Endocrinology, Diabetes & Metabolism CASE REPORTS

A M Warren and others | Hypophosphatasia found after AFF on denosumab

ID:21-0096;September 2021
DOI: 10.1530/EDM-21-0096

Bilateral atypical femoral fractures during denosumab therapy in a patient with adult-onset hypophosphatasia

Annabelle M Warren[1,2,6], Peter R Ebeling[3,4], Vivian Grill[5,6], Ego Seeman[2,6] and **Shoshana Sztal-Mazer[1,7]**

[1]Department of Endocrinology, The Alfred Hospital, Melbourne, Victoria, Australia, [2]Department of Endocrinology, The Austin Hospital, Heidelberg, Victoria, Australia, [3]Department of Medicine, School of Clinical Sciences, Monash University, Clayton, Victoria, Australia, [4]Department of Endocrinology, Monash Health, Clayton, Victoria, Australia, [5]Department of Endocrinology, Western Health, St Alban's, Victoria, Australia, [6]Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia, and [7]Women's Health Research Program, School of Public Health and Preventative Medicine, Monash University, Melbourne, Victoria, Australia

Correspondence should be addressed to A M Warren
Email
annabellemwarren@gmail.com

Summary

Hypophosphatasia (HPP) is a rare and under-recognised genetic defect in bone mineralisation. Patients presenting with fragility fractures may be mistakenly diagnosed as having osteoporosis and prescribed antiresorptive therapy, a treatment which may increase fracture risk. Adult-onset HPPhypophosphatasia was identified in a 40-year-old woman who presented with bilateral atypical femoral fractures after 4 years of denosumab therapy. A low serum alkaline phosphatase (ALP) and increased serum vitamin B6 level signalled the diagnosis, which was later confirmed by identification of two recessive mutations of the *ALPL* gene. The patient was treated with teriparatide given the unavailability of ALP enzyme-replacement therapy (asfotase alfa). Fracture healing occurred, but impaired mobility persisted. HPP predisposes to atypical femoral fracture (AFF) during antiresorptive therapy; hence, bisphosphonates and denosumab are contraindicated in this condition. Screening patients with fracture or 'osteoporosis' to identify a low ALP level is recommended.

Learning points:

- Hypophosphatasia (HPP) is a rare and under-recognised cause of bone fragility produced by impaired matrix mineralisation that can be misdiagnosed as a fragility fracture due to age-related bone loss.
- Antiresorptive therapy is contraindicated in HPP.
- Low serum alkaline phosphatase (ALP) provides a clue to the diagnosis.
- Elevated serum vitamin B6 (an ALP substrate) is indicative of HPP, while identification of a mutation in the *ALPL* gene is confirmatory.
- Enzyme therapy with recombinant ALP (asfotase alfa) is currently prohibitively costly.
- Treatment with anabolic bone agents such as teriparatide has been reported, but whether normally mineralized bone is formed requires further study.

Background

Hypophosphatasia (HPP) is a rare genetic cause of osteomalacia and fracture that is underdiagnosed. Bisphosphonates are contraindicated due to an increased risk of atypical femur fracture. We report a case of atypical femoral fracture associated with denosumab therapy in a patient subsequently diagnosed with adult-onset HPP.

https://edm.bioscientifica.com/
Published by Bioscientifica Ltd

ID:21-0096;September 2021
DOI: 10.1530/EDM-21-0096

Only two such cases have been reported. We propose that denosumab should also be avoided in this clinical setting. This case highlights the ease and importance of screening for HPP in patients with fracture to facilitate alternative therapy to antiresorptives, which increase fracture risk.

Case presentation

A 40-year-old female from rural Victoria, Australia of European (Scottish) ancestry was referred to a tertiary hospital osteoporosis clinic after sustaining bilateral atypical femoral fractures (AFFs) 10 months earlier. At the time of referral, she was mobilising with crutches and required a wheelchair over longer distances as a consequence of her fractures and hip osteoarthritis.

