

Low-energy trauma-induced intercondylar femoral fracture

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Summary

We present a 44-year-old female patient with recurrent fragility fractures including an intercondylar femoral fracture and with normal planar bone densitometry. Diagnosis of hypophosphatasia was suggested by low volumetric cortical bone mineral density and laboratory findings. DNA sequencing revealed heterozygous mutations in the exons 5, 6 and 9 of the ALPL gene, thus confirming the suspected diagnosis.

KEY WORDS: hypophosphatasia; fragility fracture; DXA; intercondylar; pQCT.

Introduction

Hypophosphatasia is a rare inherited disease with an autosomal recessive or autosomal dominant pattern and is characterized by impaired bone mineralization, formation/remodeling and teeth mineralization due to reduced activity of serum and bone alkaline phosphatase (1, 2). We present a 44-year-old female patient with recurrent fragility fractures and normal planar bone densitometry. Although the initial fracture, an intercondylar femoral fracture, was highly suggestive of a metabolic bone disease, diagnosis of hypophosphatasia was made only several years and two additional fractures later. Recognizing this rare and unfamiliar disease is important, especially as traditional treatments (bisphosphonates) should be avoided.

Case report

A 44-year-old female with a recent, atraumatic, subtrochanteric femoral fracture was referred to the rheumatology outpatient clinic of the Inselspital. Her past medical history included a low-energy trauma, and an intercondylar distal femur fracture sustained in 2005 (Figure 1 and 2). Additionally, an atraumatic and poorly healing fracture of the second metatarsal had occurred in 2007. The patient was otherwise healthy, without any other complaints, with no history of intestinal bowel disease or malabsorption. The family history was also unremarkable. She was taking NSAID as needed and using a levonorgestrel intrauterine device. Clinical examination of dynamic motion showed that the patient had a marked antalgic gait. There was a slightly decreased range of motion in all directions on the right hip. The remainder of the clinical examination was unremarkable, except for obesity (BMI of 32 kg/m²). An X-ray of her pelvis showed a thickening of the lateral corticalis with a subtrochanteric thin fracture line (Figure 2). A DXA scan, performed in 2006 and repeated in 2013, revealed normal values at the lumbar spine, hip and tibia (minimal Z-Score of 0.1 SD). Peripheral quantitative computed tomography (pQCT) revealed a low cortical volumetric bone mineral density (vBMD) of 1034 mg/cm³ at the femoral shaft and tibia. The 25(OH)D₃ level was decreased (41 nmol/l), but calcium, phosphorus, parathyroid hormone (PTH), total procollagen type 1 N-terminal propeptide (P1NP) and beta-CrossLaps (Beta-CTX) in fasting serum were all in the normal range, as were creatinine and thyroid-stimulating hormone (TSH). Surprisingly, we detected repeatedly very low serum alkaline phosphatase levels (5 U/L, range: 35–105 U/l). We therefore measured the serum pyridoxal 5-phosphate (PLP), which was more than two times the upper limit of normal (285 nmol/L, range 35–110 nmol/L). This finding raised the suspicion of genetic hypophosphatasia as a possible diagnosis. To verify this possibility, we carried out a search for a mutation of the alkaline phosphatase liver-type (ALPL) gene encoding for the tissue-nonspecific alkaline phosphatase (TNAP) isoenzyme. Genetic analysis revealed heterozygous mutations in the exons 5, 6 and 9 of the ALPL gene, confirming the diagnosis of hypophosphatasia. In detail, direct sequencing of exons 2–12 and flanking intronic sequences when compared to the database at NM_000478.4 revealed the following mutations: exon 5 c.455G>A, p.Arg152His; exon 6 c.571G>A, p.Glu191Lys; exon 9 c.892G>A, p.Glu298Lys. The femoral fracture was treated by internal fixation. Additionally, we recommended dietary phosphate restriction and symptomatic treatment with non-steroidal anti-inflammatory drugs as needed. Because of the three documented mutations, the patient's relatives will be screened for this disorder by measuring the serum levels of alkaline phosphatase.

Discussion

Here we describe a rare case of recurrent fragility fractures with the main focus on a low-energy trauma, intercondylar femoral fracture due to hypophosphatasia. Hypophosphatasia is an inborn error of metabolism initially recognized by Rathbun in 1948 (3). It



Figure 1 - Intercondylar femoral fracture that occurred after a fall from a standing height.



Figure 2 - Hallmark of adult hypophosphatasia: femoral pseudofracture, involving the lateral subtrochanteric diaphysis.

is a rare inherited disease, with an autosomal recessive or dominant pattern and is characterized by impaired mineralization due to reduced activity of serum and bone alkaline phosphatase. Defects in mineralization affect normal development of bones and teeth (1, 2). It is due to a mutation of the ALPL gene (liver/bone/kidney alkaline phosphatase) encoding the TNAP enzyme. This enzyme cleaves phosphate from inorganic pyrophosphate, pyridoxal 5-phosphate (PLP) and phosphoethanolamine (PEA). In addition, adenosinetriphosphate (ATP), -diphosphate (ADP) and -monophosphate (AMP) are substrates for ALPL, indicating that ALPL is also a modulator of purinergic signaling (4). The loss-of-function mutations lead to an accumulation of phosphorylated forms of the above-mentioned compounds and a decrease in local inorganic phosphate, which is needed for the hydroxyapatite crystallization, and results in bone mineralization defects of varying severity depending on the degree of functional impairment. Furthermore, the accumulated inorganic pyrophosphates directly inhibit the normal mineralization process, and accumulated adenosine-derived compounds may at the same time impair bone formation (1, 5).

