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SHORT COMMUNICATION

Reducing diagnostic delay in hypophosphatasia: a case series of 14 patients presenting to general rheumatology

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Abstract

Objectives Hypophosphatasia (HPP) is a rare genetic metabolic bone disease that can cause chronic pain and fractures. Its hallmark is a persistently low serum ALP. HPP is now recognised by many osteoporosis specialists, but other specialists, such as rheumatologists and primary care physicians, may be less aware of this condition, causing diagnostic delay and possible harm to these patients. Our objective was to highlight features that can reduce this delay.

Methods We retrospectively analysed 14 patients that presented with musculoskeletal pain to general rheumatology clinic at St. George's Hospital and were subsequently diagnosed with HPP.

Results Median diagnostic delay was 13 years. All patients had an ALP below reference range for age and gender, with lowest mean ALP of 16 IU/L. All but one patient were women with median age of 51 years. Most common presentation was peripheral joint pain in 85.7% of patients. This was due to early-onset CPPD (calcium pyrophosphate deposition disease) in 71.4% of patients, osteoarthritis in 50%, or bursitis in 50%. Axial pain was reported in 64% of patients due to osteoarthritis or spinal stenosis. Fifty percent of patients had a history of long bone pain. Fifty percent had previous fracture(s). A total of 28.6% of patients had psoriatic arthritis, of which 1 patient had spondyloarthropathy, and 4 patients also had enthesitis.

Conclusion Patients with HPP can present to rheumatology with musculoskeletal pain, and if a persistently low ALP is confirmed, this may reduce the diagnostic delay of this rare disease. Similar to other rheumatologic patients, musculoskeletal pain in HPP was noted in peripheral joints and in the spine with almost a third of patients having psoriatic arthritis. Pain was also noted in the long bones, a feature consistent with metabolic bone disease. The diagnosis of HPP was also more likely in those patients with a personal or family history of dental disease or arthritis.

Keywords Alkaline phosphatase · Hypophosphatasia · Musculoskeletal pain

Introduction

Hypophosphatasia (HPP) is a genetic disease caused by mutations in the gene encoding tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP) [1]. This results in low serum ALP level which is the hallmark of the disease. Reduced ALP activity leads to an accumulation of ALP substrates; inorganic pyrophosphate (PPi), pyridoxal-5'-phosphate (PLP), and phosphoethanolamine (PEA) [2].

Accumulation of PPi can result in defective mineralisation of bone and cementum leading to fractures and premature dental loss, as well as formation of calcium pyrophosphate (CPP) crystals leading to early-onset CPP disease (CPPD) and osteoarthritis.

Hypophosphatasia has 5 forms based on age of onset and clinical presentation: perinatal, infantile, childhood, adult, and odontohypophosphatasia. Perinatal- and infantile-onset HPP can be fatal without treatment, whereas adult-onset HPP is usually milder and associated with a normal lifespan but can significantly reduce quality of life [1, 3].

The most common symptoms in adults are fractures (particularly femoral and metatarsal) and musculoskeletal (MSK) pain [4, 5]. Diagnosis is considered if there

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is unexplained persistently low serum ALP with relevant symptoms, and is confirmed by raised fasting vitamin B6 and/or a pathogenic ALPL gene mutation.

Patients with undiagnosed HPP and fractures may present to osteoporosis or metabolic bone disease specialists who are aware of HPP. However, those with predominantly musculoskeletal pain can present to rheumatologists who may be less familiar with HPP. Therefore, we are reporting a case series of 14 patients with musculoskeletal pain presenting to general rheumatology clinic who were subsequently diagnosed with HPP.

Method

We retrospectively analysed data from 14 adults presenting with musculoskeletal pain to general rheumatology clinic at St. George's Hospital, who were subsequently diagnosed with HPP. Ethics approval was not required as all data was anonymised, retrospective and treatment decisions had been made prior to the study.

Results

Patients (13 female, 1 male) were referred over 10 years between 2011 and 2021 to 10 different clinicians in our department. One patient was the daughter of another, but they were referred independently. Ethnic variability was noted within our 14 patients, with 28.6% white, 28.6% asian, 7% black, and 35.7% other.

