, but osteoblast numbers and morphology can vary.[26,49] Electron microscopy of perinatal and infantile HPP reveals normally distributed MVs[11,49] containing HA crystals, yet with only isolated or tiny groups of HA calcospherites nearby.[11] Weak muscles seem normal on routine laboratory testing (eg, EMG, muscle enzymes) including biopsy.[34]

Shed deciduous teeth, even if unpreserved, show hypomineralized cementum. Large pulp chambers suggest retarded dentinogenesis. Wide predentin, increased interglobular dentin, and impaired calcification of cementum seem analogous to the osteoidosis in bone. Enamel is also compromised. Permanent teeth are altered less.

TNSALP (*ALPL*) mutation or deletion analysis is available from a number of fee-for-service laboratories in the United States and elsewhere, and in HPP is expected to reveal one or two defective alleles.[14] For index cases, mutation analysis examines all splice sites and coding exons; infrequently, deletions must be sought. Sporadic cases are quite uncommon, and those from uniparental isodisomy extremely rare.[15,58] Mutation "dosage" generally reflects HPP severity,[14] with severe childhood HPP representing the form of HPP for which there is about equal likelihood of inheritance involving one versus two defective *TNSALP* alleles.[14] Nevertheless, phenotype/genotype correlation is often too imprecise for useful prognostication (personal experience). Although most HPP is readily diagnosed without *TNSALP* mutation analysis,[14] molecular information is crucial for inheritance pattern, recurrence risk, and prenatal assessments.[3,4,59]

I consider that a diagnosis of HPP requires documentation of one or more HPP complications. Carriers of HPP can have the serum ALP and PLP changes of HPP and harbor one defective *TNSALP* allele.

Supportive Treatment

For severely affected babies with HPP, mechanical ventilation can be challenging owing to thoracic deformity, muscle weakness, gracile ribs, fractures, tracheomalacia, and perhaps pulmonary hypoplasia.[60] Vitamin B_6-dependent seizures respond to pyridoxine administration but then become refractory.[12] Hypercalcemia may improve with hydration and restriction of dietary calcium but can require a loop diuretic or glucocorticoid therapy.[5,35] Bone resorption is impaired by the osteoidosis, and antiresorptives may not help. In fact, BPs being PPi analogues could exacerbate HPP hypomineralization directly or by binding Zn^{2+} or Mg^{2+}, thereby compromising any residual TNSALP activity.[28,46] Neurological complications from "functional" or bony craniosynostosis can require craniotomy.[5] Expert dental assessment is important. Premature loss of many teeth can impair speech and nutrition. Severely affected children might need surgery for scoliosis.[6] Fractures may mend, but delayed healing has followed, including postosteotomy (personal observation). Naproxen sometimes diminishes pain, including from bone marrow edema.[56] Physical therapy management for infants and children with HPP was reviewed in 2016.[61] In adults, femoral fractures or pseudofractures heal best with load-sharing intramedullary fixation, whereas load-sparing plates can be problematic.[29] Ankle-foot orthoses may help metatarsal fractures. PPi or HA crystal deposition sometimes benefits from nonsteroidal anti-inflammatory medication.[13,31]

Medical Treatment

Conventional therapies for rickets or osteomalacia (eg, vitamin D and mineral supplements) seem best avoided unless deficiencies are identified.[5] Excesses could provoke or exacerbate hypercalcemia or hypercalciuria.[5] Discussed above, BPs are shunned.[28]

ALP replacement for HPP was tested in the 1980s using IV infusions of soluble ALP in Paget bone disease plasma[35,48] or purified from a human placenta.[62] Hyperphosphatasemia was achieved transiently but caused no clinical or radiographic improvement.[48,62] Thus, correction of ALP deficiency within skeletal tissue seemed necessary for HPP.[46,62] Subsequently,

marrow and bone cell transplantation appeared to rescue two girls dying from infantile HPP.[63,64] Then, healing of a femoral pseudofracture and metatarsal stress fractures was documented using "off label" treatment with teriparatide (PTH fragment 1–34) for an adult HPP patient.[44] Subsequently, several additional adults with HPP apparently benefitted from PTH therapy.[65]

