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CASE REPORT

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Young woman with hypophosphatasia: A case report

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Abstract

Hypophosphatasia is a rare inherited disease defined by teeth and bone mineralization impairment leading to depletion of tissue non-specific alkaline phosphatase. We define a young woman diagnosed with hypophosphatasia (after several times alkaline phosphatase levels were low) was discovered following femoral fracture. A 30-year-old woman who presented for a history of early permanent teeth loss during the last 5 years and HPP-like symptoms in family history and bone radiograph verified bowing, deficient mineralization, and symmetrical subtrochanteric stress fractures of femurs was referred to our clinic for further management. Blood test findings defined raised phosphorus levels on two occasions at 6.2 and 5.7 mg/dl and insufficient 25-hydroxy vitamin D level. HPP early diagnosis and adequate treatment, depending on the clinical symptoms along with laboratory tests, could be effective in decreasing the suffering of the disease and side effects.

KEYWORDS

25-hydroxy vitamin D, alkaline phosphatase, hypophosphatasia, multisystem disease

1 | INTRODUCTION

Hypophosphatasia (HPP) is a rare inherited condition characterized by bone and teeth mineralization impairment leading to depletion of tissue non-specific alkaline phosphatase (TNSALP).[1,2] It is caused by a loss-of-function mutation in the ALPL gene which encodes TNSALP.[3] According to the age of onset, HPP involves a wide range of clinical presentation.[4] Generally, teeth and skeletal mineralization disorders are the most common symptoms of HPP patients and less common clinical presentations include musculoskeletal abnormalities, multiple fractures, fatigue, and migraine.[5] HPP is classified into the following groups based on severe to mild symptoms since before birth to adulthood: perinatal lethal HPP, prenatal benign HPP, infantile HPP, childhood HPP, adult HPP, and ordontohypophosphatasia.[6]

Lethal perinatal is the most severe subtype of HPP characterized by deformed and shorted arms and legs, deformity of the chest during delivery because of skeletal mineralization blocking due to low alkaline phosphatase level. Some of the neonates that survive, eventually die after few days because they are suffering from respiratory insufficiency due to chest deformity, but some of them are never born.[4,7]

Benign prenatal HPP presents as bowed limb. It is less severe than the previous type, affected neonate with this little malformation resolve slowly after birth.[7,8] Infantile HPP's clinical signs appear in the first 6 months; however, they have no complication at birth. The initial clinical

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manifestation may be poor feeding and failure to grow. Intracranial hypertension due to craniosynostosis because of bone fuse, proptosis, and papilledema as the finding of rising cerebral spinal fluid pressure, hypocalcemia, bone softening, rickets, hypotonia, and seizure are the other problems that neonates could face during their life. In neonates who survive, remission of skeletal mineralization and other clinical difficulties are often observed spontaneously.[7,9]

In contrast with the infantile type, the childhood HPP diagnosed after 6 months of age is classified from severe to mild forms. The most characteristic clinical signs are skeletal malformation, delayed walking, and waddling gait. Short stature in the result of rickets, bowed limbs, premature primary teeth loss, bone fracture present as other clinical symptoms. Spontaneously emissions occur in the life of young adults; however, complications could be re-present within middle or late adult age.[10,11]

Affected grown-ups with HPP may experience early loss of secondary teeth, pseudogout, joint inflammation due to calcium phosphate crystals reposition, osteomalacia, and the most common symptom which is painful feet following metatarsal stress fractures or pseudo fractures.[12,13]

The only clinical complication of odontohypophosphatasia is dental abnormalities. It should be assumed in any patients with unexpected teeth loss history.[8] The perinatal and infantile forms are autosomal recessive; however, the other forms can be autosomal recessive or autosomal dominant.[6] Inheritance patterns of HPP could be in two manners, autosomal recessive (among brothers and sisters) or autosomal dominant (multiple generations).[14]

Hypophosphatasia can be recognized based on medical history, laboratory tests, radiograph, and physical examination,[7,15] specifically decreasing in total alkaline phosphatase (ALP) serum level and normal vitamin D (25-hydroxy and 1,25-dihydroxy) concentration.[10,16,17] The prevalence of severe forms of HPP which are transmitted as an AR has been estimated to be 1/100,000.[18-22] More than 400 different defects have been described in the ALPL gene are known to be responsible for a wide spectrum of clinical manifestations.[23-25] As well as the hallmark of ALPL gene mutation is the low blood level of TNSALP activity.[26] We define a young woman diagnosed with hypophosphatasia after low ALP activity (hypophosphatasemia) was discovered following femoral fracture.