Table 1 summarises patient demographics, clinical symptoms, musculoskeletal diagnoses and comorbidities, relevant medications, key investigations, and duration of diagnostic delay.

The most common musculoskeletal symptom was peripheral joint pain (85.7%). Nine patients (64%) had axial pain due to osteoarthritis, of these, 3 had facet joint osteoarthritis and 4 had spinal stenosis. Three patients had buttock pain; MRI showed degenerative change in 2, and active sacroiliitis in 1. This patient was HLA B27 negative and was later diagnosed with psoriatic spondyloarthropathy after developing psoriasis.

Of the 10 patients (71.4%) diagnosed with CPPD, in 5 cases, the diagnosis was supported by positive imaging on X-ray or ultrasound. There was only sufficient synovial fluid to aspirate in 1 patient, but calcium pyrophosphate crystals were not identified. Seven patients (50%) had early-onset peripheral joint osteoarthritis. Seven patients (50%) had bursitis affecting the shoulder and hip girdle, particularly trochanteric bursitis which affected 4 patients. Enthesopathy, diagnosed by clinical symptoms, X-ray, and ultrasound, affected achilles tendons in 3 patients and finger flexor tendons in 1 patient. Two of the 4 patients with enthesopathy had an additional diagnosis of psoriatic arthritis due to their clinical features and a personal/family history of psoriasis. Psoriasis was present in 4 patients (28.6%) and 3 relatives (21.4%).

Disease modifying anti-rheumatic drugs (DMARDs) were prescribed to help with joint pain and continued after diagnosis of HPP if they proved effective.

Most common fracture site was lower limb (36%), upper limb (29%), vertebrae (7%), and rib (7%). All fractures were low trauma except 1 ankle fracture sustained by falling down 2 steps. No fracture had delayed healing and there were no atypical fractures.

Three patients had previous high dose vitamin D. One patient was previously diagnosed with osteoporosis based on Z-score and received both alendronate and denosumab for 13 years. Three patients started asfotase alfa for hypophosphatasia after HPP diagnosis.

Relevant dental disease occurred in 11 patients (78.6%), in 5, it affected primary dentition. It included premature tooth removal/loss (50%), fillings (29%), tooth decay (14%), gum disease (7%), and jaw displacement (7%).

Of those patients with peripheral joint pain, 36% had weakly positive ANA, 7% had weakly positive RF, and no patient had anti-CCP antibodies. One patient had a family history of both psoriasis and arthritis.

At presentation, all patients had normal serum calcium, parathyroid hormone, phosphate, and creatinine. Five patients (35.7%) had low vitamin D. Their mean vitamin D was 30 nmol/L.

Other causes of low ALP were excluded (see Table 2).

One patient was not tested for pathogenic ALPL mutation, but their daughter was heterozygous for a pathogenic ALPL mutation, making testing unnecessary. Nine patients were heterozygous for pathogenic ALPL mutations. Three of them had the same mutation: c.[318G > C]. The remaining genetic results were c.[1171C > T], c.[227A > G], c.[648 + 1G > A], c.[1328C > T], c.[340G > A], and c.[1336G > A]. One patient had a variant of uncertain significance: c.[906C > A]. In 3 patients, no pathogenic ALPL mutation was identified, but HPP diagnosis was confirmed by raised fasting vitamin B6 and clinical features.

Median diagnostic delay was 13 years (range 5–37). Four patients (28.6%) had childhood onset of musculoskeletal pain (< age 18). A further 5 patients had childhood onset of HPP dental disease or fractures. Median diagnostic delay in the 3 patients receiving enzyme replacement was 11 years. Only 5 patients developed the first symptom of HPP after age 18 years.