Accordingly, asfotase alfa (AA), a first-in-class, recombinant, mineral-targeted, human TNSALP was evaluated. AA couples the catalytically active homodimeric soluble TNSALP domain, the Fc fragment of IgG1 (to aid purification and to prolong circulating half-life), and a deca-aspartate motif for HA targeting.[5,8,66] In 2008, *TNSALP* knockout mice that recapitulate infantile HPP[67] remained healthy if given AA subcutaneously (sc) from birth.[66] Then, trials for infants or young children with perinatal or infantile HPP began.[5,8] Each of 11 patients was to receive one iv infusion of AA, followed by thrice weekly sc injections. One patient was withdrawn by his parents during a moderately severe infusion reaction and then had prolonged and substantial skeletal deterioration and one died from sudden sepsis unrelated to the treatment.[5] For the remaining 9 patients, the clinical, radiographic, and biochemical improvements and adverse events during the first year of treatment were detailed in 2012.[5] Muscle strength and skeletal mineralization improved substantially, sometimes rapidly, and were associated with better pulmonary, cognitive, and motor function.[5] Now, after more than 5 years of treatment, no patient requires respiratory support and all have made further gains (in manuscript). Investigation of a larger number of similar young patients is supporting this experience.[68] Concomitantly, 13 children who were survivors of infantile HPP or had severe childhood HPP were studied. In 2016, we delineated their rapidly improved skeletal health assessed radiographically, better muscle strength, and resolution of pain and disability persisting after 5 years of therapy.[6] Preliminary evaluation of AA treatment for adolescents and adults with HPP has indicated better mobility.[69] AA studies have included HPP patients of nearly all ages (ClinicalTrials.gov). Adverse events attributed to AA treatment are primarily injection site reactions.[5,6] When therapy begins, areas at the sc injection site may show transient erythema preceding chronic purplish discoloration and wrinkling of skin there, sometimes with lipohypertrophy. Injection site rotation is crucial to minimize such problems. However, there is a good safety profile and development of generally low titers of anti-AA antibodies has not been associated with clinical resistance to this biologic.[5,6]

In 2015, 67 years after HPP was characterized,[2] AA (Strensiq) was approved by the regulatory agency of Japan for HPP, then in Canada, European Union, and United States and elsewhere for patients of any age with pediatric-onset HPP.

Challenges

Following the substantial therapeutic successes and then multinational approvals of AA for HPP in fall 2015, this "orphan disease" entered a certain limelight and ALP ("our favorite enzyme") and PPi became especially well appreciated. Published and online information available to patients and physicians proliferated but varies in quality. In fact, challenges remain and have emerged. Now, AA treatment for HPP has broad-based recognition but calls for even better understanding and appreciation of HPP's pathophysiology and extraordinarily wide-ranging severity.

Before the physician prescribes AA, he/she must correctly diagnose HPP, and I have summarized (see above) how and why achieving this foundation should be straightforward for most patients. I can envision adverse consequences from excessive mineralization if AA is otherwise administered (see below). Importantly, not everything that causes hypophosphatasemia is HPP.[3,4,50] Secondary causes are actually many but have been tallied and discussed.[2,3,50] Mutation analysis of *TNSALP* is increasingly available to help, but a positive result, even when accompanied by characteristic biochemical findings, does not establish the diagnosis of HPP. HPP disease must be present. It is apparent to me from our experience with more than 200 pediatric patients with HPP that their young parents who carry one *TNSALP* mutation, often with some modest reduction in serum ALP and/or modest elevation in PLP, typically do not have HPP disease. This comes from questioning them and our biochemical, radiographic, and DXA studies. As emphasized, such carriers can be estimated to be 1 in every 250 to 300 Americans or Europeans (ie, at least 1 million people on both continents). We are exploring, using longitudinal and multigenerational kindred studies, what individual *TNSALP* mutations might beget for carriers over a lifetime. Learning from senior family members, we hope to understand for specific *TNSALP* mutations any likelihood, timing, and pattern of HPP disease emergence. Perhaps molecular information will someday help choose among therapeutic interventions.

