Adult-onset hypophosphatasia diagnosed following bilateral atypical femoral fractures in a 55-year-old woman

This case emphasises the importance of viewing persistent low ALP as a ‘red flag’ in patients presenting with musculoskeletal symptoms. Timely diagnosis and treatment of HPP can reduce the risk of serious complications, such as those experienced by this patient.

KEY WORDS: hypophosphatasia; genetics; bone turnover; atypical fracture.

Introduction

Hypophosphatasia (HPP) is an inborn error in metabolism that is caused by mutation in the gene coding for tissue non-specific alkaline phosphatase (TNSALP), resulting in a decrease in serum ALP concentrations (1, 2). The age at which it presents which can vary from early childhood to middle age (3), with symptoms ranging from perinatal death to late-onset osteomalacia. The loss-of-function mutation in HPP results in the accumulation of TNSALP substrates outside of the cell, including inorganic pyrophosphate which inhibits bone mineralisation (4). In those patients who survive to adulthood, there is a subsequent predisposition to fractures, including atypical subtrochanteric femoral fractures (ASFFs) (5). These are defined as any fracture meeting four out of five of the major criteria described by the American Society for Bone and Mineral Research (ASBMR) task force in 2013 (Table 1) (7). They are most commonly associated with the use of bisphosphonates, which are thought to have adverse effects on bone biology in a small proportion of patients (8, 9). Outcomes following these fractures are generally poor with 25% patients surviving less than two years and greater than half of all patients failing to return to their previous level of functioning in this time (10).

We discuss a 55-year-old lady who woke who noticed swelling and deforming in her right thigh when waking from sleep. Radiographs revealed bilateral atypical subtrochanteric femoral fractures (ASFFs), together with low serum ALP led to a diagnosis of adult-onset HPP which was later confirmed from bone histology and genetic testing.

Case report

A 55-year-old Caucasian woman presented to the emergency department in August 2016 having woken that morning with painless right sided thigh swelling. Pelvic radiographs revealed bilateral atypical subtrochanteric femoral fractures (ASFFs). In the two years leading up to this admission, the patient had experienced gradually increasing pain and weakness in her legs which had resulted in a decrease in her mobility from fully mobile to bed-bound. During this time a neurologist had organised a magnetic-resonance imaging (MRI) scan of the brain and spine which was normal. There was no history of bisphosphonate (BP) use. Historical and admission blood tests revealed a persistently low serum alkaline phosphatase (ALP), with all other results within normal limits. The patient was treated with intramedullary nailing of both femurs and histological analysis of bone reamings were characteristic of hypophosphatasia (HPP). The patient was independently mobilising with a walking frame on discharge. Subsequent genetic testing revealed bi-allelic pathogenic variants in the TNSALP gene: c.526G>A, p.(Ala176Thr) and c.1171C>T, p.(Arg391Cys).

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Summary

We report the case of a 55-year-old woman who presented to the emergency department having woken from sleep with right sided thigh swelling. Pelvic radiographs revealed bilateral atypical subtrochanteric femoral fractures (ASFFs). In the two years leading up to this admission, the patient had experienced gradually increasing pain and weakness in her legs which had resulted in a decrease in her mobility from fully mobile to bed-bound. During this time a neurologist had organised a magnetic-resonance imaging (MRI) scan of the brain and spine which was normal. There was no history of bisphosphonate (BP) use. Historical and admission blood tests revealed a persistently low serum alkaline phosphatase (ALP), with all other results within normal limits. The patient was treated with intramedullary nailing of both femurs and histological analysis of bone reamings were characteristic of hypophosphatasia (HPP). The patient was independently mobilising with a walking frame on discharge. Subsequent genetic testing revealed bi-allelic pathogenic variants in the TNSALP gene: c.526G>A, p.(Ala176Thr) and c.1171C>T, p.(Arg391Cys).

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Introduction

Hypophosphatasia (HPP) is an inborn error in metabolism that is caused by mutation in the gene coding for tissue non-specific alkaline phosphatase (TNSALP), resulting in a decrease in serum ALP concentrations (1, 2). The age at which it presents which can vary from early childhood to middle age (3), with symptoms ranging from perinatal death to late-onset osteomalacia. The loss-of-function mutation in HPP results in the accumulation of TNSALP substrates outside of the cell, including inorganic pyrophosphate which inhibits bone mineralisation (4). In those patients who survive to adulthood, there is a subsequent predisposition to fractures, including atypical subtrochanteric femoral fractures (ASFFs) (5). These are defined as any fracture meeting four out of five of the major criteria described by the American Society for Bone and Mineral Research (ASBMR) task force in 2013 (Table 1) (7). They are most commonly associated with the use of bisphosphonates, which are thought to have adverse effects on bone biology in a small proportion of patients (8, 9). Outcomes following these fractures are generally poor with 25% patients surviving less than two years and greater than half of all patients failing to return to their previous level of functioning in this time (10).

