Diagnostic challenges in hypophosphatasia in adult patients

Camila Fernandes, Fabrício Alves Paro, Isabela Zani, Jessica Veloso, Zumira Aparecida Carneiro, Charles Marques Lourenço

ABSTRACT

Introduction: hypophosphatasia is a metabolic disorder affecting bone and tooth mineralization, caused by mutations in the ALPL gene leading to enzymatic deficiency of tissue non-specific alkaline phosphatase. The adult form is characterized by atypical femur fractures, osteomalacia, osteoporosis, severe osteoarthropathy, chondrocalcinosis, and arthralgia. Objective: to demonstrate diagnostic challenges related to hypophosphatasia through the report of two cases. Patient 1: female, 59 years old, referred for clinical evaluation due to pathological fractures of difficult consolidation and generalized osteoporosis of genetic cause. She reports early tooth loss in the upper arch, fractures in the spine, left shoulder and femur. Currently, he complains of severe chronic pain, with use of multiple medications. Clinical, laboratory, and radiological findings were compatible with the diagnosis of hypophosphatasia. Patient 2: male, 31 years old, son of patient 1, referred for clinical evaluation due to an early pathological fracture in the left femur and unclear osteoporosis. He currently reports pain and significant claudication in the left lower limb, associated with chronic low back pain. Confirmation of the diagnosis of hypophosphatasia by laboratory and radiological tests and sequencing of the ALPL gene combined with the diagnosis of his mother. Discussion: hypophosphatasia is a rare disease of autosomal dominant and recessive inheritance. Affected patients have constant fractures, low bone mineral density, and impaired bone healing. It is common for hypophosphatasia to be misdiagnosed as osteopenia and/or primary osteoporosis, which can be harmful to the patient. The importance of a complete clinical history and family history is emphasized in order to obtain an early diagnosis, ensuring adequate follow-up and therapeutic management.

Keywords: Hypophosphatasia, Alkaline phosphatase, Pathological fractures, Osteoporosis

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INTRODUCTION

Hypophosphatasia (HPP) (OMIM: 146300) is a rare inherited disease that affects the mineralization of bones and teeth. It is a metabolic disorder caused by mutations in the ALPL gene that encodes alkaline phosphatase causing a deficiency in its enzymatic action. Alkaline phosphatase is a tissue-specific isoenzyme responsible for the dephosphorylation of inorganic pyrophosphate (IPP), an inhibitor of bone mineralization produced by osteoblasts and chondrocytes. IPP accumulation impairs the formation of hydroxyapatite, a bone mineral component formed by inorganic phosphate and calcium, resulting in bone non-mineralization and consequent impaired bone calcification.

The phenotypic spectrum of HPP in all its forms is extremely varied, the most common symptoms being shared among its different clinical presentations: joint and musculoskeletal pain, premature loss of teeth with intact roots, and recurrent bone fractures. The adult presentation of HPP occurs in patients with an average age between 40-50 years, and is characterized by the presence of atypical femoral fractures, osteomalacia, osteoporosis, osteoarthritis, severe osteoarthropathy, chondrocalcinosis, and joint pain. Bone density in these patients is often low, and fracture healing is more difficult and slower.

Although these are relatively common and typical symptoms and signs of this form of the disease, they are not pathognomonic, thus making diagnosis difficult.

An important diagnostic indicator of HPP is the low total serum alkaline phosphatase level for age and sex, helping in the differential diagnosis of other bone pathologies in which alkaline phosphatase is usually elevated. Other useful biochemical markers are the dosage of serum vitamin B6 and urinary phosphoethanolamine. Recently, the biochemical measurement of alkaline phosphatase combined with sequencing of the ALPL gene has been used as diagnostic confirmation, although not all patients have mutations identified by traditional gene sequencing, making it important to perform alkaline phosphatase testing in all suspected cases of HPP.

