Clinical management of hypophosphatasia

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Summary

HPP is a rare disease that manifests in different ways across the life course. Accurate diagnosis depends upon the use of appropriate age-related normative data. A new therapy is undergoing clinical trials; the preliminary published data is encouraging, but the scope of clinical application remains to be determined.

KEY WORDS: low alkaline phosphatase; bone mineralisation; pyrophosphate; enzyme replacement therapy.

Hypophosphatasia: genetics and biochemistry

Hypophosphatasia (HPP) is caused by mutations in the tissue non-specific alkaline phosphatase (TNSALP) gene (1). The function of the enzyme in skeletal tissues is to break down mineralisation inhibitors, principally pyrophosphate, and contribute to the balance of minerals and mineralisation inhibitors required to ensure that mineralisation occurs in an appropriate temporal and spatial manner (2). In addition, the generation of phosphate from pyrophosphate likely contributes to the supply of phosphate that is needed to ensure that hypertrophic chondrocytes undergo apoptosis as part of the coordinated changes required for endochondral ossification during growth and fracture repair. The pathological association of pyrophosphate with calcium creates calcium pyrophosphate dihydrate crystals that deposit in the kidney (contributing to nephrocalcinosis), in joints causing crystal arthritis and pseudo-gout (3, 4), and in bone tissue contributing to bone marrow oedema. In the central nervous system, the removal of phosphate from pyridoxal-5-phosphate (PLP) by alkaline phosphatase is key to the movement of pyridoxal across cell membranes; PLP is a key neurotransmitter substrate (5).

The more severe forms of HPP are usually due to homozygous, or more commonly compound heterozygous mutations, affecting the TNSALP gene (6). The protein is expressed as an homodimer; consequently, some heterozygous mutations have been described that appear to have a dominant negative effect on the enzyme's overall activity; most of the "sensitive sites" for mutation occurs in regions with clear functional importance (7). There is significant intrafamilial variability, however, in the clinical manifestations of the disease, suggesting a number of modulating factors may be in play at a tissue level (8, 9). The finding of homozygous defects in some individuals with mild disease suggests that preservation of functional activity can occur despite an abnormal protein.

Severe HPP occurs in approximately 3.3/million live births; the calculated incidence of milder forms of HPP is 1 in 6-7,000 (6).

Clinical forms of hypophosphatasia

HPP has traditionally been classified by age at presentation.

The perinatal (previously "perinatal lethal") form may be diagnosed in utero or at birth because of fractures and/or short limbs. These infants have very poorly mineralised bones and usually require ventilatory support from around the time of birth. Without enzyme replacement therapy (see below), these infants all die in the first year of life (9). Even with enzyme replacement therapy, these infants may require a prolonged period of intensive care support, and subsequently may be oxygen or ventilator-dependent at home for a period after discharge from hospital (10). A "perinatal benign" form has been described; such infants are often identified antenatally by ultrasound as having limb bowing and variable skeletal demineralisation, and show postnatal improvement in some cases to the "odontohypophosphatasia" phenotype where skeletal and other manifestations beyond the dentition essentially resolve (11).

The infantile form presents in the early months of life because of failure to thrive and increasing respiratory difficulty; some present with convulsions. Biochemical abnormalities include hypercalcaemia with hypercalciuria leading to diuresis and nephrocalcinosis, which is present in almost all cases at diagnosis. Craniosynostosis is seen in both

treated and untreated individuals presenting in the perinatal or infant period and may lead to raised intracranial pressure, necessitating craniectomy. Without enzyme replacement therapy, mortality in the infantile group is more than 50% by age 9 months (9).
In the childhood or juvenile form, individuals typically present with early loss of primary dentition with intact tooth roots, bone pain, rachitic-like lesions, low bone mass, and recurrent, poorly healing fractures. Some children may have significant motor delay. Some cases are misdiagnosed as chronic recurrent multifocal osteomyelitis in older children (12), possibly due to an inflammatory response within bone tissue to the deposition of calcium pyrophosphate dehydrate.
In adults, the presentation is less clear-cut; many cases present initially with clinical manifestations suggesting osteoporosis, such as recurrent fractures and low bone mass, along with ill-defined musculoskeletal pain (13); some (almost always women) present with crystal arthropathy. Biochemical disturbances are less common in both older children and adults, although hypercalcaemia has been described following fracture-induced immobilisation in one adult (14).
In the odontohypophosphatasia form, early loss of deciduous teeth (before the age of 4 years) is not accompanied by any other clinical manifestations.