2 | CASE REPORT

A 30-year-old woman who presented for a history of early permanent teeth loss during the last 5 years in the upper jaw (Figure 1A) and the lower jaw (Figure 1B), and HPP-like symptoms in family history, complained of pain in her lower extremities with difficulty in the walk (Figure 2) was referred to our clinic for further management. Bone radiograph demonstrated bowing, deficient mineralization of bone, and symmetrical subtrochanteric stress fractures of both femurs (Figure 3). Bone mineral density (BMD) was measured by using a dual-energy radiograph absorptiometry, lumbar spine BMD of 0.942 g/cm^2 (T-score −0.4; Z-score −0.4), left forearm BMD of 0.554 g/cm^2 (T-score −0.3; Z-score −0.4), and left femur BMD of 0.539 g/cm^2 (T-score −3.9; Z-score −3.9) which is consistent with osteoporosis were analyzed; however, her EMG and NCV of both lower limbs reported normal, and there is no electrodiagnostic evidence of lumbar radiculopathy, myopathy, or generalized peripheral neuropathy.

At the time of her evaluation, there were laboratory tests which have performed 3 months ago, revealed serum ALK-P level as low as 24 (first), 51 (second), and 60 (third)

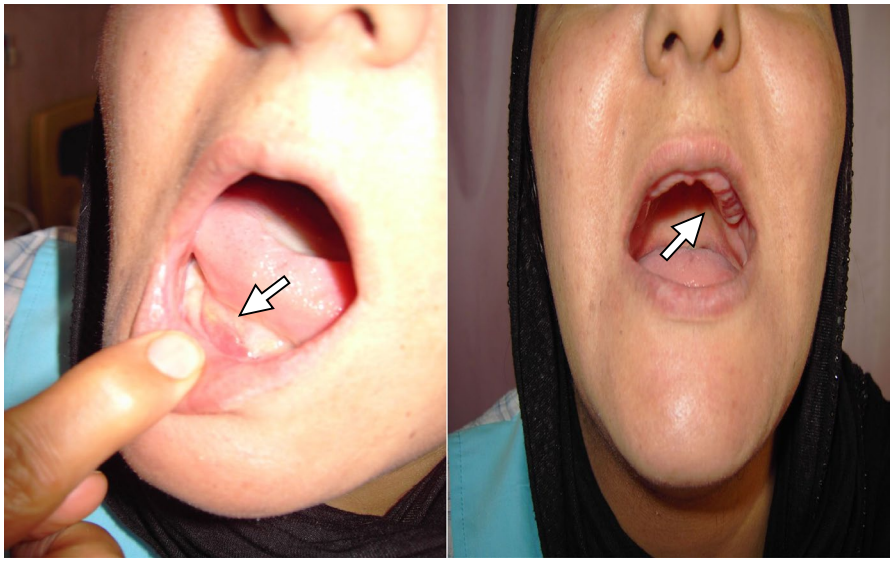

FIGURE 1 Orodental phenotype of patient. (A) Clinical view of the maxillary arch; (B) Clinical view of mandibular arch

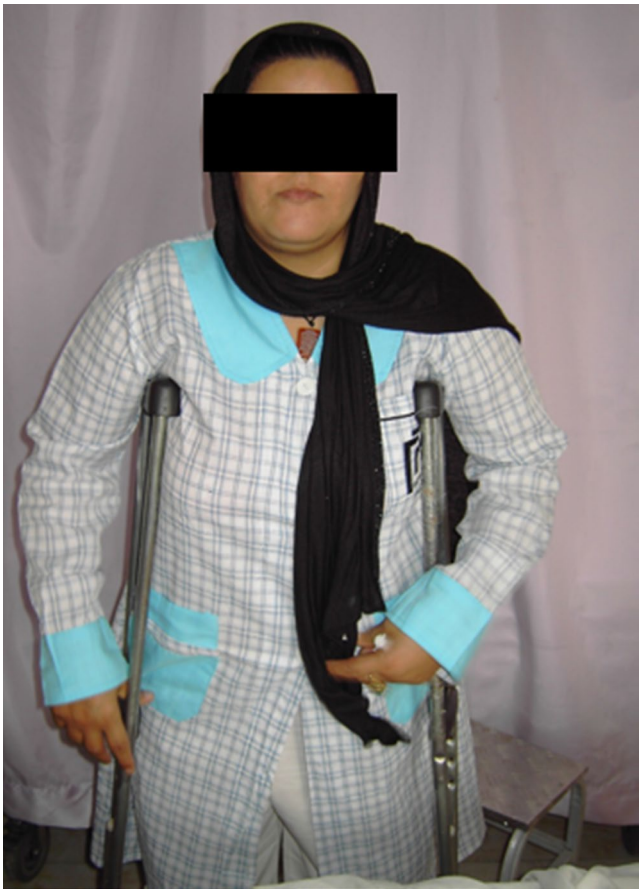

FIGURE 2 Thirty-year-old woman who complained of pain in her lower extremities with difficulty in the walk

