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Case Report

A Hidden Cause of Bone Fragility: Late Diagnosis of Hypophosphatasia in a 40-Year-Old Female

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ABSTRACT

Hypophosphatasia (HPP) is a rare inherited metabolic disorder caused by loss-of-function mutations in the ALPL gene, leading to deficient activity of tissue-nonspecific alkaline phosphatase (TNSALP). This results in impaired bone and dental mineralization, causing a wide range of clinical manifestations, from perinatal lethality to mild adult-onset forms. We report a case of a 40-year-old female with a history of joint pain, multiple fractures, dental issues, and bipolar disorder, who was diagnosed with adult-onset HPP. Laboratory investigations revealed persistently low alkaline phosphatase (ALP) levels and elevated vitamin B6. Genetic testing confirmed a pathogenic ALPL mutation. The patient was initiated on enzyme replacement therapy (ERT) with asfotase alfa, resulting in significant symptom improvement. This case highlights the importance of recognizing HPP in adults with unexplained musculoskeletal symptoms and underscores the role of genetic testing in the diagnosis and management of this condition.

1. Introduction

Hypophosphatasia (HPP) is a rare, inherited metabolic disorder that primarily affects the bones and teeth, as well as other systemic manifestations. It results from loss-of-function mutations in the ALPL gene, which encodes the tissue-nonspecific alkaline phosphatase (TNSALP) enzyme [1]. This gene, comprising 12 exons, encodes the TNSALP protein, which is expressed in various tissues, including bone, liver, and kidney [2]. TNSALP hydrolyzes inorganic phosphates, and its deficient activity in the case of HPP leads to the accumulation of its substrates, mainly Pyridoxal-5′-phosphate (PLP), inorganic pyrophosphate (PPi), and phosphoethanolamine (PEA) [3]. Defective PLP metabolism can result in seizures, whereas excessive PPi hinders bone mineralization. The effects of PEA buildup remain largely unexplored [4].

HPP was first described in 1948 by J.C. Rathbun; its genetic basis wasn't identified until 1988 by Harry Harris and the team [5, 6]. Since then, more than 300 mutations in the ALPL gene have been documented [7], causing an extremely variable clinical spectrum ranging from the very severe, mostly lethal, perinatal form to a mild form with late adult onset presenting with non-pathognomonic symptoms such as arthropathy and musculoskeletal pain [8].

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The primary clinical features stem from impaired bone and tooth mineralization, leading to rickets, osteomalacia, fractures, and tooth loss. However, in severe cases, additional systemic complications such as seizures, respiratory and renal issues, chronic pain, and muscle weakness may also occur [9]. These systemic effects could be linked to TNSALP's involvement in purinergic signaling through ATP dephosphorylation, a process crucial for the central nervous system, bones, and other organs [10, 11].

The diagnosis of HPP is confirmed through clinical symptoms, imaging studies, and laboratory evaluations. Key laboratory findings supporting the diagnosis include reduced serum alkaline phosphatase (ALP) activity adjusted for age and sex, along with elevated plasma vitamin B6 and urinary PEA levels [12]. However, due to the clinical overlap of HPP with more common conditions like osteoporosis or osteomalacia, many affected individuals are likely to remain undiagnosed or be misdiagnosed with other disorders [13]. We report a case of HHP confirmed through genetic testing in a 40-year-old female with a history of bipolar disorder, presenting with joint pain and low alkaline phosphatase levels, who was referred for further evaluation. This case highlights the importance of recognizing hypophosphatasia in patients with chronic symptoms and biochemical findings suggestive of the condition.

2. Case Presentation

A 40-year-old female occupational therapist presented with a 15-year history of progressively worsening joint pain. Initially, the pain predominantly affected her hands, fingers, and toes, and after 10 years, she developed intermittent knee pain. Over time, she experienced multiple fractures, including a leg fracture after a fall, an arm fracture, and several toe fractures from regular activities.