Clinical manifestations of hypophosphatasia

There are distinct skeletal manifestations that vary with age. Slowing of the growth of bone through the disturbance of endochondral ossification at growth plates occurs as in other rachitic disorders. Softening of bone tissue as a result of failure to mineralise osteoid at remodelling sites (i.e. where bone previously existed and has been removed) combined with the failure to mineralise at modelling sites on the periosteal surface, results in a failure to increase the width of mineralised bone tissue, and results in narrow bones that bend more easily, and may eventually result in significant bony deformity.
The shape of the chest in infancy is similar to other forms of severe rickets with a narrow inlet, flaring of the costal margin and a rachitic rosary. The gracile, poorly mineralised ribs bend easily and failure to support appropriate chest expansion, leading to atelectasis, poor gas exchange and respiratory failure; tracheobronchomalacia may contribute to difficulties with maintaining normal respiratory function in severely affected infants (personal observation and communications).
Pyridoxine-dependent convulsions are seen in both the perinatal and infantile forms; in the past, such convulsions have heralded lethality, but those treated with enzyme-replacement (see below) have survived (10).
Craniosynostosis is a frequent finding at the more severe end of the clinical spectrum, with a characteristic elevation of the membrane covering the anterior fontanelle often seen in early infancy. Some children go on to develop raised intracranial pressure and regular monitoring of the optic discs (at intervals of six months or less) is an essential part of management.
The dentition is affected both by lack of cementum contributing to early exfoliation of the primary teeth, but also by poor enamel formation leading to accelerated carious deterioration.
Motor delay is evident in affected children to a variable extent; universally in those presenting in infancy, less commonly in those presenting later. The motor delay can affect the acquisition of other skills, resulting in apparent cognitive delay in some cases (unpublished observations).

Making the diagnosis

Diagnosis is the first step in management; the rarity of the condition means that diagnosis may be delayed because signs and symptoms are interpreted as being indicators of some other more common disease, and sometimes treatment is given that is inappropriate.
The differential diagnosis usually reflects the age at presentation; antenatal scans showing short bowed limbs suggest other skeletal dysplasias and disorders such as osteogenesis imperfecta. Perinatal presentation with a rachitic, demineralised phenotype similarly requires differentiation from neonatal severe hyperparathyroidism, type V osteogenesis imperfecta and I-cell disease (mucolipidosis II); true congenital rickets can be seen in infants of osteomalacic mothers, typically from refugee populations. The infantile presentation needs to be distinguished from nutritional rickets, other causes of failure to thrive, idiopathic hypercalcaemia (usually vitamin D 24-hydroxylase deficiency) and other causes of nephrocalcinosis. In older children, the combination of short stature, bony pain and motor difficulties can raise a number of possibilities including mild *osteogenesis imperfecta*, nutritional rickets, and myopathic disorders whilst the presentations with arthropathy and bony lesions need to be distinguished from inflammatory arthritides and chronic recurrent multifocal osteomyelitis, and fibrous dysplasia. The adult presentation is easily mistaken for osteoporosis (recurrent fractures, low bone mass) or osteoarthritis (crystal arthritis).
The key to diagnosis in each setting is the measurement and appropriate interpretation of serum alkaline phosphatase activity. Alkaline phosphatase assays vary widely in their normal ranges, and the activity of the enzyme also varies substantially with age. It is critical to ensure that age and gender appropriate normative data for each assay are provided for clinicians requesting these assays. In milder disease, the measured alkaline phosphatase may be within the lower part of the normal range. For the more severely affected individuals it would be expected that the values would be below the lower limit of the normal range.