Discussion

Diagnosis and its difficulties

In our patients, median delay from first musculoskeletal symptom to diagnosis of HPP was 13 years. The literature describes

Table 1 Patient demographics, key clinical details, and relevant findings. *N*, number of patients. *SD*, standard deviations. *IU/L*, international units/litre

Demographics $N=14$	
Female: male	13:1
Median age at hypophosphatasia diagnosis (years) [range]	51 [24–70]
Ethnicity *N* (%)	
White	4 (28.6)
Black	1 (7.1)
Asian	4 (28.6)
Other	5 (35.7)
Presenting musculoskeletal (MSK) symptoms *N* (%)	
Peripheral joint pain	12 (85.7)
Axial pain	9 (64)
Buttock pain	3 (21.4)
Long bone pain (thighs and shins)	7 (50)
Musculoskeletal diagnoses *N* (%)	
Early-onset calcium pyrophosphate deposition (onset < 60 years)	10 (71.4)
Early-onset osteoarthritis (onset < 60 years)	7 (50)
Bursitis	7 (50)
Enthesitis	4 (28.6)
Spinal stenosis	4 (28.6)
Psoriatic arthritis or other spondyloarthropathy	4 (28.6)
Median number of MSK diagnoses [range]	2 [1–4]
Previous fractures *N* (%)	7 (50)
Median age of first fracture (years) [range]	26 [12–62]
Relevant dental disease *N* (%)	11 (78.6)
Family history *N* (%)	
Relevant dental disease	7 (50)
Arthritis	10 (71.4)
Psoriasis	3 (21.4)
Comorbidities *N* (%)	
Psoriasis	4 (28.6)
Mood disorders	4 (28.6)
Migraine	2 (14.3)
Vitamin D levels at presentation *N* (%)	
Insufficiency (< 50 nmol/L)	4 (28.6)
Deficiency (< 25 nmol/L)	1 (7.1)
DXA (dual-energy X-ray absorptiometry) *N* (%)	
Normal	11 (78.6)
Low bone density (defined as Z-score < − 2.5 SD)	3 (21.4)
Median Z-score [range]	
Lumbar spine	0.25 [− 2.4–1.1]
Neck of femur	0.05 [− 2.8–0.8]
Total hip	− 0.1 [− 2.0–1.0]
Alkaline phosphatase (ALP)	
Mean ALP (normal 44–147 IU/L) [range]	22.1 [14–35]
Median lowest ALP (normal 44–147 IU/L) [range]	16 [5–22]
Mean number of low ALP results before diagnosis [range]	16 [3–37]
Hypophosphatasia diagnostic tests	
Median fasting vitamin B6 [normal 5–50 μg/L] $N=14$ [range]	228 [126–415]
Urine PEA (phosphoethanolamine) (%detected)	7 (21)
Genetic testing for ALPL pathogenic mutation performed (%)	13 (92.9)
Pathogenic ALPL mutation identified (%)	9 (64.3)
Variant of uncertain significant indentified on genetic testing (%)	1 (7.1)
Bone medication *N* (%)	
Prior high dose vitamin D	3 (21.4)
Prior antiresorptive treatment (inc. bisphosphonates, denosumab)	1 (7.1)
Asfotase alfa	3 (21.4)

Table 1 (continued)

Joint medication *N* (%)	
Non-steroidal anti-inflammatories	5 (35.7)
Colchicine	4 (28.6)
Sulfasalazine	2 (14.3)
Hydroxychloroquine	3 (21.4)
Leflunomide	1 (7.1)
Methotrexate	2 (14.3)
Anti-TNF	2 (14.3)
Diagnostic delay (years) [range]	
Median age at onset of first MSK symptom	26 [10–62]
Median age that low ALP was noticed	50 [24–70]
Median diagnostic delay from first musculoskeletal symptom	13 [5–37]

Table 2 Other causes of low serum ALP adapted from [6]

Persistent causes	Transient causes
Celiac disease	Cardiac bypass surgery
Cushing syndrome	Clofibrate therapy
Hypothyroidism	Improperly collected blood (oxalate, ethylenediaminetetraacetic acid)
Inappropriate reference range	Massive transfusion
Multiple myeloma	Milk-alkali syndrome
Osteogenesis imperfecta, type 2	Profound anaemia
Pernicious anaemia	Starvation
Radioactive heavy metals	Vitamin C deficiency
Wilson disease	Vitamin D intoxication
	Zinc or magnesium deficiency

a similar diagnostic delay. In an international registry study of 148 adults with HPP, there was a delay of 10 years, with a mean age at diagnosis of 43.2 ± 17.5 years [3].

