

Atypical femur fractures: a distinctive tract of adult hypophosphatasia

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Summary

Hypophosphatasia (HPP) is a congenital, rare and heterogeneous bone disorder, characterized by a deficit of calcified tissue mineralization, leading to skeletal deformities and osteomalacia in adults, rickets in infants and children, and fragility fractures and premature loss of dentition in children and adults. The disease is caused by a reduced or absent expression and activity of the tissue non-specific alkaline phosphatase (TNSALP) enzyme, derived from inactivating mutations of the alkaline phosphatase (ALPL) gene.

Six different clinical variants have been reported, defined by the onset age and characterized by different degrees of severity.

The adult form of HPP presents a wide range of clinical manifestations, many of which are non-specific, mild, and often overlapping with other metabolic bone diseases. Consequently, many cases of adult HPP are, commonly, undiagnosed or misdiagnosed, and, subsequently, wrongly or non-treated with severe consequences for patients and a very negative impact on their quality of life and life expectancy, as well as with costs due to the administration of wrong therapies and treatments of their side effects.

The occurrence of a fragility atypical femur fracture in the adulthood can be suspected as a clinical indication of an undiagnosed adult mild form of HPP; and the presence of at least one of this kind of fracture can help in the diagnosis of adult HPP, together with conventional HPP biochemical signs.

KEY WORDS: adult hypophosphatasia; fragility atypical femur fractures; differential diagnosis; amino-bisphosphonates; side effect.

Introduction

Hypophosphatasia (HPP) is a rare congenital heterogeneous

bone disorder (OMIM #241500, #241510, #146300) characterized by a deficit in the mineralization of calcified tissues. This disorder was described for the first time in 1948 by Rathbun, who diversified this novel disease from *osteogenesis imperfecta* and chondrodysplasia, because of the presence of specific clinical signs, like a very low serum level of alkaline phosphatase (ALP) and the occurrence of convulsions.

The incidence of lethal and severe forms of HPP varies from about 1/100,000 in Canada, 1/300,000 in Europe to 1/900,000 in Japan, while the incidence of mild and adult forms cannot be correctly estimated since they are undiagnosed, or, commonly, misdiagnosed for other metabolic bone diseases which overlap some clinical signs and symptoms.

HPP is caused by inactivating mutations of the alkaline phosphatase (*ALPL*; MIM 1717160) gene encoding the tissue-nonspecific alkaline phosphatase (TNAP) enzyme, that accounts about 95% of the total serum ALP activity (1). *ALPL* mutations can be homozygote, heterozygote or composed homozygote, with an autosomal dominant or recessive pattern of inheritance. Over 270 different mutations (including missense, nonsense, frameshift and splicing-site variations) have been described, to date, affecting the entire coding region and intron-exon junctions of the gene. Different mutations are responsible for HPP different clinical presentations, age of onset and disease severity. Lethal and severe forms of HPP are associated with *ALPL* mutations that affect crucial domains of TNAP enzyme leading to a mutated protein that is rapidly degraded with a subsequent highly reduced or absent enzymatic activity and a severe hypomineralization. Conversely, mild and adult forms of HPP are associated with *ALPL* mutations that affect non-essential amino acid of TNAP enzyme, granting residual enzymatic activity and mineralization. It is also probable that some mild and adult forms can be due to the presence of one or more functional polymorphism of the *ALPL* gene, polymorphisms which demonstrated to be positively associated with variations in serum ALP concentration and bone mineral density (BMD) (2, 3).

Main clinical manifestations of HPP are rickets in children and osteomalacia in adults, associated with bone deformities, early bone mass loss, and fragility fractures. Clinical expression is highly variable and six different forms of the disease have been classified, mainly according to the age of onset and the severity of the disease: 1) perinatal (lethal), 2) benign prenatal, 3) neonatal (lethal in 50% of cases), 4) childhood (infantile), 5) adulthood and 6) odontohypophosphatasia (a mild form affecting only teeth but not bones). A very rare variant, named pseudohypophosphatasia, has been also described and it is clinically indistinguishable from infantile variant but with a normal range of serum ALP.

An earlier age of onset is always associated with a more severe pathology and a worse prognosis. Main clinical characteristic of the six HPP forms are depicted in Table 1.

Table 1 - Main characteristics of the different clinical forms of hypophosphatasia.