Management

Until recently, management was essentially symptomatic - infusions of alkaline phosphatase-rich plasma were ineffective and bone marrow and stem cell transplantation had only a small effect on overall clinical outcome.
Hypercalcaemia is managed with hydration, restriction of dietary calcium and vitamin D, and in some instances, thiazide diuretics. There is no place for the use of bisphosphonates, which are chemical analogues of one of the min-

eralisation inhibitors, pyrophosphate, that accumulate in HPP.

Ventilatory support may be required for months in severely affected infants – some go on to require a tracheostomy as part of their management, and this can lead to problems with speech and language development and tolerance of oral feeds. Input from specialist therapists and a dietician may be required in such cases.

Pain is often cited by patients as a major problem, and many have some degree of motor difficulty. They may need physiotherapy, occupational therapy and chronic pain management team input. Fractures can fail to heal and surgical interventions including indwelling metalwork may be required.

There is a single published peer-reviewed paper describing the effects of a human recombinant enzyme replacement therapy (ERT), asfotase alfa, on the skeleton in human subjects whose onset of symptoms was at less than 6 months age. There were significant improvements in the X-ray appearances of bone tissue and concomitant clinical improvements in growth, respiratory function, motor development and calcium homeostasis after 6-12 months of treatment (10).

Children entered into the original study have now received more than three years'-worth of treatment, without apparent major side effects, and with continuing improvement in affected systems. Convulsions have ceased in those who previously had convulsions. Some children have developed craniosynostosis that required neurosurgical intervention, but it is unclear whether this is a treatment-related effect, since some untreated individuals have similar problems. Gross and fine motor function, growth and respiratory function have all been reported as showing improvement. Personal experience of the use of the ERT in infants suggests that early institution of therapy is an important factor in preventing a decline in respiratory function that can then take many months to restore.

The broader application of this form of intervention requires further study; at present, the ERT is being assessed by regulatory authorities to determine the extent of the licence that will be granted.

Alternative therapies have been tried in both the infant and adult settings; bone marrow and stem cell transplantation in infancy and childhood have ameliorated the severity of the disease, but without providing a long term improvement in bone architecture or metabolism (15-17). PTH has been administered to adults with HPP to aid fracture healing; in some reports, serum markers of bone formation including ALP are reported to rise, pain reduced and mobility improved, although the fractures took up to 15 months to heal (18-20); however others have reported no effect with treatment lasting up to 12 months (21).

The use of bisphosphonates is certainly contraindicated and likely to worsen clinical outcomes (22); adults with HPP may present with low bone mass and fractures, so it is important to consider HPP when starting bisphosphonate therapy in older patients with a low ALP at presentation.

Conflicts of interest

Author's institution receives grant income for studies of enzyme replacement therapy in hypophosphatasia; Author has received support from Alexion to attend meetings and present talks on hypophosphatasia.

