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Case Report

A Rare Case Presentation of Hypophosphatasia: Bone Pain and Mild Fatigue in a 79-Year-Old Male

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Abstract

Hypophosphatasia (HPP) is an uncommon metabolic bone condition resulting from mutations in the *ALPL* gene and is defined by reduced levels of alkaline phosphatase (ALP). It presents in various forms ranging from severe perinatal cases to milder adult-onset forms. Adult HPP often mimics rheumatologic diseases, making diagnosis challenging, especially with mild symptoms. The case of a 79-year-old man who came in with symptoms of mild bone pain and fatigue is presented. His medical history included pre-diabetes, hypertension, and vitamin D deficiency. Laboratory tests showed persistently low ALP and elevated pyridoxal-5-phosphate (Vitamin B6), suggesting HPP. No significant findings were observed on radiographs, and other causes such as hypermetabolic conditions were ruled out. The patient's symptoms, along with consistently reduced ALP levels and increased Vitamin B6, confirmed a diagnosis of adult-onset HPP. Treatment using Asfotase alfa for the replacement of the enzyme was advised. His symptoms were mild, and no previous fractures, early tooth loss, or bone deformities were noted. This case underscores the significance of considering HPP in patients presenting with unexplained bone pain and fatigue, particularly when ALP levels are low. Early diagnosis can prevent inappropriate treatments and guide effective management, even in asymptomatic or mild cases. Further genetic testing and monitoring were recommended for this patient.

Keywords: Alkaline phosphatase, hypophosphatasemia, hypophosphatasia, inorganic pyrophosphate, phosphoethanolamine, pyridoxal-5-phosphate

Introduction

Hypophosphatasia (HPP) is an uncommon metabolic bone condition caused by mutations in the ALPL gene, which codes for tissue-nonspecific alkaline phosphatase. This condition results in abnormally reduced levels of circulating alkaline phosphatase (ALP) known as hypophosphatasemia.[1] Hypophosphatasia is diagnosed when either 2 major criteria are met—such as the presence of a pathogenic ALPL mutation, elevated levels of enzyme substrates (like pyridoxine), pseudofractures, or recurrent fractures of the metatarsals—or when one of these major criteria is accompanied by 2 minor criteria, including musculoskeletal, dental, and kidney-related symptoms in adults, along with neurological signs in children.[2]

The exact prevalence of hypophosphatasia remains unclear; however, 1 study guessed the occurrence of severe cases to be 1 out of 100 000 live births.[3] Other research suggests that milder forms of the disease may occur more frequently.[4] Approximately 1 in 200 people in the United States might be HPP carriers. Hypophosphatasia is observed predominantly in Caucasians rather than in other populations; however, other ethnic groups such as Japanese, Hispanic, and Native American populations have also reported cases but very seldom in African-Americans.[5]

HPP is a highly complex disorder, with its presentation influenced by the specific mutation, mode of inheritance, and the age at which the condition develops. The condition is inherited autosomally, with the perinatal and infantile forms following a recessive pattern, while the milder variants can be inherited either recessively or dominantly. The disease can present anytime during childhood or adulthood, and usually, the adult patient population has a pediatric history of associated symptoms or surgeries to cure those symptoms.[6] A mutation in the TNSALP gene causes reduced or absent ALP activity, hence leading to a build-up of phosphate-containing substances which cause a variety of symptoms.[6]

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Table 1. Laboratory Values

Date (mm/dd/yy)	09/13/2022	1/17/2023	5/03/2023
TSH 0.40 - 4.0 uIU/mL	2.23	2.7	3.0
ALT / AST 9 - 41 / 9 - 34 IU/L	26 / 23	34 / 26	32 / 29
Calcium 8.5 - 10.5 mg/dl	9.0	9.3	9.1
Phosphorus 2.5 - 4.5 mg/dl	2.8	3.1	3.0
Vitamin D 20 - 40 ng/mL	29	32	30
LDL Cholesterol <130 mg/dl	53	68	68
CPK 25 -286 IU/L	80	84	79

TSH, Thyroid stimulating hormone; ALT, Alanine transaminase; AST, Aspartate transaminase; LDL, Lactate dehydrogenase; CPK, Creatine phosphokinase.

The clinical manifestations of hypophosphatasia can differ significantly and encompass a range of symptoms. These include mineralization-related issues such as rickets, osteomalacia, stress fractures, atypical femoral fractures, and tooth loss. Additionally, patients may experience systemic complications, including pyridoxine-responsive seizures, respiratory failure resulting from rachitic chest, nephrocalcinosis, kidney stones, muscle weakness, chronic pain, and fatigue. The most severe types of hypophosphatasia (HPP) usually present at a very young age, often appearing during the perinatal stage. On the other hand, the milder variants tend to occur later, typically during adolescence or even extending into adult life.[1] In adults, musculoskeletal pain is the primary clinical symptom of HPP, often resembling conditions seen in rheumatologic diseases.[7] Differentials for the skeletal manifestations include hypermetabolic diseases causing bone loss such as hyperthyroidism, hyperparathyroidism, and other bone resorptive pathologies like multiple myeloma, Cushing's syndrome, etc.

Main Points

- Hypophosphatasia (HPP) results from an *ALPL* gene mutation and leads to reduced alkaline phosphatase (ALP) levels.
- Hypophosphatasia can manifest in various forms, from perinatal to adult, and include both musculoskeletal and systemic symptoms.
- The prevalence of HPP is rare, with severe forms estimated at 1:100 000 live births.
- Diagnosis relies on persistently reduced levels of ALP and elevated enzyme substrates and is confirmed through genetic testing.
- Treatment with calcium or vitamin D is relatively contraindicated due to the risk of nephrolithiasis and hypercalcemia.