Clinical form	OMIM	Inheritability	Age of diagnosis	Bone manifestations	Dental manifestations	Other associated signs and symptoms	Clinical diagnosis
Perinatal (lethal)	#241500	AR	Before birth	Severe hypomineralization. Diffuse osteochondral exostoses. Reduced length of long bones.	Non valuable	Severe breathing complications due to rickets of rib cage and hypoplastic lungs. Epileptic crisis and seizures.	Radiography and/or prenatal ultrasonography. Dosage of serum ALP from umbilical cord.
Benign prenatal	#241510	AD	Before birth	Reduced length and bowing of long bones. Bone deformities and reduced mineralization improve during the third trimester of pregnancy. A spontaneous improvement of bone defects immediately after birth	Non valuable	None	Prenatal ultrasonography. Dosage of serum ALP from umbilical cord.
Neonatal (lethal in 50% of cases)	#241500	AR	Children appear normal at birth. Sign and symptoms appear during the first six months of life.	Premature craniosynostosis associated with increased intracranial pressure. Diffuse hypomineralization. Rickets. Fragility fractures (i.e. rib cage).	Premature loss of deciduous teeth.	Breathing complications due to rickets of rib cage. Hypercalcemia. Irritability. Anorexia, vomiting, hypotonia, polyuria, polydipsia, dehydration and constipation, associated with reduced nutrition and insufficient weight growth. Hypercalciuria and possible nephrocalcinosis. Epilepsy non responsive to the vitamin B6 administration.	Radiography. Bone scintigraphy. Medical examination. Serum dosage of ALP, PEA and PLP.
Childhood	#241510	AR (frequent) AD (rare)	Signs and symptoms appear during the early childhood (usually after the first six months and before the first 5 years of life).	Diffuse bone deformities. Rickets. Low height. Dolichocephaly. Articular weakness. Possible articular pain (mostly at the extremities). Fragility fractures.	Premature loss of deciduous teeth (before 5 years of age)	Ataxic gait (duck gait). Delay in growth and walking. Muscle hypotonia. Intra-cranial hypertension.	Radiography. Bone scintigraphy. Medical examination. Serum dosage of ALP, PEA and PLP. BMD evaluation (DXA).

to be continued

Continue from Table 1

Adulthood	#146300	AR or AD	Signs and symptoms appear during the adulthood even if a low percentage of patients refer a mild rickets during childhood, a history of delay in fracture healing, premature loss of deciduous teeth, all of them followed by a good health status.	Severe osteoarthropathy. Osteomalacia. Osteoporosis. Osteoarthritis. Chondrocalcinosis and articular pain due to deposition of calcium pyrophosphate dehydrate salts. Metatarsus and tibia stress fractures often associated with reduced and delayed fracture healing. Femur atypical fragility fractures (pseudo-fractures).	Recurrent dental pathologies. Premature exfoliation of deciduous teeth, and, more rarely, of permanent teeth. Possible premature loss of permanent teeth at 40-60 years.	Myopathy and muscular pain. Fatigue. Nephrocalcinosis. Insomnia. Depression. Anxiety.	Radiography. Medical examination. Serum dosage of ALP, PEA and PLP. BMD evaluation (DXA).
Odontohypophosphatasia	#146300	AR or AD	Childhood	None	Premature exfoliation of deciduous teeth (particularly incisor teeth). Recurrent and severe dental caries. Reduced dentin thickness and enlargement of cavities containing the dental pulp. Premature loss of deciduous and permanent teeth.	None	Medical and dentistry examination. Serum dosage of ALP, PEA and PLP.

Footnotes: AR = autosomal dominant; AD = autosomal recessive; ALP = alkaline phosphatase; PEA = phosphorylethanolamine; PLP = pyridoxal phosphate; BMD = bone mineral density; DXA = Dual-energy X-ray absorptiometry.

Diagnosis of HPP

A correct diagnosis of HPP and a differential diagnosis with respect to other bone disorders, mostly for mild and adult forms which are often undiagnosed or misdiagnosed for osteomalacia, osteopenia and/or early osteoporosis, are fundamental for the correct treatment of this disease to be started as soon as possible (an enzyme replacement therapy is now available).

In perinatal HPP, the diagnosis is made prevalently by skeletal radiographs and it allows to distinguish HPP from *osteogenesis imperfecta* and rare forms of congenital dwarfism. Intrauterine diagnosis is performed during the second trimester of pregnancy by the finding of bone anomalies, polydramnios, diffuse skeletal hypomineralization (particularly skull and spine), reduced bone length, dwarfism, bowed bones. Perinatal form (lethal), whose intrauterine diagnosis is almost always associated with a decision for a voluntary pregnancy interruption, has to be distinguished, through an accurate radiographic and ultrasound analysis, from the benign prenatal form whose signs and symptoms usually normalize during the third trimester of pregnancy or immediately after birth.