The cases of patients with the adult form of HPP whose diagnosis proved to be a clinical challenge will be reported here, reinforcing the need for physicians to be aware of this diagnostic possibility in patients with atypical fractures and “idiopathic” osteoporosis. In this report, data were obtained through medical record review with the authorization of the ethics committee of the hospital and the patients, obtained by signing an informed consent form.

CASE REPORT

Patient 1

A 59-year-old female patient, self-employed salesperson, daughter of non-consanguineous parents, was referred for clinical evaluation due to the presence of pathological fractures and generalized osteoporosis of genetic cause.
Her gestational and neonatal history was uneventful, and during pregnancy there was no exposure to teratogenic agents. During childhood and adolescence, she reported no health problems.

Among her medical history, at the age of 34 she had a convulsive crisis and started phenobarbital therapy. She has hypothyroidism and is on levothyroxine replacement therapy. The patient also reports dental loss in the upper arch, requiring the use of prosthesis.

At 53 years of age, she had osteoporotic fractures of the spine (Figure 2 A) after “lifting a gas cylinder”, presenting with stabbing pain in the back at thoracolumbar transition without sphincter repercussion. Even with the use of a brace and analgesics, the patient developed refractory pain and was referred to the neurosurgery department for evaluation. She was submitted to decompressive laminectomy and posterior approach arthrodesis from T12 to L3.

Because of the pathological fractures and loosening of the spinal screws due to ossification difficulties, the patient was referred to the endocrinology sector when findings of severe osteoporosis were confirmed, through densitometry studies of the lumbar spine + femur and bone scintigraphy, which showed increased osteogenesis in T11, T12, L1, L3, and L4, in the anterior segment of the second and third costal arches on the right, and from the second to the fifth costal arches on the left, with an osteoarticular degenerative process of the shoulders and knees. Moreover, during the entire period of outpatient and surgical care of the patient, laboratory tests were performed for research and diagnostic aid (Table 1).

### Table 1. Laboratory investigation of the patient 1.

<table>
<thead>
<tr>
<th>EXAM</th>
<th>VALUE FOUND</th>
<th>REFERENCE VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>5.520 mU/L</td>
<td>0.4 a 4.5 mU/L</td>
</tr>
<tr>
<td>Inorganic Phosphorus</td>
<td>3.58 mg/dL</td>
<td>2.5 a 2.6 mg/dL</td>
</tr>
<tr>
<td>Total calcium</td>
<td>9.12 mg/dL</td>
<td>8.4 a 10.5 mg/dL</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>47 U/L</td>
<td>40 a 150 U/L</td>
</tr>
<tr>
<td>PTH</td>
<td>13.5 pg/ml</td>
<td>14.5 a 87.1 pg/ml</td>
</tr>
<tr>
<td>25- hydroxyvitamin D</td>
<td>47.7 ng/ml</td>
<td>20 a 50 NG/ml</td>
</tr>
</tbody>
</table>

**Source:** The authors (2020).

At 59 years of age, he presented a fracture in the left shoulder after unbalancing when getting up from bed, and two subsequent fractures in the femur with an interval of one week, the first one in the head of the femur caused by a fall from his own height, which required surgical intervention and placement of a prosthesis. The second fracture occurred in the middle third of the femur, just below the prosthesis, as a result of a possible fall from the bed (Figure 2.B).

Currently, the patient complains of chronic severe pain in the lower limb associated with asthenia with periods of improvement and worsening, requiring the use of multiple medications such as nonsteroidal anti-inflammatory drugs and analgesics. In addition, she uses psychotropic drugs to treat psychotic disorder, generalized anxiety disorder, and depression such as diazepam, duloxetine, biperidene, and risperidone.
The genetic-clinical examination revealed: height 1.50m (below the 3rd percentile), weight 53.9kg (between the 25th and 50th percentiles) and head circumference between the 50th and 97th percentiles; patient oriented in time and space, but with moderate bradypsychism; absence of significant facial dysmorphisms, ocular motricity within normality, palate raised symmetrically, tongue centered, osteotendinous reflexes grade 1-2 in LLLL and grade 2 in upper limbs, absence of signs of spinal cord compression, eumetric patient with eudiadocokinesis; deep sensibility preserved; significant kyphoscoliosis; antalgic gait with support.