Case Presentation

This case involves a male, aged 79 years with a background that includes borderline high sugar, hypertension, hyperlipidemia, vitamin D deficiency, and a clinically inactive, benign thyroid nodule, who presented for the management of his chronic conditions. He had complaints of mild bone pain and fatigue for the past few months. He appeared well-built, weighed 170 lbs, had normal stature, was 6 feet tall, and had no past history of fractures, early tooth loss, bone deformities, or significant family history of metabolic disorders. His medical records did not mention a previous diagnosis of any hypermetabolic conditions, including thyroid, parathyroid, or adrenal glands. Physical examination revealed normal musculoskeletal strength, range of motion, and an unremarkable comprehensive systemic examination.

Laboratory investigations were conducted, including Complete Blood Count (CBC), basic metabolic panel, PTH, Vitamin D, serum calcium, magnesium, and phosphate, all of which were normal except for a low to low-normal ALP level and elevated pyridoxal-5-phosphate (Vitamin B6) (as shown in Table 1). His renal and hepatic profile, including AST and ALT, was also normal. Radiographs showed benign results indicating no bone resorption or pathology, and the patient denied any prescription history for bisphosphonate therapy as well. His current medications include simvastatin 40 mg, aspirin 81 mg, amlodipine 10 mg, telmisartan, carvedilol, and vitamin D.

The patient's skeletal and neuropsychiatric complaints, in addition to persistently low alkaline phosphatase levels, provided a clue towards the diagnosis of hypophosphatasia. His elevated vitamin B6 levels confirmed the diagnosis and the patient was counseled about enzyme replacement therapy with asfotase alfa. His condition will be monitored with further follow-up visits (e.g., Table 2).

The patient has provided written informed consent for the disclosure of his medical records for publication in a medical journal.

Discussion

The hallmark characteristic of hypophosphatasia is reduced functioning of alkaline phosphatase, which should be assessed whenever there is a clinical suspicion of HPP. The interpretation of lab results requires precision as the reference range specifically depends on age and gender. For physicians, it is convenient to order this test because of its availability, simpler techniques, and quick-yielding results.[8] Persistently low ALP can be defined as having 2 lab values below normal at intervals of more than 30 days (e.g., Table 2).[9] In some conditions, such as hypothyroidism, and zinc and magnesium deficiency, ALP decreases transiently. However, in HPP, these levels are found to be persistently low.[10]

This patient's mild symptoms and laboratory findings most likely represent adult-onset hypophosphatasia, as the below-normal ALP

Table 2. Levels of ALP and its metabolite

Date (mm/dd/yy)	01/18/2022	5/10/2022	09/13/2023	10/23/2023	05/22/2024
Alkaline phosphatase level Normal (44-147 IU/L)	42	43	34	40	35
Vitamin B6 level Normal (2.1-21.7 ng/mL)	NR	NR	NR	133	140.4

levels on consecutive days are not explained by alternative factors.[10] This makes this case rare because of the late diagnosis due to being overlooked by healthcare professionals.

Low serum ALP levels indicate the diagnosis, which is further assured by its elevated metabolites. These metabolites are named pyridoxal-5'-phosphate (PLP, the functional by-product of vitamin B6), inorganic pyrophosphate (PPi), and phosphoethanolamine (PEA) and are often confirmed with biochemical analysis of genes.[11] The assessment of PPi in clinical practice is currently not attainable. A less reliable diagnostic test constitutes elevated TNSALP metabolite phosphoethanolamine (PEA) in both serum and urinary analysis.[12] A specific and sensitive test that can detect HPP biochemically would be the PLP marker.

Muscle and bone ache are prominently known manifestations found in adults with HPP;[13] however, fatigue has not been much focused upon before. Given the higher prevalence of a milder disease form of hypophosphatasia, it can be useful to include the work-up of serum ALP levels when identifying the underlying cause of generalized fatigue before concluding the presence of chronic fatigue syndrome or fibromyalgia, which remains a secondary diagnosis after eliminating other causes.

Offering treatment to these patients in the form of calcium and/or vitamin D is a relative contraindication that runs the risk of renal stone formation and hypercalcemia if given without any baseline indication of vitamin D deficiency, whereas lower doses are considered safe.[14]

We report a rare case of a previously healthy 79-year-old male patient presenting with mild symptoms of hypophosphatasia. Patients who have reduced ALP levels along with either elevated metabolic products and/or a positive *ALPL* mutation, in the absence of clinical symptoms, are termed as carriers of an asymptomatic trait. All HPP variants have low serum ALP levels adjusted for age and can be low to normal in the carriers.[10]

Unknowingly, patients might receive symptomatic management which could potentially worsen the underlying condition, such as supplementing Vitamin D or calcium, irrespective of the severity. Therefore, the diagnosis of HPP remains crucial to prevent the inadvertent use of such prescriptions.

Secondly, some syndromes form a diagnosis of exclusion for symptoms of chronic fatigue or widespread pain. If HPP is confirmed, it would prevent further testing to detect the underlying cause of these symptoms.[11]

Data Availability Statement: The data that support the findings of this case are available on request from the corresponding author.

Informed Consent: Written informed consent was obtained from the patient who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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