Table 1: Laboratory Test Results

Laboratory Test	Patient Result	Reference Value
ALP	20–40 U/L	44–147 U/L
Vitamin B-6	157.2 mcg/L	5–50 mcg/L
Calcium	9.1 mg/dL	8.5–10 mg/dL
Phosphorus	3.9 mg/dL	2.5–4.5 mg/dL
25-OH Vitamin D	54.1 ng/mL	20–50 ng/mL
Bone-specific ALP	860 U/L	6.5–20.1 U/L

ALP, Alkaline Phosphatase;

Additional clinical features included dental caries with cavities, jaw pain, and difficulties with chewing. Her past medical history was notable for bipolar II disorder with depressive symptoms and anxiety, managed with carbamazepine and venlafaxine, as well as asthma. The patient's family history is significant for her mother having experienced a vertebral fracture and metastatic renal cancer, while both of her children have a history of metatarsal fractures. This complex clinical presentation, along with progressive skeletal issues and dental abnormalities, warranted further investigation. The patient's previous rheumatology evaluations identified early signs of non-arthritis-related joint issues and mild Raynaud's phenomenon. On physical examination, her vital signs, including blood pressure, heart rate, respiratory rate, and temperature, were within normal limits. Her BMI was 30.04 kg/m², indicating obesity. Physical examination findings were notable for discomfort during fist-making and joint palpation, with no other significant abnormalities. Laboratory investigations revealed persistently low ALP levels since the age of 34, ranging from 20 to 40 U/L (reference range: 44–147 U/L), alongside elevated vitamin B6 levels at 157.2 mcg/L (reference range: 5–50 mcg/L). Her bone mineral density (BMD) was low. Notably, her 25-OH vitamin D levels were elevated at 54.1 ng/mL (reference range: 20–50 ng/mL), and bone-specific ALP was markedly elevated at 860 U/L (reference range: 6.5 to 20.1 U/L). Calcium and phosphorus levels were within normal limits at 9.1 mg/dL and 3.9 mg/dL, respectively. Despite a prolonged 15-year diagnostic challenge, genetic analysis revealed a pathogenic mutation in the ALPL gene, confirming a diagnosis of hypophosphatasia associated with this pathogenic variant. Management included calcium supplementation and injury prevention strategies. The patient was initiated on Strensiq (asfotase alfa) injections at a dose of 2 mg/kg (125 mg) three times per week, which she continued for one year. The treatment was well-tolerated, with only localized soreness and burning at injection sites as side effects, which were manageable. Adherence to the treatment plan resulted in stabilization of BMD and significant improvement in joint symptoms. The patient reported an improved functional status and a reduction in jaw pain. Additionally, her ALP levels stabilized, and no new fractures were reported.

3. Discussion

HPP is a rare genetic disorder linked to mutations in the ALPL gene, which encodes the TNSALP enzyme, crucial for bone and dental mineralization [14] . The molecular mechanisms underlying HPP are complex. TNSALP is an enzyme found on the surface of cells in the bone, kidney, and liver [6]. When ALP activity is deficient, its substrates— inorganic PPi and PLP—can accumulate outside cells [15] The buildup of PPi can interfere with the mineralization of bones and teeth and contribute to pseudogout [15, 4]. Additionally, reduced hydrolysis of PLP can lead to vitamin B6 deficiency in the central nervous system and a decrease in neurotransmitter production, potentially resulting in pyridoxine-responsive seizures in severely affected infants [16, 4]. PEA, another substrate of TNSALP and a biochemical marker for HPP, is elevated in patients with this condition, although its physiological significance remains unclear. PEA levels can be measured through plasma or urine amino acid testing [4].

In this case of the 40-year-old female patient, the combination of her psychiatric symptoms, including bipolar disorder and depression, alongside musculoskeletal complaints like hand and toe joint pain, knee pain, jaw pain, and difficulty chewing, suggested a possible systemic issue. The patient's elevated vitamin B6 levels and consistently elevated ALP levels were red flags that led clinicians to suspect HPP.

The clinical picture of this patient was further complicated by a history of multiple fractures, including childhood leg fractures and recent toe fractures, which are characteristic of the brittle bones often seen in HPP [17]. However, her hand X-ray appeared normal, suggesting that significant bone mineralization defects were not yet visible, though her significant dental issues, such as cavities and difficulty chewing, further supported the presence of mineralization defects. Additionally, the patient's family history is significant for her mother having experienced a vertebral fracture and metastatic renal cancer. Notably, both of her children have a history of metatarsal fractures, which may be clinically relevant in the context of the patient's confirmed ALPL mutation. Given the autosomal dominant inheritance pattern of many adult-onset hypophosphatasia cases, the absence of formal genetic counseling and family screening represents a critical oversight. Early identification of affected family members, particularly in children with signs suggestive of skeletal fragility, is essential for proactive management. Genetic counseling should be offered to the patient and her family to explain inheritance risks, discuss the utility of biochemical screening (e.g., ALP and vitamin B6 levels), and consider genetic testing for at-risk relatives. A structured approach to evaluating her children—starting with a thorough musculoskeletal and dental history, followed by targeted laboratory assessments and genetic confirmation if indicated—can facilitate timely diagnosis and early intervention, thereby minimizing potential complications and improving long-term outcomes.