Her first fracture was sustained in 2005 at the age of 25 when she suffered left navicular, third and fifth metatarsal fractures after a fall from standing height. She experienced delayed fracture healing for many years and a diagnosis of complex regional pain syndrome was made. Evaluation of delayed fracture healing using CT in 2013 revealed radiographic osteopenia, which was later confirmed using dual energy X-ray absorptiometry (DXA). The patient was commenced on a weekly oral bisphosphonate by her general practitioner, but experienced gastrointestinal intolerance and ceased it after 4 months. Denosumab was commenced in 2014, which she received every 6 months for 4 years. Relevant past history included a seizure at the age of 28, for which sodium valproate was prescribed. She denied any developmental or pubertal delay, early dental loss, periodontal disease or family history of fractures.

In December 2018, at the age of 39, the patient sustained bilateral AFFs after a fall from standing height. No prodromal thigh pain was reported. As the right diaphyseal fracture was symptomatic and complete, it was surgically fixed on 28 December 2018. The pre-operative X-ray showed features of an AFF with beaking of the lateral femoral periosteum at the fracture site (Fig. 1). Imaging of the left femur demonstrated a nondisplaced asymptomatic partial AFF which was conservatively managed. Both fractures fulfilled the 2013 ASBMR criteria for AFF, and denosumab was discontinued (final dose June 2018). DXA in February 2019 showed bone mineral density (BMD) at the lumbar spine of 1.150 g/cm^2 (T score: +0.8, Z score: +0.9) and left total hip BMD of 0.730 g/cm^2 (T score: –1.7, Z score: –1.4).

Upon presentation to the bone clinic in October 2019, the patient's height was 153.1 cm and weight was 69.2 kg, giving her a BMI of 29.5 kg/m^2, in the overweight range. There was no clinical evidence of craniofacial abnormality.

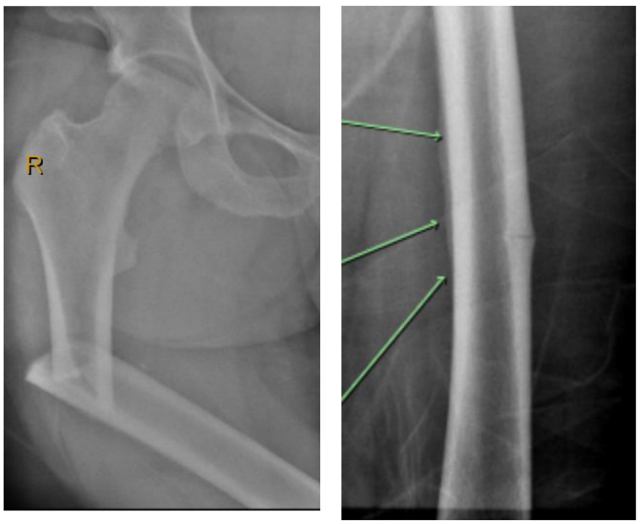

Figure 1
Pre-operative X-ray images of bilateral atypical femoral fractures December 2018, showing right symptomatic complete femoral diaphyseal fracture and left asymptomatic partial AFF.

Investigation

In October 2019: serum calcium was 2.31 mmol/L (normal range (NR): 2.10–2.60), parathyroid hormone: 2.9 pmol/L (NR: 1.1–6.0) and renal function (eGFR: >90 mL/min/1.73m^2) were normal. Serum phosphate was slightly elevated at 1.55 mmol/L (NR: 0.75–1.50). Serum alkaline phosphatase (ALP) was low at 11 U/L (NR: 30–110), and had been even lower in 2016 when it was 7 U/L (NR: 30–120) during denosumab therapy. Serum concentration of carboxy-terminal collagen crosslinks (CTX) was low at 127 ng/L (NR: 150–800) and serum N-terminal propeptide of type I procollagen (P1NP) was normal at 32 µg/L (NR: 15–70). The serum 25-hydroxyvitamin D was 96 nmol/L (NR: 50–100). Vitamin B6 (pyridoxine) was markedly elevated >2000 nmol/L (NR: 35–110). Cranial X-ray showed no evidence of craniosynostosis. Repeat femoral X-ray revealed non-union of the right AFF and near completion of the left AFF with the exception of an intact medial cortex (Fig. 2). Knee and hip imaging demonstrated mild degenerative arthrosis of the left hip.