For all the other forms of HPP, the diagnosis is the result of an association between biochemical tests, instrumental evaluation of the skeleton and a specific medical examination together with the mutation screening of the *ALPL* gene.

Biochemical evidences for HPP include: 1) reduced serum level of ALP (reduction level is directly proportional to disease severity); 2) high plasma level of pyridoxal phosphate (PLP; also known as the active form of vitamin B6); 3) increased level of TNAP specific substrates [urinary phosphorylethanolamine (PEA) and urinary inorganic pyrophosphate (PPI)]. The single finding of low serum level of ALP alone is not sufficient to diagnose the HPP. Indeed, low circulating level of ALP can be ascribed also to other clinical conditions like severe anemia (pernicious and profound forms), hypothyroidism, celiac disease, malnutrition, vitamin C, folic acid or vitamin B12 insufficiency, vitamin D intoxication, hypomagnesemia, hypoparathyroidism, Wilson's disease, cleidocranial dysplasia, Cushing's syndrome, multiple myeloma, *osteogenesis imperfecta* type II or Zn^{2+} deficiency. In case of equivocal situations, biochemical measurements of plasma PLP and urinary PEA could be useful. In few cases of mild and adult HPP levels of PEA and PPI can be within the normal range, but PLP is always an indicative marker, since, unless an excessive dietary intake of active vitamin B6, the plasma level of PLP is not expected to be elevated in pathological conditions other than HPP.

Instrumental diagnostic screening is principally made by radiographs of the skeleton; in childhood and adulthood forms a Dual-energy X-ray absorptiometry (DXA) is performed for the evaluation of BMD.

Mutation test of the *ALPL* gene is principally useful to confirm the biochemical diagnosis or it can help in a diagnosis when biochemical and clinical data are not completely clear. However, a negative *ALPL* genetic test in patients with low serum level of ALP and reduced bone mass should not make them to be excluded as mild forms of HPP.

In childhood and adulthood HPP forms, in association with biochemical and instrumental screenings, a specific and complete medical examination is important for a clear diagnosis, through the investigation for the presence of HPP-associated manifestations, including both the common ones

and the rare and asymptomatic ones. Indeed, especially for adult forms of HPP many manifestations are mild and often overlap with other metabolic bone disorders, often resulting in a wrong or no diagnosis. In most cases, the diagnosis of adult HPP is made after a low serum level of ALP is casually detected during routine blood screening, or when tested after a direct family member was diagnosed with the condition. However, today a percentage of adult HPP with low BMD and bone fragility is still misdiagnosed for early-onset osteoporosis or other metabolic bone disorders, with the risk of administration of a wrong pharmacological therapy that is not only ineffective but it can also get worse the mineralization status, resulting in a great reduction of quality of life and an increase of side effect hospitalization costs. In this light, the correct and early diagnosis of mild and adult forms of HPP is very important. Serum ALP level, and other HPP-related biochemical markers, should be routinely checked as possible cause of low BMD and bone fragility, even in individuals over 50 years, to distinguish HPP from osteoporosis and avoid administration of anti-resorptive drugs.

Fragility atypical femur fractures in HPP

Clinical manifestations and disease severity are variable between patients in adult form of HPP, even in presence of the same *ALPL* mutation; many of the knowledge of clinical presentation of this HPP form has been derived from case reports and pedigree studies (4). Some patients can be asymptomatic with only low serum level of ALP and a reduced bone mass; therefore, the disease can remain undiagnosed for years. Symptoms of adult HPP usually appear after 40-50 years of age (even if a careful interrogation of clinical history often reveals signs also during childhood or even infancy), and they consist principally of diffuse osteomalacia and osteoarthritis. Many patients refer a history of joint pain and of foot and leg pain caused, respectively, by chondral deposition of calcium pyrophosphate dehydrate and by metatarsal stress fractures associated with poor and slow healing and frequent fracture non-union. Also premature exfoliation and structural alterations of deciduous teeth, and, more rarely, of permanent teeth, as well as an increased occurrence of severe dental caries can characterize adult HPP. Low bone mass and fragility fractures represent distinctive signs of adult HPP, and, in patients over 50-55 years, they can lead to a wrong diagnosis of osteoporosis.