We discuss a 55-year-old lady who woke who noticed swelling and deforming in her right thigh when waking from sleep. Radiographs revealed bilateral ASFFs, which together with low serum ALP led to a diagnosis of adult-onset HPP which was later confirmed from bone histology and genetic testing.

Case report

A 55-year-old Caucasian woman presented to the emergency department in August 2016 having woken that morning with painless right sided thigh swelling in the context of increasing pain and weakness in the lower limbs over the preceding two years. This began with an awareness of a worsening ache in the right leg and by one year prior to admission she was unable to walk more than a short distances. Six months prior to admission she required the use of a single crutch due to a feeling of unsteadiness and following this fell from standing onto her right side. Two further falls from standing occurred six weeks prior to admission with no injury.
The patient continued to recover and on discharge seven-teen days after admission was mobilising with a walking frame. A skeletal survey was performed at orthopaedic fol-low-up which revealed further fractures in the right tibia, right sided ASFF and taken to the operating room (OR) the following day. The procedure went as planned, with ream-ings taken during the procedure sent for histological analy-sis. The patient made a good post-operative recovery and was mobilizing full weight bearing with crutches for support. The patient’s mobility continued to decline and the patient was bed bound in the two weeks prior to admis-sion. In March 2016 she had been investigated by a neurologist for her symptoms however following normal magnetic reso-nance imaging (MRI) scans of the brain and spinal cord and normal cerebrospinal fluid (CSF) analysis (including elec-trophoresis) no cause for the patient’s symptoms could be identified. She had subsequently been referred to a physio-therapy service. Other medical problems included well-con-trolled bronchiectasis, bilateral carpal tunnel syndrome, chronic kidney disease stage 1 following pre-eclampsia, frequent cystitis, trigeminal neuralgia and juvenile tooth loss. There was no history of osteoporosis or rickets and menopause had been at the age of 53. There was no history of bisphosphonate therapy.

A plain-film anterior-posterior (AP) radiograph of the pelvis was organised which revealed a shortened, laterally angulat-ed atypical subtrochanteric femoral fracture (ASFF) on the right side with endosteal thickening visible in the sub-trochanteric region of the left femur (Figure 1 a, b). A subse-quent radiograph of the left femur revealed an incomplete ASFF involving the lateral cortex only (Figure 1 c).

Admission blood tests revealed a low alkaline phosphatase (ALP) of 5 U/L (44-147 NI), with remaining blood tests all within normal limits. The patient was consented for intramedullary fixation of the right sided ASFF and taken to the operating room (OR) the following day. The procedure went as planned, with ream-ings taken during the procedure sent for histological analy-sis. The patient made a good post-operative recovery and underwent intramedullary nailing of the contralateral femur four days later. Reamings showed deposited nuclear / cellu-lar material at the osteoid - bone interface in keeping with hypophosphatasia (Figure 2 a, b).

The patient continued to recover and on discharge seven-teen days after admission was mobilising with a walking frame. A skeletal survey was performed at orthopaedic fol-low-up which revealed further fractures in the right tibia, right 4th and 5th metatarsals and sclerosis of the left 5th metatarsal (Figures 3, 4 a, b). The tibial fracture was treated with in-tramedullary nailing, with the remaining fractures treated non-operatively and monitored with serial radiographs which showed gradual improvement to follow-up in June 2017 (Fig-ure 5).

Follow-up with a clinical geneticist was arranged for October 2016 and mutation analysis revealed bi-allelic pathogenic variants in TNSALP gene. Subsequent testing of the pa-tient’s two children revealed that each had inherited only of the two one variant alleles. The patient did not meet the criteria for treatment with asfo-tase alfa (a bone-targeted, recombinant human TNSALP) which is only currently approved for use in perinatal, infantile and paediatric-onset HPP [although these treatments are not available on the National Health Service (NHS) in the UK]. The patient was mobilising full weight bearing with crutches for support.

Materials and methods

Serum biochemistry: Informed verbal consent was obtained from the patient for blood sampling in the emergency department in August 2016 using the Sarstedt Monovette blood collection system (Sarstedt AG & Co, Numbrecht, Germany). Analysis was performed using the Siemens Dimension RxL Integrated Chemistry System (Siemens Healthcare, Erlan-gen, Germany).

Radiographs: Informed verbal consent was obtained from the patient at admission and post-operatively for radiographs of the pelvis and both femurs. Images were analysed using the Centricity Enterprise Web version 3.0 Picture Archiving and Communication System (General Electric, Boston, Mas-sachusetts, USA).

Bone histological analysis: Reaming of the medullary canal was performed intraoperatively in keeping with the standard protocol for intramedullary fixation of the femur using an in-tramedullary nail. Samples obtained from the reamer were
deposited into 70% ethanol for transport to the laboratory, where they were embedded in 5ppm hydroquinone hydrophilic acrylic resin prior to sectioning. Samples were treated with toluidine blue and von Kossa stains prior to light microscopy.

**Mutation analysis:** Next Generation Sequencing (NGS) of the coding region of the TNSALP gene was performed using the Illumina TruSight One sequencing panel (Illumina, San Diego, California, USA). Variants detected by this method were confirmed using Sanger sequencing.

