Hypophosphatasia in adults: a new manifestation, a new mutation. A case report

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Summary

Tissue non-specific alkaline phosphatase (TNSALP) is an ubiquitary enzyme fundamental for bone tissue development and growth. Adult Hypophosphatasia (HPP) is a rare genetic disease caused by a defective TNSALP activity. HPP is frequently misdiagnosed due to the lack of clinical manifestation. We report an asymptomatic woman with HPP that during 5 years follow-up suffered of a bone fracture. Sequencing of genomic DNA revealed a previously unreported mutation at nucleotide 1252G > A (Gly418Arg) leading to a defective enzyme product in the subject. HPP was suspected because of the lack of the expected increase of serum TNSALP at menopause. Our case report underlines the importance of early diagnosis and that the lack of increase of TNSALP at menopause must be a wake-up call for clinicians.

KEY WORDS: hypophosphatasia; bone turnover markers; menopause; osteoporosis.

Introduction

Hypophosphatasia (HPP) is a rare, inherited disease invariably characterized by bone fragility. HPP is due to a mutation in tissue non-specific alkaline phosphatase (TNSALP) gene. TNSALP is a cell-surface homodimeric phosphohydrolase that is richly expressed in the skeleton, liver, kidney and developing teeth. Six clinical forms are usually recognized: perinatal lethal, perinatal benign, infantile, childhood, odontohypophosphatasia and adult. A reduced enzymatic activity of alkaline phosphatase (TNSALP) is the key marker of the disease (1, 2). The overall prevalence of HPP is around 0,3 and 1/100,000 (3), but adult low-expression disease might be substantially more frequent, with a prevalence of 1 on 1544 individuals (4, 5). Adult HPP is characterized by osteoporosis, osteomalacia, myalgia, muscular asthenia, multiple stress fractures, defective teeth growth and calcium pyrophosphate dihydrate crystal deposition disease (CPPD) (6-8). However, adult HPP might be unrecognized because of lacking of clinical important manifestation. Nowadays genetic analysis of TNSALP gene is available and can rule out doubtful cases. Since today, more than 300 TNSALP mutations have been identified in HPP, 70% of which are missense (9). Recently a new enzyme target therapy has been developed (1). In the present work, we report an almost asymptomatic individual with HPP with a new mutation never previously described.

Case report

In November 2012 a 54-year-old female individual was seen at our outpatients' clinic for the evaluation of bone health. The patient never suffered of clinical relevant bone fracture or nephrolitiasis; she had an active life and recently entered the menopause. Prior to her visit at the Rheumatology Unit of the University of Verona the patient performed a dualenergy X-ray absorptiometry (DXA) in 2010 that showed a T-score of -1,6 at lumbar spine and -2.3 at femoral neck and total hip. Physical examination was normal, excepting for mild spine scoliosis. Serum calcium, phosphorous, parathyroid hormone, osteocalcin, C-telopeptide of type I collagen, 25-hydroxyvitamin D (25OHD) were within the normal range. Serum TNSALP was low on repeated tests (19 IU/L). All other causes of low TNSALP were ruled out. Serum levels of vitamin B6 was 199 nmol/L (normal values 25-120 nmol/L). The patient started only with supplementation of vitamin D (800 UI/die), no other drugs were prescribed.
DXA follow-up in the next years showed a worsening in bone mineral density (BMD) at lumbar spine, femoral neck and total hip (Figure 1). From 2010 to 2016, BMD decreased at lumbar spine from 0,878 g/cm^2 (T-score -1.6) to 0,702 g/cm^2 (T-score -3.2), at femoral neck from 0,714 g/cm^2 (T-score -2.3) to 0,531 g/cm^2 (T-score -2.9) and at total hip from 0,657 g/cm^2 to 0,594 g/cm^2. A total spine X-ray was performed and showed a grade 1 fracture of T10 according to the Genant classification of vertebral fractures (10).
During those 5 years follow-up serum TNSALP remained stable under 20 IU/L (Figure 1). HPP was suspected and genetic analysis was performed. The coding regions of the