However, Berkseth et al. reported a shorter mean diagnostic delay of 6 years in 22 cases with adult-onset HPP [5].

There are several challenges to making a diagnosis of HPP which might contribute to this delay. Firstly, some rheumatologists may be unaware of HPP due to its rarity, with an estimated maximum prevalence of mild HPP genotypes estimated at 1:508 [7]. Secondly, HPP can manifest as several heterogenous phenotypes. The fracture and dental phenotypes usually present to metabolic bone disease clinics where there is an awareness that HPP can mimic osteoporosis. However, chronic musculoskeletal pain phenotypes may present to other specialties such as rheumatology, where less awareness of HPP may contribute to diagnostic delay.

Why is diagnosis important?

Benefits of a prompter diagnosis of HPP include avoiding misdiagnosis of osteoporosis and subsequent bisphosphonate treatment, initiating appropriate treatment such as colchicine for CPPD, enabling family screening, and identifying candidates for enzyme replacement therapy.

It is particularly important to distinguish HPP from osteoporosis in order to avoid inadvertent bisphosphonate treatment. Bisphosphonates can exacerbate hypomineralisation of bone and precipitate atypical femoral fractures (AFF) in patients with HPP [8]. In our study, 1 patient (7.1%) was previously treated with antiresorptive drugs for presumed osteoporosis for 13 years. This patient did not suffer an atypical femoral fracture and, once diagnosed with HPP, antiresorptive treatment was stopped. However, 17.6% of HPP cases in the Global Registry study had previously been treated with bisphosphonates [3]. This also underlines the importance of measurement and interpretation of bone bloods, including historic ALP levels, before starting antiresorptives, because a fracture can transiently elevate ALP to the normal range, masking underlying HPP [8, 9].

Since 2015, asfotase alfa enzyme replacement therapy has been available for adults with HPP and symptom onset in childhood. It has been shown to improve functional abilities such as gross motor function and muscle strength [10].

Musculoskeletal presentations of HPP

Chronic pain is very common in HPP, with a prevalence of 74.5% in the Global Registry [3]. Whereas long bone pain is well recognised in HPP, peripheral joint and spine pain is less well characterised. In our patients, peripheral joint pain was very common (85.7%) and the predominant cause was early-onset CPPD although early-onset osteoarthritis and bursitis were also common. Whilst peripheral joint pain and axial pain are common presentations to rheumatology, HPP is often also accompanied by long bone pain, which should raise suspiscion for metabolic bone disease.

An accumulation of PPi in HPP favours calcium pyrophosphate crystal deposition in and around joints leading to CPPD [1]. CPPD is more common in women with HPP [5, 11].

CPPD affected 10 patients (71.4%), this is a far higher prevalence than the Global Registry study, where only 5.8% of 148 adults were affected [5], despite a comparable age at

enrolment across both studies. This may be due to referral bias, as HPP patients with inflammatory joint pain are more likely to present to rheumatology. Additionally, CPPD can be difficult to diagnose and therefore may be underdiagnosed in non-rheumatology specialties.

Many of our cases first experienced symptoms suggestive of acute CPPD at a very young age which should have prompted earlier investigation for an underlying metabolic cause such as HPP [12]. CPPD is also related to the development of osteoarthritis [13].

Chronic CPPD is more difficult to diagnose than acute CPPD because it commonly lacks a clinically apparent effusion and unequivocal inflammatory signs, mimicking osteoarthritis [12]. Imaging features of CPPD often appear late, necessitating a clinical diagnosis based on joint distribution and absence of features of other types of arthritis [14, 15].

Trochanteric bursitis was highly prevalent in our patients. Bursitis has been described in CPPD and in view of the sudden onset and severity in our cases, the authors postulate that CPPD was the main aetiology of bursitis in our patients [16].