Finally, it is known that, except for the son (patient 2), no other similar case was evidenced in the family. Since the clinical, laboratory and radiological findings were compatible with a diagnosis of adult onset hypophosphatasia, molecular genetic sequencing of the ALPL gene was performed, which showed the presence of the missense mutation c.787T>C (p.Tyr263His) in heterozygosis, confirming the clinical diagnosis of hypophosphatasia. Thus, the patient was referred to specific therapy.

**Patient2**

A 31-year-old male patient, plastic artist, son of nonconsanguineous parents, was referred for clinical evaluation due to the presence of a pathological fracture in the left femur (Figure 3. A) and osteoporosis of unknown cause.

His birth was at term, without complications during pregnancy or exposure to teratogenic agents, normal delivery, weighing 3.280 kg and measuring 47 cm. Although the mother had retained placenta with significant hemorrhage during delivery, the patient was born without any complications.

As for the history of neuropsychomotor development, it remained within normality. He showed good school performance, denying any cognitive delays, symptoms of weakness or difficulty walking during this period. In addition, he did not present early tooth loss and had no surgical procedure.

During adolescence, around the age of 14, the patient reported consecutive hospitalizations due to infections and behavioral changes. He was later diagnosed with generalized anxiety disorder, panic syndrome, and depression.

Regarding family history, the patient’s mother (patient 1) has a similar clinical picture.

The fracture in question (Figure 3.A) occurred at 27 years of age and was caused by sudden movement of the leg due to an isolated tonic seizure, for which treatment with phenobarbital was initiated. The fracture was identified only 2 years after the described event, when he was referred to the endocrinology clinic for evaluation of familial osteoporosis due to his mother’s condition. Several laboratory tests were performed for diagnostic investigation and elucidation (Table 2) and during the evaluation a diagnosis of osteoporosis was confirmed through bone densitometry (lumbar spine + femur). As an aid, imaging exams were performed, including a tomography of the spine, which showed fractures due to bone fragility. Even after the diagnosis, the patient did not undergo surgery for fracture fixation, evolving with pseudoarthrosis of the femoral neck (Figure 3.B).

### Table 2. Laboratory investigation of patient 2.

<table>
<thead>
<tr>
<th>EXAM</th>
<th>VALUE FOUND</th>
<th>REFERENCE VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>2.570 mU/L</td>
<td>0.4 a 4.5 mU/L</td>
</tr>
<tr>
<td>Total calcium</td>
<td>9 mg/Dl</td>
<td>8.5 a 10.5 mg/Dl</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>60 U/L</td>
<td>40 a 150 U/L</td>
</tr>
<tr>
<td>PTH</td>
<td>30.60 PG/mL</td>
<td>14.5 a 87.1 PG/Ml</td>
</tr>
<tr>
<td>25- hydroxyvitamin D</td>
<td>27.30 NG/ml</td>
<td>20 a 50 NG/ml</td>
</tr>
</tbody>
</table>

Source: The authors (2020).
Currently, the patient presents pain and significant claudication in the left lower limb associated with muscle weakness and restricted movement. The patient also complains of chronic low back pain, but denies joint pain and other musculoskeletal complaints. The patient uses diazepam, lorazepam, paroxetine, clomipramine, and mirtazapine for the treatment of chronic pain and psychiatric symptoms, and phenobarbital for seizures.

The genetic-clinical examination revealed stature 1.67m (between the 50th and 75th percentiles) and weight 62.4kg (between the 10th and 25th percentiles); cephalic perimeter 57cm (between the 50th and 75th percentiles) patient oriented in time and space; facies symmetrical, ocular motricity within normality, elevates palate symmetrically, tongue centered; eumetry and eudiadocokinesis; Osteotendinous reflexes grade 2 in LLLL (with grade 3 in the left patellar) and grade 2 in upper limbs; muscle strength grade 4 in upper and lower limbs (except for the lower limb that presents grade 3); preserved deep sensibility; significant kyphoscoliosis; atypical gait - needs cane support to walk.