The clinical history, low ALP and elevated vitamin B6 supported a diagnosis of HPP. *ALPL* gene testing performed by Sydney Children's Hospital Network Genetic Service revealed two pathogenic heterozygous *ALPL* variants: c.526G>A p.(A176T) and 881A>C p.(D294A) consistent with the diagnosis of recessive HPP. The patient's parents have no history of fractures, and she has no siblings or offspring, and as such further genetic testing of family members has not been pursued due to cost.

ID:21-0096;September 2021
DOI: 10.1530/EDM-21-0096

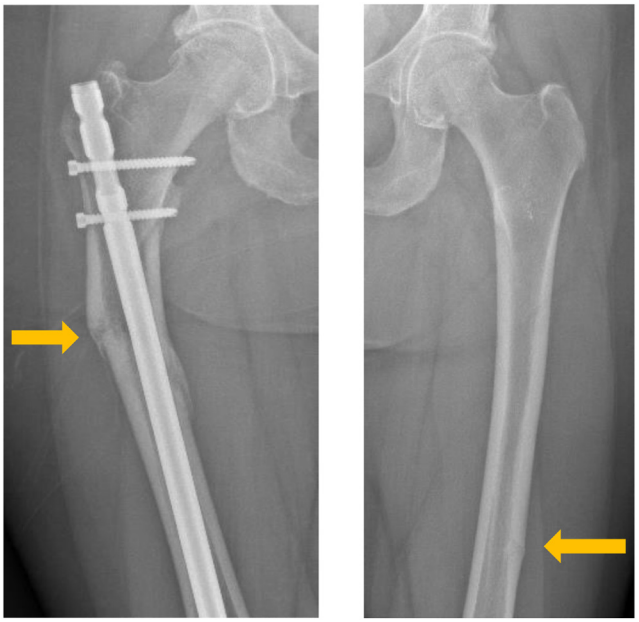

Figure 2
X-ray images in October 2019 showing persistent non-union of bilateral atypical femoral fractures, 10 months post right-sided internal fixation with an intramedullary nail.

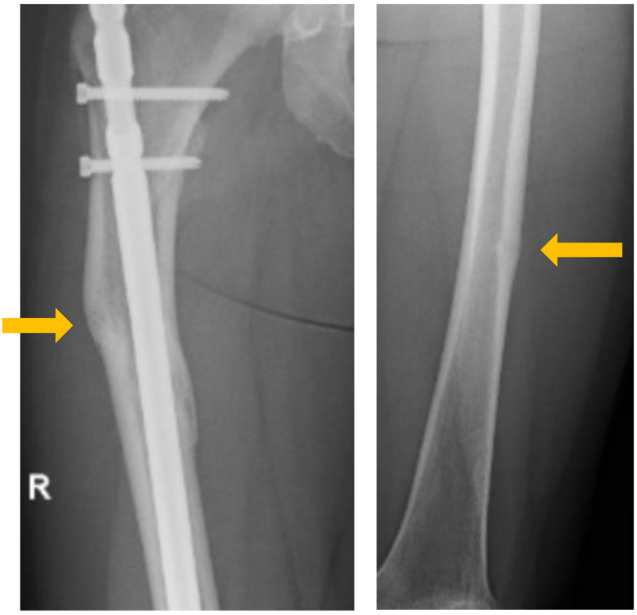

Figure 3
X-ray images from September 2020 showing the progression of healing of bilateral atypical femoral fractures following 7 months of teriparatide therapy.

Treatment

In February 2020, 18 months of s.c. teriparatide 20 mcg daily therapy was commenced via a hospital individual patient usage program. This was continued for another 6 months upon the most recent review given approval of increased treatment duration by the Australian Therapeutic Goods Administration. Asfotase alfa was not accessible due to cost.