Psoriatic arthritis affected 4 patients and 2 additional patients had a family history of psoriasis. This was an unexpected finding, although the sample size is too small to conclude an association. HPP can mimic spondyloarthropathies and can be associated with enthesopathies [11]. In these patients, psoriatic arthritis could be driving enthesitis and HPP could be driving tendon calcification. In 2 of 4 cases with psoriatic arthritis, clinical and imaging features were strongly suggestive of psoriatic arthritis, e.g., sacroiliitis and spondyloarthropathy, with coexistent psoriasis. In the other 2 cases, the clinical features and imaging did not distinguish between psoriatic arthritis and CPPD; therefore, it was unclear whether the patients had either or both conditions.

To our knowledge, an increased prevalence of psoriasis has not been reported in other studies of HPP. However, one study found that HPP in children can cause a chronic autoinflammatory process in bones and joints similar to CRMO (chronic recurrent multifocal osteomyelitis) or SAPHO (synovitis, acne, pustulosis, hyperostosis) syndrome, both of which are associated with psoriasis [17].

Six patients were treated with either DMARDs or anti-TNF (tissue necrosis factor) treatment or both. DMARDs and anti-TNF drugs are proven treatments for psoriatic arthritis; however, there are also small studies showing benefit of treating CPPD with some DMARDs, so these drugs might have treated both conditions [18].

Reported fracture prevalence in adults with HPP ranges from 39 to 73.9% [4, 19]. The most common fracture sites include metatarsal, femur, and vertebra. Similarly, half of our patients had sustained fractures. However, fracture sites were different, none of our patients had metatarsal fractures or atypical femoral fractures, and only 1 had a vertebral fracture. The most common fracture site in our patients was the ankle. In hypophosphatasia, BMD varies according to where it is assessed, it does not correlate with age or sex, and it may not necessarily indicate fracture risk [20], as seen in our patients. Additional non-invasive tests such as trabecular bone score (TBS), biomechanical-CT (B-CT), opportunistic (O-CT), and/or HRpCT may be important to assess this in the future.

The main strengths of this paper are that, to our knowledge, it is the first case series of HPP highlighting its important rheumatological features. Secondly, each HPP diagnosis was made with a high degree of certainty. Thirdly, it presents a comprehensive and detailed review of the medical records of each patient.

The limitations of this study are firstly, all patients were referred to rheumatology for investigation of musculoskeletal pain; therefore, there will be referral bias towards this phenotype of HPP. Secondly, we cannot exclude the presence of coexistent HPP and psoriatic arthritis. Thirdly, due to a lack of radiological features, or significant joint fluid for aspiration, some patients were diagnosed with CPPD on the basis of clinical features alone.

Conclusion

Patients with musculoskeletal pain due to undiagnosed HPP can present to rheumatology. This pain can originate from the peripheral joints, due to early-onset CPPD/osteoarthritis or bursitis, the axial spine, due to osteoarthritis, or from the long bones. It commonly occurs alongside a history of fractures, dental disease, and psoriasis or psoriatic arthritis. Many of these features can also be found in patient's family histories. These features, together with a persistently low ALP, should lead to investigation for HPP. This could reduce the significant diagnostic delay that these patients can otherwise face.

Data availability The data that support the findings of this study are available from the corresponding author, Dr. Muhammad Atif Rauf, upon reasonable request.

Declarations

Conflicts of interest None.