Given the diagnosis of his mother and because he presented laboratory and radiological evidence suggesting hypophosphatasia, the ALPL gene was also molecularly sequenced, which showed the presence of the same missense mutation c.787T>C (p.Tyr263His) in heterozygosis, confirming the clinical diagnosis of hypophosphatasia, and he was therefore referred for specific therapy.

**DISCUSSION**

Hypophosphatasia (HPP) is a rare, inherited disease characterized by low plasma alkaline phosphatase (ALP) activity. The disease presents several specific age-related clinical manifestations, including skeletal problems, muscle weakness, impaired walking, pain, dental, neurological, and renal changes that may vary considerably between individuals.

The disease follows a pattern of autosomal dominant and recessive inheritance. Autosomal recessive inheritance is associated with severe forms of the disease, whereas mild forms can be transmitted either autosomal dominant or recessively, with autosomal dominant being the most common form.

Thus, at least one of the parents must be a carrier of ALPL gene mutations for the individual to manifest the disease, thus pointing to the importance of family history of this pathology. Szabo and collaborators demonstrated in a systematic review of the literature that 27.9% of the 265 individuals analyzed have family inheritance. Similarly, there was also family history in patients 1 and 2 for being mother and son, respectively, suggesting a dominant autosomal inheritance pattern.

HPP in the adult form predominantly affects females and individuals in middle age. It presents great clinical variability, with the most prevalent manifestations being chronic bone and muscle pain, myasthenia, dental alterations, headaches, sleep disorders, recurrent fractures and pseudo-fractures. Other characteristics, however, less common are: delayed and ineffective bone healing, osteomalacia, arthropathy, chondrocalcinosis, enthesopathy, altered gait, early tooth loss, osteopenia, depression and anxiety. Consistent with the typical clinical picture of the adult form of this disease, in the patients discussed in this report, chronic bone and muscle pain, sleep disturbances, fractures, delayed and ineffective bone healing, altered gait, osteopenia, depression and anxiety were observed.

An important manifestation of HPP is significant early tooth loss, which could be observed in patient 1 between the third and fourth decade of life. It is known that patients presenting unexplained early tooth loss with intact and not resorbed roots or with other significant dental abnormalities such as enamel wear, abnormal color and shape, in the presence of low ALP, should be investigated for HPP.

On the other hand, in some cases, the carriers of HPP can be asymptomatic and the diagnosis of the disease is made from specific laboratory tests such as: serum Alkaline Phosphatase (ALP), vitamin B6, inorganic phosphate and phosphoethanolamine dosage in urine. Although the determination of alkaline phosphatase with values corrected for age and sex is essential for the diagnosis of the disease, some patients may have borderline values or even within normality and not decreased as expected by the very definition of the disease. Thus, it is important that serial determinations of alkaline phosphatase are made, because their values can be influenced, for example, by fractures that commonly course with increased serum alkaline phosphatase and can lead to a false negative in a patient with HPP.
Moreover, patients affected by this disease have a high frequency of fractures, which are mostly recurrent. Atypical femoral fractures are reported in several metabolic disorders, including in HPP. It is also known that femur curvature, patient age and low bone mineral density act as risk factors for these fractures. The pathophysiology of atypical femoral fractures includes: bone remodeling deficit, low stress fractures or even absence of traumatic stress, and finally aspects of predisposed femoral geometry. Such aspects are also observed in the cases reported here, considering that both patients presented consistent risk factors and were diagnosed with atypical femoral fractures, since patient 1’s fracture was caused by falling from his own height, and patient 2’s occurred in the absence of trauma.