Currently, almost 300 distinct ALPL mutations are known (6). There is a highly variable clinical expression because of the wide range of mutations and penetrance (1, 2, 7, 8). There are several forms of hypophosphatasia, based on age at onset of the disease and severity of symptoms. One form is the adult hypophosphatasia, which typically presents in middle age and is associated with a lower morbidity compared with other forms. The exact prevalence of adult hypophosphatasia is not known and may be underestimated as there may be asymptomatic or oligosymptomatic patients and misdiagnoses (2), but a prevalence of 1/6370 in an Eu-

ropean population has been suggested (9). Presenting symptoms may be poorly healing stress fractures, especially of the metatarsals and the femur (1, 2, 10). A hallmark feature is the femoral pseudofracture (Looser's zones), involving the lateral subtrochanteric diaphysis, as was the case in our patient (11, 12). As opposed to hypophosphatasia, pseudofractures due to other forms of osteomalacia rather involve the medial cortex. An increased incidence of chondrocalcinosis and eventually attacks of pseudogout, osteoarthritis, calcific periarthritis and enthesiopathy as well as diffuse idiopathic skeletal hyperostosis (DISH) have been reported (2, 10, 12). Hypophosphatasia should be suspected in these patients in the presence of a persistently and markedly low serum alkaline phosphatase, a rather uncommon laboratory finding. However, differential diagnoses associated with low alkaline phosphatase should also be considered (e.g. anemia, hypothyreosis, medications, early pregnancy, celiac disease, multiple myeloma among others) (1, 2). Helpful in the evaluation of a possible hypophosphatasia is the finding of elevated pyridoxal 5-phosphate (PLP) levels in blood or elevated phosphoethanolamine (PEA) in blood or urine; both of these are accumulated substrates of the alkaline phosphatase. The first is considered a sensitive marker for hypophosphatasia, whereas the second may occur in other metabolic bone diseases (1). Bone mineral density in patients with hypophosphatasia may be normal (2) or reduced (13). The detection of a TNAP-gene mutation may be useful to confirm the diagnosis of hypophosphatasia, so a mutation screening should be considered. Subsequently, genetic counseling and testing of relatives may be performed. The mutations found in our patient have already been described earlier in hypophosphatasia databases (14). The Arg152His mutation has earlier been described as a poly-

morphism without substantial alteration of ALPL activity (15). The Glu191Lys mutation causes mild alteration of ALPL activity resulting in a residual activity of 68%; the mutation is not dominant negative, as we have previously shown (8). The Glu298Lys mutation was described in the context of severe hypophosphatasia (16). Although genetically not totally proven, the clinical picture together with the finding of the mutations in the ALPL gene in our patient suggests a compound heterozygous situation with two functionally relevant mutations.

To date, there is no curative treatment (1, 2). As many patients are hyperphosphatemic, besides non-steroidal anti-inflammatory drugs to reduce pain, dietary phosphate restriction may be of help (1, 7). Additionally, teriparatide may enhance fracture healing, although the reports are inconsistent. Unless there is documented deficiency of vitamin D or minerals, supplementation should be avoided (12). Importantly, there is no role for bisphosphonates in the treatment of hypophosphatasia. On the contrary, they should be avoided as bisphosphonates are inorganic pyrophosphate analogs, inhibit TNAP activity and may be associated with fractures (2, 17). The use of enzyme replacement therapy is promising and may offer an effective treatment in the future (18), as may anabolic treatment options (e.g. anti-sclerostin antibodies) (19). Internal fixation, especially intramedullary nails, is recommended for fractures and symptomatic or progressive pseudo-fractures (12).

Interestingly, based on new medical and archaeological findings, it was recently hypothesized that Tutankhamun, one of the most famous pharaohs, suffered from hypophosphatasia (20). If this is established by testing DNA samples of Tutankhamun for mutations in the ALPL gene, it would show that hypophosphatasia, though rare, has a long history behind it.

Conclusion

Hypophosphatasia should be suspected in patients with poorly healing or unusual stress fractures as well as in patients with chondrocalcinosis, calcific peri-arthritis and diffuse idiopathic skeletal hyperostosis (DISH) in combination with a persistently and markedly low level of serum alkaline phosphatase. Diagnosis is based on laboratory findings and identification of a mutation in the TNAP gene. Recognition of this rare disorder is necessary so that bisphosphonates therapy, which is associated with an exacerbation of the symptoms of this disorder, can be avoided. Furthermore, appropriate genetic counseling can be offered to families. To date, there is no curative treatment.

Conflict of interests

Franz Jakob has received honoraria from Alexion for lectures and advice. Mathias Aeby, Tobias Wyss, Birgit Mentrup, Erdmute Kun-

strmann, and Daniel Aeberli declare that they have no conflict of interest.

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