It's well known that fragility atypical femur fractures are a hallmark of adult form of HPP, and they represent an important marker for the diagnosis (5). Atypical femur fractures (subtrochanteric, diaphyseal or femoral shaft fractures) represent a small fraction (10-30%) of all hip/femur fractures; usually, many of them (about 75%) are associated with major traumas, while only 25% of them consist of spontaneous or low-trauma fragility fractures. In particular, fragility atypical femur fractures account for about 3% of all femur fractures in the elderly. Atypical femur fractures can occur also in other bone disorders such as X-linked hypophosphatemia, osteopetrosis, pycnodysostosis, and in a percentage of osteoporosis patients long-term treated with amino-bisphosphonates (NBPs) or denosumab. However, if the occurrence of these fractures is associated with low level of ALP, this is a strong suspect of an adult form of HPP.

Fragility atypical femur fractures in HPP present distinctive features that should be considered as helpful for the differen-

tial diagnosis. Adult HPP typically presents bilateral femoral pseudo-fractures (Looser's zones) that are chronic and prodromically painful, and they, usually, occur in the lateral cortex of the subtrochanteric diaphysis; conversely, more common forms of osteomalacia and X-linked hypophosphatemia manifest their typical pseudo-fractures principally within the medial cortex of the femoral neck (6). Moreover, atypical femur fractures in HPP show, at the radiograph examination, a transverse or short oblique orientation, in contrast to the typical spiral aspect of fragility femur fractures in osteoporosis; and when the HPP fracture is complete it usually shows the presence of medial spikes and lack of comminution. Therefore, the radiological localization of the fracture within the femur and the radiological evaluation of fracture edge and orientation are important parameters for HPP diagnosis.

Moreover, fragility atypical femur fractures in HPP are often associated with prodromal pain which manifests even weeks and months before the occurrence of the real fracture event. These fractures origin as stress micro pseudo-fractures that can remain asymptomatic, and untreated, for years, progressively advancing till their occurrence (usually by low or no trauma). The presence of prodromal pain (both dull or aching) at hip, groin or thighs, especially in case of bilateral symptoms, could be an indication of presence of stress micro pseudo-fractures and should be consider at the time of medical examination, and followed by a bilateral radiographic evaluation of both femurs. If plain radiographs do not evidence micro-fractures or images are controversial, MRI or radionuclide scintigraphy should be performed. MRI is able to detect cortical stress fractures associated with bone and marrow edema or with hyperemia.

Besides to be a useful diagnostic marker for adult HPP (7), fragility atypical femur fractures are also a possible side effect of long-term NBP treatment. An increased risk of this kind of fracture in NBP-treated osteoporosis patients has been evidenced (8-10). This risk has been also reported in HPP. One study of Sutton et al. (11) described a case of a 55-year-old Caucasian woman manifesting a fragility atypical subtrochanteric femur fracture, occurred after 4 year-therapy with alendronate and zoledronate for suspected osteoporosis; targeted analyses revealed the patient to be an adult HPP form. NBPs are synthetic molecules that mimic the chemical structure of PPI, a natural substrate of TNAP and a potent inhibitor of mineralization. Thanks to their structure these drugs, besides to inhibit mevalonate pathway and osteoclast differentiation, act also as agonist of PPI, inhibiting the activity of TNAP. The administration of NBPs in HPP patients induces a PPI-like inactivation of TNAP, in subjects with an already existing genetic-derived reduced ALP activity, and further reduces mineralization. It has been speculated that in HPP patients NBPs may intensify the inhibition of mineralization process and be responsible for an increased

risk and a higher prevalence of NBP-associated atypical subtrochanteric femur fractures. Consequently, HPP patients misdiagnosed with osteoporosis, but with a low level of serum ALP and the presence of genetic variants of the *ALPL* gene responsible for reduction of the normal expression and activity of TNAP, treated with NBPs drugs, are prone to develop atypical femoral fractures (even bilateral and recurrent) from these treatments. Thus, the correct diagnosis of HPP is fundamental to avoid the wrong therapy with NBPs or other anti-resorptive drugs, which are ineffective and detrimental in these patients. On the other hand, the presence of one or more atypical femur fractures after a treatment with NBPs should be consider an indication to suspect an adult HPP form (11), and biochemical dosage of ALP and other HPP-related biomarkers is strongly suggested to set up the right diagnosis and prevent further NBP-related atypical fractures.

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