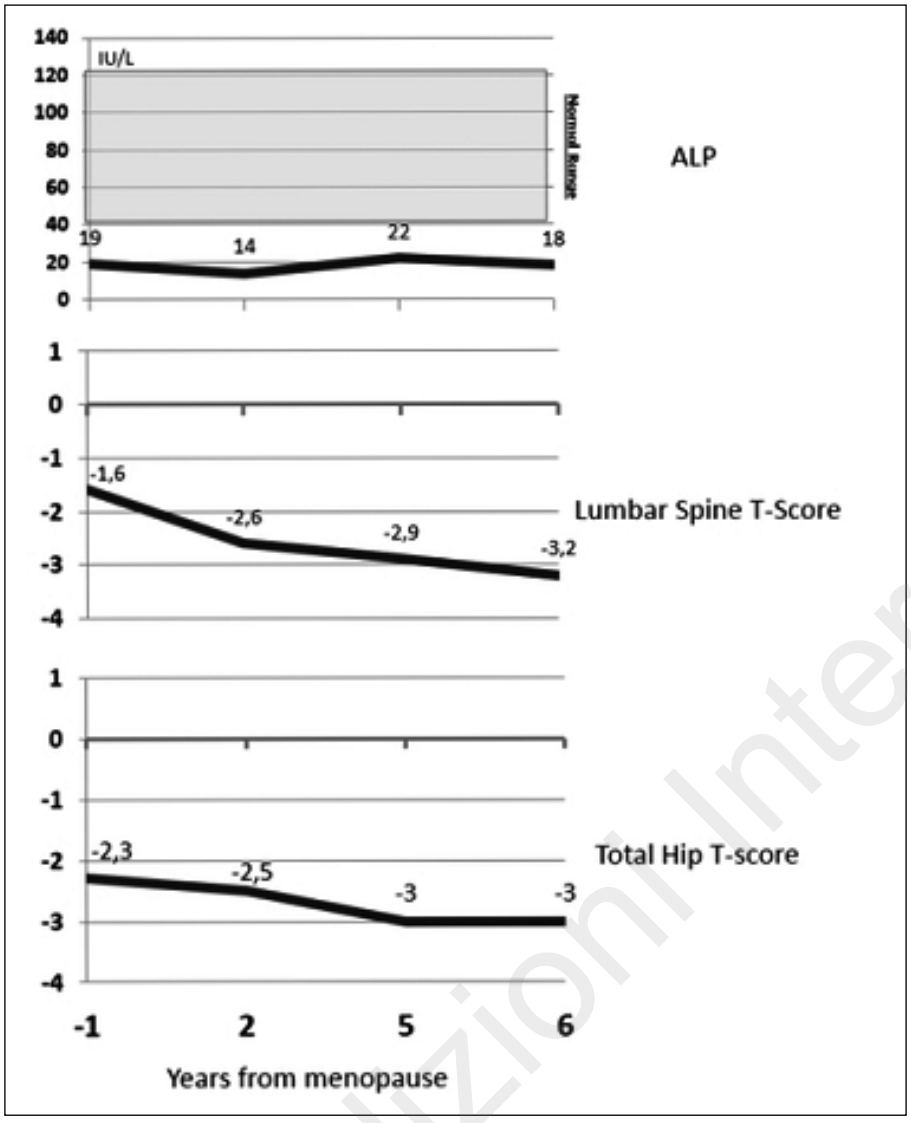

Figure 1 - Bone ALP during menopause transition.

TNSALP gene (MIM 171760; NM_000478.5) and its relative intronic boundaries were amplified by ten specific intronic couples of primers. Automated sequencing was performed on proband DNA by a CEQ8000 capillary sequencer (Beckman Coulter, Indianapolis, IN, USA) (Figure 2). The patient was discover to harbor a heterozygous mutation of TNSALP gene located on exon 11 1252G > A (Gly418Arg). The report of the case was approved by the Verona Medical School Institutional Review Board (IRB) and the woman provided written consent and assent, respectively, for the publication of this report.