Outcome and follow-up

In September 2020, nearly 2 years after the bilateral AFFs originally occurred, and after 7 months of teriparatide, repeat X-rays demonstrated further fracture healing, although it was unclear whether it was attributable to teriparatide treatment (Fig. 3). The patient continues to require a gait aid to mobilise. There have been no further fractures despite a recent fall.

Discussion

HPP is a rare disorder caused by a defect in the *ALPL* gene leading to deficiency of ALP and impaired primary mineralisation of bone (osteomalacia). There is a wide spectrum of clinical presentation. Less severe forms generally occurring in adulthood are more frequent with a prevalence around 1/500–1/2500, in comparison to severe childhood-onset forms that may be fatal and occur in 1/100 000–1/300 000 (1, 2). Manifestations in adults include delayed fracture healing, metatarsal stress fractures, pseudofractures, AFF, pyrophosphate arthropathy and seizures. A low serum ALP level and elevated serum vitamin B6 level are highly suggestive of HPP, which is confirmed by genetic testing of *ALPL*. Variations in severity reflect identification of more than 300 *ALPL* mutations, both autosomal dominant and recessive (3).

Tissue-nonspecific ALP (TNSALP, also known as ALP) encoded by *ALPL* is important in mineralisation: it liberates phosphate (which is used to mineralise bone matrix) from precursor inorganic pyrophosphate (PPi), a substrate molecule which inhibits mineralisation. When ALP is deficient, accumulation of PPi plus deficiency of phosphate impairs the formation of hydroxyapatite crystals responsible for producing rigidity of the skeleton. Instead, unmineralized osteoid tissue is formed, which makes the bones vulnerable to fracture. ALP is also involved in dephosphorylation of vitamin B6 (pyridoxal 5'-phosphate, PLP). The accumulation of vitamin B6 substrate (PLP) elevates the serum vitamin B6 levels, which may assist in the diagnosis of HPP (3).

HPP is one of the several monogenic bone diseases that can result in AFF, and antiresorptive therapy increases this risk (4, 5). There are at least 11 reported cases of AFF

ID:21-0096;September 2021
DOI: 10.1530/EDM-21-0096

following bisphosphonate use in patients with HPP (6, 7, 8). Bisphosphonates are contraindicated in HPP as they exacerbate the underlying pathophysiology through a number of mechanisms (3). Bisphosphonates are analogues of inorganic pyrophosphate (PPi), and like the PPi which accumulates because of ALP deficiency, bisphosphonates may also deactivate TNSALP and block hydroxyapatite crystal growth, exacerbating osteomalacia. They are also thought to bind zinc and magnesium ions which may reduce the activity of TNSALP further (7). Bisphosphonates reduce bone remodelling, increase completeness of secondary mineralisation and glycation of bone contributing to worsening of bone's material strength (9).

An association between denosumab and increased risk of atypical femoral fracture in HPP is not well established, with only two published cases of AFF in HPP following denosumab treatment, one of whom had also received bisphosphonate therapy (10, 11). Denosumab inhibits RANK ligand which is responsible for osteoclast synthesis, action and lifespan. Impaired resorption of damaged bone, combined with impaired mineralisation of new bone in HPP may increase the risk of AFF in patients treated with denosumab (6). Our patient received only 4 months of bisphosphonate therapy followed by 4 years of denosumab treatment before developing bilateral AFFs suggesting that denosumab may have been more important in the pathogenesis of AFF. However, without bone biopsy evidence, we cannot distinguish whether the fractures are the result of failed primary mineralisation due to osteomalacia (pseudo fractures) (12), or due, in part, to more complete secondary mineralisation associated with prolonged remodelling suppression by antiresorptive therapy (atypical fractures) (7).