A key aspect of HPP diagnosis is the measurement of serum ALP levels but by itself is not sufficient for a diagnosis as this is complicated by the fact that other several conditions unrelated to bone can also present with low ALP, such as celiac disease, severe anemia, hypothyroidism, Wilson's disease, malnutrition, massive transfusion of blood or plasma, early pregnancy, and drugs [18, 19]. It has also been reported in severe osteogenesis imperfecta [20], cleidocranial dysplasia [21], and osteochondrodysplasia [22]. It's also worth noting that serum ALP levels do significantly vary with age and sex.

Measuring serum ALP level is an affordable and reasonable parameter for HPP. However, to reach a definitive diagnosis in this case, genetic testing played a crucial role. Genetic testing revealed a heterozygous mutation in the ALPL gene (c.980T>G, p.Phe327Cys), which is associated with low serum ALP levels and low bone mineral density, confirming the diagnosis of adult-onset HPP. This mutation, although less severe than homozygous mutations [23], was consistent with the patient's clinical presentation of joint pain, fractures, and dental issues.

This case also highlights the importance of bone-specific ALP measurements and the testing of TNSALP substrates, such as PLP and PEA, as they can provide more accurate insights into the patient's condition. Although total ALP levels may appear normal in some cases, as reported by Dattagupta [24], the bone-specific ALP test can help detect TNSALP deficiency, along with elevated PLP and PEA. Additionally, radiological findings such as osteopenia, pseudofractures, and calcific periarthritis, although not observed in this patient's X-ray, are commonly seen in individuals with HPP [25].

Despite the challenges in diagnosing HPP in adults, the patient's diagnosis prompted an adjustment to her treatment plan. Although there is no definitive treatment for adult-onset HPP [26], enzyme replacement therapy (ERT) with Strensiq (asfotase alfa) has been shown to improve bone mineralization, reduce fractures, and alleviate musculoskeletal pain in pediatric patients with HPP [27]. Although Strensiq is not officially approved for adult-onset HPP [27], the patient began treatment and reported significant improvements in her symptoms after one year, including better bone health, reduced pain, and improved dental health. This illustrates that even in cases of retroactive diagnosis in adults, ERT can provide substantial benefits, significantly improving quality of life and potentially enabling patients to continue their careers and daily activities.

This case report is limited by its single-patient design, which restricts generalizability and precludes causal conclusions. Retrospective data collection introduces potential recall bias, and some aspects of the patient's medical and psychosocial history were not fully documented. The short follow-up period limits evaluation of long-term treatment outcomes. Outcome assessment relied on subjective reports without objective functional measures, and the absence of a control group prevents comparison with natural disease progression or alternative management strategies.

4. Conclusion

This case report highlights the importance of recognizing HPP in adults presenting with unexplained musculoskeletal pain, multiple fractures, and dental abnormalities. The patient faced a prolonged diagnostic delay despite persistent ALP levels and characteristic clinical features. Genetic testing ultimately confirmed the diagnosis, emphasizing its crucial role in definitive diagnosis when biochemical markers alone are inconclusive.

The initiation of ERT with asfotase alfa (Strensiq) led to marked clinical improvements. This underscores the potential benefits of ERT in adult-onset HPP, despite its primary approval for pediatric patients. This case reinforces the need for early recognition and comprehensive evaluation of HPP in adults. Increased awareness among clinicians can prevent misdiagnosis, allowing timely intervention and improved patient outcomes. Further research is warranted to optimize treatment strategies for adult-onset HPP and assess the long-term benefits of ERT in this population. Patient

Conflicts of Interest

The authors declare no conflicts of interest related to this manuscript.

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Large Language Model

No large language models were used in manuscript preparation.

Authors Contribution

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Data Availability

All data supporting the findings of this study are included in the article. Additional information is available from the corresponding author upon reasonable request.

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