Discussion

Adult form of HPP typically presents with poor healing atypical fractures, especially in patients previously given antiresorptive therapy (4, 11). Another frequent presentation of HPP is calcium pyrophosphate dihydrate (CPPD) deposition disease and sometimes it presents only with calcific periarthritis (12). Although HPP is a well described disease, in clinical practice, many HPP affected individuals may be unrecognized or misdiagnosed. The diagnosis is crucial and we should avoid some medications commonly used in the treatment of osteoporosis, as bisphosphonates or denosumab, which might be harmful in patients with HPP. Encouraging results have been achieved with teriparatide in patients with HPP but those results seems to disappeared when stopping the treatment (13-15). Enzyme replacement therapy could be curative of the disease but nowadays is reserved to infantile or severe form of HPP (1, 16). In our female patient TNSALP was found low (19 IU/L) in pre- and remained stable and under normal values in postmenopause (18 IU/L). The menopause transition was associated with a progressive and faster worsening of BMD (Figure 1). HPP was suspected and genetic analysis was performed. The coding regions of the TNSALP gene (MIM 171760; NM_000478.5) and its relative intronic boundaries were amplified by ten specific intronic couples of primers. Automated sequencing was performed on proband DNA by a CEQ8000 capillary sequencer (Beckman Coulter, Indianapolis, IN, USA) (Figure 2). This mutation was never previously described. We performed a prediction analysis with Polymorphism Phenotyping v2 (PolyPhen-2) software to test the functionality of the protein product; this

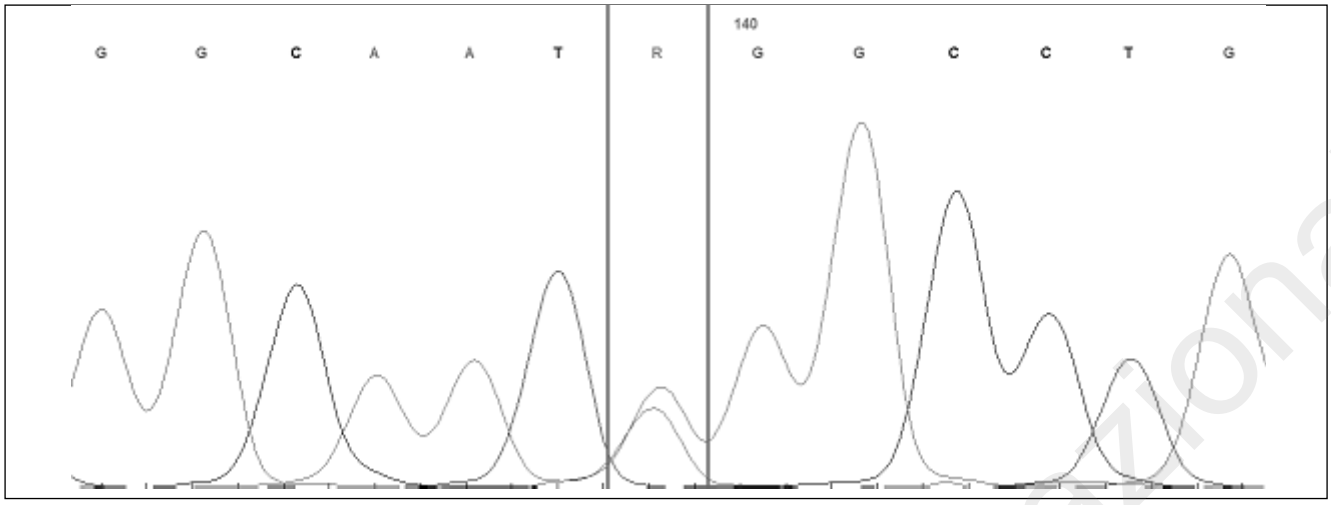

Figure 2 - ALPL genetic mutation.

analysis revealed a probable harmful effect of the mutation.
Recently, in a small cohort of patients with HPP, bone quality has been assessed with high-resolution peripheral quantitative computed tomography (HR-pQCT). Similarly to dual energy X-ray absorptiometry (DXA) measurement, total volumetric density was not generally reduced in HPP patients. However, cortical thickness and cortical volumetric density values were reduced in most patients (Schmidt et al). That clearly indicates that DXA analysis might be a pitfall when evaluating bone health in HPP, in particular in non-symptomatic subjects.
That strengthen the idea that TNSALP dosage must be part of the blood routine laboratory testing of the evaluation for osteopenia, osteoporosis and fragility fractures. The latter advice is even more important when evaluating women entering into menopause, because the lack of the expected increase of serum TNSALP (17) might be clinically significant and attributable to HPP.

Disclosure

The Authors have nothing to disclose.

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