References

1. Kaur J, Nourabadi S, Chavez L, Sachemchi I (2016) A concise review on hypophosphatasia with case report. Int J Med 4(2):39
2. Conti F (2017) Hypophosphatasia: clinical manifestation and burden of disease in adult patients. Clin Cases Miner Bone Metab 14(2):230
3. Högler W, Langman C, Gomes Da Silva H, Fang S, Linglart A, Ozono K et al (2019) Diagnostic delay is common among patients with hypophosphatasia: initial findings from a longitudinal, prospective, global registry. BMC Musculoskelet Disord 20(1):1–9
4. Schmidt T, Mussawy H, Rolvien T, Hawellek T, Hubert J, Rüther W et al (2017) Clinical, radiographic and biochemical characteristics of adult hypophosphatasia. Osteoporos Int 28(9):2653–2662
5. Berkseth KE, Tebben PJ, Drake MT, Hefferan TE, Jewison DE, Wermers RA (2013) Clinical spectrum of hypophosphatasia diagnosed in adults. Bone 54(1):217. https://doi.org/10.1016/j.bone.2013.01.024
6. Whyte MP. Hypophosphatasia — aetiology, nosology, pathogenesis, diagnosis and treatment. Nat Rev Endocrinol [Internet]. 2016 Apr 19;12(4):233–46. Available from: http://www.nature.com/articles/nrendo.2016.14
7. Mornet E, Taillandier A, Domingues C, Dufour A, Benaloun E, Lavaud N, et al (2021) Hypophosphatasia: a genetic-based nosology and new insights in genotype-phenotype correlation. Eur J Hum Genet [Internet] 29(2):289–99. Available from: https://doi.org/10.1038/s41431-020-00732-6
8. Sutton RAL, Mumm S, Coburn SP, Ericson KL, Whyte MP (2012) "Atypical femoral fractures" during bisphosphonate exposure in adult hypophosphatasia. J Bone Miner Res
9. Bianchi ML, Bishop NJ, Guañabens N, Hofmann C, Jakob F, Roux C et al (2020) Hypophosphatasia in adolescents and adults: overview of diagnosis and treatment. Osteoporos Int 31(8):1445–1460
10. Kishnani PS, Rockman-Greenberg C, Rauch F, Bhatti MT, Moseley S, Denker AE, et al (2019) Five-year efficacy and safety of asfotase alfa therapy for adults and adolescents with hypophosphatasia. Bone [Internet] 121(December 2018):149–62. Available from: https://doi.org/10.1016/j.bone.2018.12.011
11. McKiernan FE, Berg RL, Fuehrer J (2014) Clinical and radiographic findings in adults with persistent hypophosphatasemia. J Bone Miner Res 29(7):1651–60. https://doi.org/10.1002/jbmr.2178
12. Rosenthal AK, Ryan LM (2016) Calcium pyrophosphate deposition disease. Campion EW, editor. N Engl J Med [Internet]. Jun 30;374(26):2575–84. Available from: http://www.magonlinelibrary.com/doi/10.12968/hmed.2014.75.Sup4.C61
13. Jaovisidha K, Rosenthal AK (2002) Calcium crystals in osteoarthritis. Curr Opin Rheumatol 14(3):298–302
14. Catelli A, Venetucci P, Castaldo A, loiudice G, Tarulli FR, Carpiniello M, et al (2020) Calcium pyrophosphate deposition disease: the role of imaging in their detection and in differential diagnosis of crystal arthropathies. Radiol Case Reports
15. Abhishek A (2014) Calcium pyrophosphate deposition. Br J Hosp Med 75(SUPPL. 4):61–64
16. Di Carlo M, Draghessi A, Carotti M, Salaffi F (2015) An unusual association: iliopsoas bursitis related to calcium pyrophosphate crystal arthritis. Case Rep Rheumatol 2015:1–5
17. Beck C, Morbach H, Richl P, Stenzel M, Girschick HJ (2009) How can calcium pyrophosphate crystals induce inflammation in hypophosphatasia or chronic inflammatory joint diseases? Rheumatol Int 29(3):229–238
18. Andres M, Sivera F, Pascual E (2012) Methotrexate is an option for patients with refractory calcium pyrophosphate crystal arthritis. J Clin Rheumatol 18(5):234–236
19. Szabo SM, Tomazos IC, Petryk A, Powell LC, Donato BMK, Zarate YA et al (2019) Frequency and age at occurrence of clinical manifestations of disease in patients with hypophosphatasia: a systematic literature review. Orphanet J Rare Dis 14(1):1–9
20. Genest F, Claußen L, Rak D, Seefried L (2021) Bone mineral density and fracture risk in adult patients with hypophosphatasia. Osteoporos Int 32(2):37710–385. https://doi.org/10.1007/s00198-020-05612-9