Currently, complications from HPP initiate consideration of therapy. AA for perinatal, infantile, and severe childhood HPP has uncontestable important benefits and an excellent safety profile.[5–7] Perinatal and infantile HPP require considerable time and expertise to manage—particularly for those patients who require intensive care, sometimes with prolonged mechanical ventilation.[58,60] Prompt referral to a medical center with the necessary expertise is key for life-threatening disease.[70] Expeditious initiation of AA therapy will likely minimize intensive care, including ventilation.[70] If so, in utero therapy of perinatal HPP could in the future represent an important advance. In 2010, we discussed in detail the relatively prevalent benign prenatal form of HPP that manifests at birth with skeletal deformity but improves spontaneously ex utero.[23] Importantly, clinicians must not confuse perinatal HPP with benign prenatal HPP. Whether benign prenatal HPP merits AA therapy requires follow-up because the outcome ranges from infantile to odonto HPP.[23] Understandably, mild childhood HPP and odonto HPP are managed by attention to the dental issues. Classic adult HPP has not received approval for AA treatment, but I believe many such patients would benefit. This form of HPP will seem orphaned until one is sanctioned. However, the physician must ascertain which, if any, of their patient's signs, symptoms, findings, worries, or complaints are from HPP and then select the appropriate treatment. Attributing poorly characterized signs or symptoms to HPP because they have been occasionally noted in HPP patient surveys would seem insufficient. In adults, this can be especially challenging because of unrelated dento-osseous, arthritic, painful, etc., problems. Thus, for whom to prescribe AA treatment can require circumspect clinical judgment from understanding HPP and following HPP patients of all ages. Clinicians, patients, and parents together must discuss a treatment's risks and benefits and thus its appropriateness for a given HPP patient. Such experience will help to properly

manage patients but also hopefully to underpin clinical investigation.

Follow-up during AA treatment is important. Weighing pediatric patients every 3 months for dose adjustment is necessary. If dosing becomes insufficient, weakness can soon reappear followed by radiographic deterioration.[6] Physicians can counsel that substantial clinical deterioration can recur if AA treatment stops (personal observation). Injection site reactions are problematic predominantly in children.[6] I do worry about the HA crystal targeting of AA for adults with HPP who have calcific periarthritis, syndesmophytes, and especially if there is vascular or cardiac valve calcification. ALP seems important in the pathogenesis of the vascular calcification of diabetes mellitus, chronic kidney disease, etc., by lowering ePPi levels locally.[8] Overexpression of TNSALP in the vasculature of mice has caused ectopic mineralization and heart disease.[71] Theoretically, inappropriate or excessive AA treatment could lower ePPi levels sufficiently to recapitulate generalized arterial calcification of infancy (GACI).[46] GACI is the inborn error of metabolism that features impaired ePPi biosynthesis within, or channeling to, the extracellular space. The low ePPi enhances mineralization that manifests as vascular calcification.[46] Surveillance for ectopic mineralization during clinical trials of AA, especially in the vasculature,[5,6] has involved routine radiography, retinal examination, and kidney sonography. Worrisome findings have not emerged,[5,6] although small, clinically inapparent, calcific deposits in the conjunctiva and cornea have occurred, but increasingly we believe this is a natural complication of HPP perhaps because of the disrupted mineral homeostasis (unpublished). Not creating or exacerbating such problems seems important for consideration as we treat especially elderly adults with AA. Perhaps assay of PPi as well as PLP in serum will help us monitor AA treatment, but currently AA activity in patient serum specimens is not inhibited at venipuncture, perhaps diminishing the levels that will be reported.

Patients with HPP will probably fare best at academic medical centers that have specialists interested in metabolic bone diseases. Multidisciplinary skills will likely be necessary for those HPP patients who are candidates for AA treatment. Optimal management and understanding of HPP seem most likely if AA treatment can commence after careful baseline assessments, and then follow-up experience is reported. Even so, experience may derive from just several HPP patients at a given facility; thus, long-term observation and sharing of findings must continue.

We have entered a new and exciting era for HPP, yet with additional work to do.

Disclosures

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