References

1. Weiss MJ, Cole DE, Ray K, Whyte MP, Lafferty MA, Mulivor RA, et al. A missense mutation in the human liver/bone/kidney alkaline phosphatase gene causing a lethal form of hypophosphatasia. Proc Natl Acad Sci U S A. 1988 Oct;85(20):7666-9.
2. Millan JL. The role of phosphatases in the initiation of skeletal mineralization. Calcif Tissue Int. 2013 Oct;93(4): 299-306.
3. Abhishek A, Doherty M. Epidemiology of calcium pyrophosphate crystal arthritis and basic calcium phosphate crystal arthropathy. Rheum Dis Clin North Am. 2014 May;40 (2):177-91.
4. Beck C, Morbach H, Richl P, Stenzel M, Girschick HJ. How can calcium pyrophosphate crystals induce inflammation in hypophosphatasia or chronic inflammatory joint diseases? Rheumatol Int. 2009 Jan;29(3):229-38.
5. Wang HS, Kuo MF. Vitamin B6 related epilepsy during childhood. Chang Gung Med J. 2007 Sep-Oct;30(5):396-401.
6. Mornet E, Yvard A, Taillandier A, Fauvert D, Simon-Bouy B. A molecular-based estimation of the prevalence of hypophosphatasia in the European population. Ann Hum Genet. 2011 May;75(3): 439-45.
7. Silvent J, Gasse B, Mornet E, Sire JY. Molecular evolution of the tissue-nonspecific alkaline phosphatase allows prediction and validation of missense mutations responsible for hypophosphatasia. J Biol Chem. 2014 Aug 29;289(35): 24168-79.
8. Hofmann C, Girschick H, Mornet E, Schneider D, Jakob F, Mentrup B. Unexpected high intrafamilial phenotypic variability observed in hypophosphatasia. Eur J Hum Genet. 2014 Oct;22(10): 1160-4.
9. Leung EC, Mhanni AA, Reed M, Whyte MP, Landy H, Greenberg CR. Outcome of perinatal hypophosphatasia in manitoba mennonites: a retrospective cohort analysis. JIMD Rep. 2013;11:73-8.
10. Whyte MP, Greenberg CR, Salman NJ, Bober MB, McAlister WH, Wenkert D, et al. Enzyme-replacement therapy in life-threatening hypophosphatasia. N Engl J Med. 2012 Mar 8;366(10):904-13.
11. Wenkert D, McAlister WH, Coburn SP, Zerega JA, Ryan LM, Ericson KL, et al. Hypophosphatasia: nonlethal disease despite skeletal presentation in utero (17 new cases and literature review). J Bone Miner Res. 2011 Oct;26(10):2389-98.
12. Whyte MP, Wenkert D, McAlister WH, Mughal MZ, Freemont AJ, Whitehouse R, et al. Chronic recurrent multifocal osteomyelitis mimicked in childhood hypophosphatasia. J Bone Miner Res. 2009 Aug;24(8):1493-505.
13. McKiernan FE, Berg RL, Fuehrer J. Clinical and radiographic findings in adults with persistent hypophosphatasemia. J Bone Miner Res. 2014 Jul;29(7):1651-60.
14. Whyte MP, Leelawattana R, Reinus WR, Yang C, Mumm S, Novack DV. Acute severe hypercalcemia after traumatic fractures and immobilization in hypophosphatasia complicated by chronic renal failure. J Clin Endocrinol Metab. 2013 Dec;98(12):4606-12.
15. Cahill RA, Wenkert D, Perlman SA, Steele A, Coburn SP, McAlister WH, et al. Infantile hypophosphatasia: transplantation therapy trial using bone fragments and cultured osteoblasts. J Clin Endocrinol Metab. 2007 Aug;92(8):2923-30.
16. Whyte MP, Kurtzberg J, McAlister WH, Mumm S, Podgornik MN, Coburn SP, et al. Marrow cell transplantation for infantile hypophosphatasia. J Bone Miner Res. 2003 Apr;18(4):624-36.
17. Taketani T, Oyama C, Mihara A, Tanabe Y, Abe M, Hirade T, et al. Ex Vivo Expanded Allogeneic Mesenchymal Stem Cells with Bone Marrow Transplantation Improved Osteogenesis in Infants with Severe Hypophosphatasia. Cell Transplant. 2014 Nov 13.
18. Schalin-Jantti C, Mornet E, Lamminen A, Valimaki MJ. Parathyroid hormone treatment improves pain and fracture healing in adult hypophosphatasia. J Clin Endocrinol Metab. 2010 Dec;95 (12):5174-9.
19. Doshi KB, Hamrahian AH, Licata AA. Teriparatide treatment in

adult hypophosphatasia in a patient exposed to bisphosphonate: a case report. Clin Cases Miner Bone Metab. 2009 Sep;6(3):266-9.
20. Whyte MP, Mumm S, Deal C. Adult hypophosphatasia treated with teriparatide. J Clin Endocrinol Metab. 2007 Apr;92(4):1203-8.
21. Laroche M. Failure of teriparatide in treatment of bone complications of adult hypophosphatasia. Calcif Tissue Int. 2012 Mar;90 (3):250.
22. Sutton RA, Mumm S, Coburn SP, Ericson KL, Whyte MP. "Atypical femoral fractures" during bisphosphonate exposure in adult hypophosphatasia. J Bone Miner Res. 2012 May;27(5):987-94.