**Results**

Serum biochemistry results on admission revealed a low ALP activity of 5 U/L (44-147 NI). Inspection of historical blood test results revealed an ALP of 9 U/L (44-147 NI) from samples taken by the patient’s general practitioner six months previously. Remaining liver function tests, full blood count, urea & electrolytes and coagulation were within normal limits on admission. Secondary screening blood tests for osteoporosis, including vitamin D, folate, calcium, vitamin B12, thyroid function and erythrocyte sedimentation rate (ESR) were all within normal limits.

Histological analysis of bone samples using Von Kossa stain revealed mineralised bone with wide osteoid seams and scalloping of cement lines. Further analysis with toluidine blue stain revealed deposited nuclear / cellular material at the osteoid - bone interface in keeping with hypophosphatasia.

Mutation analysis revealed two heterozygous single nucleotide polymorphisms in the TNSALP gene: c.526G>A, p.(Ala176Thr) and c.1171C>T, p.(Arg391Cys).
Hypophosphatasia (HPP) is an inborn error in metabolism caused by loss-of-function mutations in the gene coding for tissue non-specific alkaline phosphatase (TNSALP) located on chromosome 1p36.1-34 (1, 2, 11). Over 300 mutations have been identified to date which result in a variable loss of function in the enzyme and a consequent decrease in serum ALP concentrations (1, 2, 6). TNSALP substrates including inorganic phosphate accumulate in the extracellular space, inhibiting bone mineralisation (4). The age at which it presents which can vary from early childhood to middle age, with symptoms ranging from perinatal death to late-onset osteomalacia (3). Adult-onset HPP can be a consequence of both autosomal dominant and autosomal recessive inheritance of TNSALP mutations, and has characteristically variable penetrance and severity (12).

Discussion

Hypophosphatasia (HPP) is an inborn error in metabolism caused by loss-of-function mutations in the gene coding for tissue non-specific alkaline phosphatase (TNSALP) located on chromosome 1p36.1-34 (1, 2, 11). Over 300 mutations have been identified to date which result in a variable loss of function in the enzyme and a consequent decrease in serum ALP concentrations (1, 2, 6). TNSALP substrates including inorganic phosphate accumulate in the extracellular space, inhibiting bone mineralisation (4). The age at which it presents which can vary from early childhood to middle age, with symptoms ranging from perinatal death to late-onset osteomalacia (3). Adult-onset HPP can be a consequence of both autosomal dominant and autosomal recessive inheritance of TNSALP mutations, and has characteristically variable penetrance and severity (12). The single nucleotide polymorphisms [SNPs] identified in
this patient’s TNSALP gene have been previously identified as causing HPP. The SNP c.526G>A, p.(Ala176Thr) is known to result in approximately 70% loss of enzyme function and is associated with mild hypophosphatasia (12). The SNP c.1171C>T, p.(Arg391Cys) has been previously reported in cases of childhood-onset HPP and is known to result in approximately 90% loss of enzyme activity (13-15). This patient presented with bilateral atypical subtrochanteric femoral fractures (ASFFs). This fracture type was given an official definition in 2009 (later updated in 2013) by the American Society for Bone and Mineral Research (ASBMR) as any fracture meeting four of five major features (Table 1) (9). There have been several cases of bilateral ASFFs documented in the literature, however the vast majority of these are associated with bisphosphonate use, which is thought to contribute to the accumulation of bone microdamage and cause dysregulation of bone mineralisation, bone turnover, collagen cross-linking and bone vascularity in some patients (8, 16-18). Whilst this case represents an unusual injury pattern for a patient with HPP, approximately 18% of the adult-onset form of disease is diagnosed following a fracture, with 23% of all patients having sustained a femoral fracture at some point in their life (19).

Prior to presentation at our institution, this patient had been extensively investigated for musculoskeletal symptoms. Included in this diagnostic workup were three sets of blood tests in the six months leading up to her admission which revealed persistently low serum ALP of between 9-11 U/L. This emphasises the importance of viewing persistent low ALP as a ‘red flag’ in patients presenting with musculoskeletal symptoms. Timely diagnosis and treatment of HPP can reduce the risk of serious complications, such as those experienced by this patient.

There is currently no approved treatment available for adult-
onset HPP, though there is some evidence to support the use of teraparatide in this cohort (4, 20, 21). The use of bisphosphonates in this disease is not advised, as this treatment can exacerbate the already dysfunctional bone turnover in HPP (22, 23). Treatment with asfotase alfa (a bone-targeted, recombinant human TNSALP) has been shown to improve survival in perinatal and infantile HPP and this drug has been approved for the treatment of these variants of the disease [though is not currently available on the UK National Health Service (NHS) (24)].

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Authors’ roles: DS and JEL admitted the patient from the emergency department and arranged initial investigations. AC was the supervising clinician. JEL, DS and JB performed the literature search and compiled the manuscript. AC edited the manuscript.

References