Targeted enzyme replacement therapy in the form of recombinant ALP, asfotase alfa, has been a significant advance in HPP treatment in the past decade. This treatment is effective at restoring skeletal mineralisation and attainment of developmental milestones in severe paediatric onset HPP, with improved mortality compared with a historical cohort (13). Biochemical evidence of effect is also seen, with reduction in serum PPi and vitamin B6 (PLP) levels. In adults with HPP, asfotase alfa promotes fracture healing (14). It is regarded as a optimal therapy, but access to asfostase alfa for adults is limited because it costs >$1 million AUD per year.

As a more accessible alternative, drugs that promote anabolic bone formation have been investigated in HPP. The PTH (1–34) peptide, teriparatide, promotes remodelling and overfilling of resorption cavities. In case reports, teriparatide improves fracture healing and may halt fracture propagation in patients with HPP, although the response may depend on the nature of the *ALPL* mutation (15, 16). Another anabolic agent, setrusumab, a sclerostin inhibitor, has undergone a phase II trial in HPP, with a 3.9% increase in BMD after 16 weeks (17). There has been no reported use of the currently available antisclerostin agent, romosozumab, in HPP to date. The limitation of anabolic agents in treating this condition may be that they do not address the underlying defect in mineralisation, hence, any new bone formed is likely to be incompletely mineralised.

HPP is a rare cause of fragility fracture in adults. HPP is an essential diagnosis of which to be aware as antiresorptive therapy with both bisphosphonates and denosumab may increase the risk of atypical femoral fracture, and therefore are not recommended. Low serum ALP on standard pathology signals the possible diagnosis, which can be further investigated by measuring serum vitamin B6 and confirmed with *ALPL* gene testing. Directed enzyme therapy with recombinant ALP (asfotase alfa) is an optimal treatment, but prohibitively expensive. Anabolic agents, including teriparatide, are a potential alternative that may assist in fracture healing, but whether mineralisation of newly formed bone is normal remains uncertain. Evaluation of serum ALP as a part of a routine osteoporosis work up is recommended to ensure that diagnosis of HPP is not missed, leading to inappropriate use of antiresorptive therapy.

Declaration of interest
A M W, S S M, V G and E S have no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported. P R E receives research funding from Alexion, manufacturers of asfotase alfa.

Funding
This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent
The patient has provided written informed consent for publication.

Author contribution statement
A M W was involved in direct care of the patient and wrote the first draft of the manuscript. S S M is the patient's senior physician, was involved in coordination of management decisions and reviewed the manuscript. P R E provided expert advice on management and reviewed the manuscript. V G provided expert advice on management and reviewed the manuscript. E S provided expert input and reviewed the manuscript.

Acknowledgements
The authors would like to acknowledge the assistance of Prof Michael P Whyte from the Division of Bone and Mineral Diseases, Department of Internal Medicine, Washington University School of Medicine and the Center for Metabolic Bone Disease and Molecular Research, Shriners Hospitals for Children, St. Louis. His learned scholarship and advice are greatly appreciated.