People with HPP usually have low bone mineral density, prolonged and sometimes incomplete fracture healing, but these symptoms are not pathognomonic, but very common in the general population with osteoporosis and osteopenia. Therefore, it is common for HPP to be misdiagnosed as primary osteopenia and/or osteoporosis, worsening the clinical picture of the patient, since bisphosphonates, used in the treatment of these diseases, have structural similarities with pyrophosphates, which act by preventing calcification and inhibiting bone resorption by the effects of osteoclasts. In contrast, in HPP, deficiency in bone mineralization is observed due to low plasma alkaline phosphatase activity and consequent accumulation of pyrophosphate. Thus, the use of bisphosphonates is an absolute contraindication in the treatment of these patients. Similarly to what occurs in patients affected by HPP, the patients reported here present deficiency in bone mineralization, thus a secondary manifestation of early osteoporosis occurs, diagnosed in both cases initially as primary osteoporosis/osteopenia, since the diagnosis of HPP had not been established.

Regarding the quality of life of patients, it was observed a great loss of locomotion, use of walking aids and wheelchairs, chronic pain, numerous surgeries and hospitalizations, failures and complications of surgical procedures, exacerbated use of painkillers, psychotropic drugs and side effects of medications. The association of these factors causes a decline in most of their daily activities. This fact is observed in both patients in this case report, since they need auxiliary treatment with analgesics and psychotropics, due to the several systemic consequences they present as depression, chronic pain and insomnia. In addition, another limiting factor is the difficulty in walking, with the need for gait devices.

With regard to therapeutic aspects, there are several studies that seek an effective and appropriate treatment for HPP. Currently, enzyme replacement therapy is used as specific therapy by means of alpha asfotase (Strensiq™), which is a recombinant ALP fusion protein composed of the enzyme TNSALP that acts by reducing the levels of substrates that accumulate due to the deficiency or absence of its activity, promoting bone mineralization. On the other hand, teriparatide, a recombinant form of parathyroid hormone, is prescribed to improve osteoporosis because it stimulates bone ALP production; however, its benefit for HPP is still conflicting.

In addition, the management of these patients involves monitoring calcium and phosphate levels and implementing appropriate diet and supplementation, restricting phosphate intake. Other medications, such as analgesics and psychotropics, may be prescribed according to the individual clinical conditions of each patient. The use of bisphosphonates, in turn, is absolutely contraindicated in all patients with HPP, since they are analogues of inorganic pyrophosphate and can inhibit the expression of alkaline phosphatase. In addition to pharmacological treatments, surgical treatment is sometimes necessary, such as intramedullary bone fixation and use of orthoses. In the reported patients, supportive treatments have been used such as vitamin supplementation, use of analgesics, psychotropics and orthoses, besides surgeries to correct fractures.

Therefore, the HPP is a rare disease of heterogeneous clinical expression, associated to the decrease of bone mineralization by ALP deficiency occurring in several age groups. The early diagnosis of the adult form of the disease by health professionals, mainly endocrinologists and orthopedists, is crucial to ensure the patient adequate follow-up and correct therapeutic management. However, studies estimate that there is a delay of at least five years between the first signs and symptoms and diagnosis. This is due to the scarcity of data regarding the clinical course, symptoms, signs and complications of the disease.
Thus, in order to ensure a timely diagnosis, research and knowledge by health professionals about the various clinical manifestations of this rare osteometabolic disease and its pathophysiological aspects is necessary. It is also worth mentioning that patients with a family history of recurrent fractures and/or early tooth loss without evident cause should present a high index of suspicion for HPP, emphasizing the importance of a complete clinical history of family background in the investigation of individuals with this diagnostic suspicion. It is in this context that the reported cases act, providing not only an impulse for the permanent education of health professionals, but also a support for the organization of the health system regarding the optimization of diagnostic and therapeutic resources.

REFERENCES

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The ethical principles of research with human beings were respected, in accordance with Resolution No. 466/2012, Resolution No. 510/2016 and that the same obtained approval by the Research Ethics Committee of our institution, under opinion number 2,190,929 on the date of July 28, 2017 under the following CAAE number 70623317.7.0000.5581 generated by Plataforma Brasil.

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Corresponding Author:
Charles Marques Lourenço
charlesgenetica@gmail.com / charles.lourenco@estacio.br

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