References

1 Mornet E, Taillandier A, Domingues C, Dufour A, Benaloun E, Lavaud N, Wallon F, Rousseau N, Charle C, Guberto M, *et al.* Hypophosphatasia: a genetic-based nosology and new insights in genotype-phenotype correlation. *European Journal of Human Genetics* 2021 **29** 289–299. (https://doi.org/10.1038/s41431-020-00732-6)
2 Högler W, Langman C, Gomes da Silva H, Fang S, Linglart A, Ozono K, Petryk A, Rockman-Greenberg C, Seefried L & Kishnani PS. Diagnostic delay is common among patients with hypophosphatasia: initial findings from a longitudinal, prospective, global registry. *BMC Musculoskeletal Disorders* 2019 **20** 80. (https://doi.org/10.1186/s12891-019-2420-8)
3 Whyte MP. Hypophosphatasia – aetiology, nosology, pathogenesis, diagnosis and treatment. *Nature Reviews: Endocrinology* 2016 **12** 233–246. (https://doi.org/10.1038/nrendo.2016.14)
4 Zhou W, van Rooij JGJ, Ebeling PR, Verkerk AJMH & Zillikens MC. The genetics of atypical femur fractures-a systematic review. *Current Osteoporosis Reports* 2021 **19** 123–130. (https://doi.org/10.1007/s11914-021-00658-y)
5 Nguyen HH, van de Laarschot DM, Verkerk AJMH, Milat F, Zillikens MC & Ebeling PR. Genetic risk factors for atypical femoral fractures (AFFs): a systematic review. *JBMR Plus* 2018 **2** 1–11. (https://doi.org/10.1002/jbm4.10024)
6 Marini F & Brandi ML. Atypical femur fractures: a distinctive tract of adult hypophosphatasia. *Clinical Cases in Mineral and Bone Metabolism* 2017 **14** 324–328. (https://doi.org/10.11138/ccmbm/2017.14.3.324)
7 Sutton RA, Mumm S, Coburn SP, Ericson KL & Whyte MP. Atypical femoral fractures during bisphosphonate exposure in adult hypophosphatasia. *Journal of Bone and Mineral Research* 2012 **27** 987–994. (https://doi.org/10.1002/jbmr.1565)
8 Genest F & Seefried L. Subtrochanteric and diaphyseal femoral fractures in hypophosphatasia-not atypical at all. *Osteoporosis International* 2018 **29** 1815–1825. (https://doi.org/10.1007/s00198-018-4552-3)
9 Seeman E & Martin TJ. Antiresorptive and anabolic agents in the prevention and reversal of bone fragility. *Nature Reviews: Rheumatology* 2019 **15** 225–236. (https://doi.org/10.1038/s41584-019-0172-3)
10 Lefever E, Witters P, Gielen E, Vanclooster A, Meersseman W, Morava E, Cassiman D & Laurent MR. Hypophosphatasia in adults: clinical spectrum and its association with genetics and metabolic substrates. *Journal of Clinical Densitometry* 2020 **23** 340–348. (https://doi.org/10.1016/j.jocd.2018.12.006)
11 Magdaleno AL, Singh S, Venkataraman S, Perilli GA & Lee YY. Adult-onset hypophosphatasia: before and after treatment with asfotase alfa. *AACE Clinical Case Reports* 2019 **5** e344–e348. (https://doi.org/10.4158/ACCR-2019-0143)
12 Coe JD, Murphy WA & Whyte MP. Management of femoral fractures and pseudofractures in adult hypophosphatasia. *Journal of Bone and Joint Surgery* 1986 **68** 981–990. (https://doi.org/10.2106/00004623-198668070-00004)
13 Whyte MP, Greenberg CR, Salman NJ, Bober MB, McAlister WH, Wenkert D, Van Sickle BJ, Simmons JH, Edgar TS, Bauer ML, *et al.* Enzyme-replacement therapy in life-threatening hypophosphatasia. *New England Journal of Medicine* 2012 **366** 904–913. (https://doi.org/10.1056/NEJMoa1106173)
14 Klidaras P, Severt J, Aggers D, Payne J, Miller PD & Ing SW. Fracture healing in two adult patients with hypophosphatasia after asfotase alfa therapy. *JBMR Plus* 2018 **2** 304–307. (https://doi.org/10.1002/jbm4.10052)
15 Gagnon C, Sims NA, Mumm S, McAuley SA, Jung C, Poulton IJ, Ng KW & Ebeling PR. Lack of sustained response to teriparatide in a patient with adult hypophosphatasia. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 1007–1012. (https://doi.org/10.1210/jc.2009-1965)
16 Whyte MP, Mumm S & Deal C. Adult hypophosphatasia treated with teriparatide. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 1203–1208. (https://doi.org/10.1210/jc.2006-1902)
17 Seefried L, Baumann J, Hemsley S, Hofmann C, Kunstmann E, Kiese B, Huang Y, Chivers S, Valentin MA, Borah B, *et al.* Efficacy of anti-sclerostin monoclonal antibody BPS804 in adult patients with hypophosphatasia. *Journal of Clinical Investigation* 2017 **127** 2148–2158. (https://doi.org/10.1172/JCI83731)

Received in final form 3 August 2021
Accepted 19 August 2021