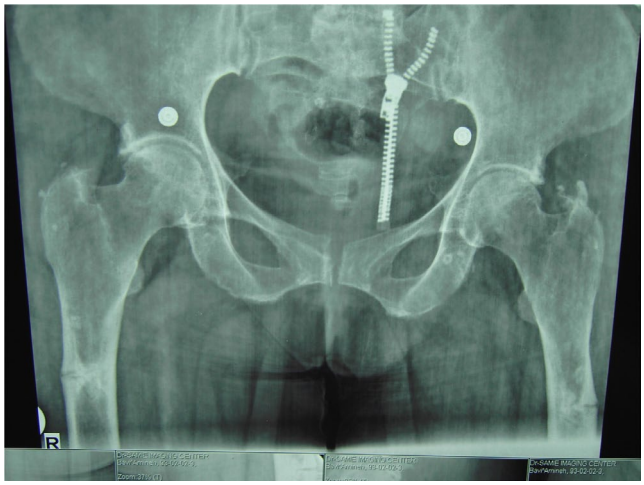

FIGURE 3 Patient radiography, bilateral subtrochanteric fractures in the lateral femur involving dialysis which is the hallmark of the adult

unit/L (reference range: 100–290 unit/L) and elevated phosphorus level 5.3 mg/dl (reference range: 2.6–4.5 mg/dl), also we had reports of her pervious laboratory tests

TABLE 1 Laboratory testing results

Test	Results
Blood urea nitrogen (n.v. 10.00–40.00 mg/dl)	21.00
Creatinine (n.v. 0.50–1.20 mg/dl)	0.72
Fasting Blood glucose (n.v. 70–110 mg/dl)	81
Sodium (n.v. 135–145 mEq/L)	143
Potassium (n.v. 3.50–5.00 mEq/L)	4.6
Calcium (n.v. 8.60–10.20 mg/dl)	9.6
Phosphorus "First" (n.v. 2.50–5.00 mg/dl)	5.3*
Phosphorus "Second" (n.v. 2.50–5.00 mg/dl)	5.7*
Alkaline Phosphatase "First" (n.v. 64–306 IU/L)	24*
Alkaline Phosphatase "Second"(n.v. 64–3.6 IU/L)	51*
Alkaline Phosphatase "Third"(n.v. 64–3.6 IU/L)	60*
Aspartate aminotransferase (n.v. 5–40 IU/L)	29
Alanine transaminase (n.v. 5–38 IU/L)	31
Lactate dehydrogenase (n.v. 225–500 IU/L)	327
Parathyroid hormone (n.v. 9.00–94.00 pg/ml)	35.7
Thyroid-stimulating hormone (n.v.0.40–6.21 μIU/ml)	2.1
Triiodothyronine (T3; n.v.0.52–1.83 ng/dl)	1.33
Thyroxine (T4; n.v.4.8–11.6 μg/dl)	14.1*
25-hydroxyvitamin D3 (Deficient <10, Insufficient: 10–29, Sufficient: 30–100 ng/ml)	58.0
Erythrocyte Sedimentation Rate (n.v. 0–20 mm/h)	40*
C-reactive protein	(+++)*
Urine analysis	Blood (+)*
Urine volume (24 h; n.v. 800–1500 ml/24 h)	2700*
Urine calcium (24 h; n.v. 100–300 mg/24 h)	230
Urine creatinine (24 h; n.v. 500–1000 mg/24 h)	1202*
Uric acid (n.v. 3–6 mg/dl)	3.6
Antinuclear Antibody	Negative
Anti-cyclic citrullinated peptide	10.9*
Human leukocyte antigen B27	Negative
Zinc (0.66–1.10 mcg/ml)	0.87

Significant tests were mentioned with *.

that have done in 3 years ago described ALK-P serum level decreased along with high amount of phosphorous level. Blood test findings described, respectively, elevated phosphorus levels on two occasions at 5.3 and 5.7 mg/dl (reference range: 2.5–4.5 mg/dl) also sufficient 25-hydroxy vitamin D (25(OH) D) level 58.0 ng/ml (sufficient reference range: 30–100 ng/ml). CBC, plasmatic calcium (9.6 mg/dl), parathyroid (PTH; 35.7 pg/ml) and thyroid hormone, kidney function, lactate dehydrogenase (LDH), and urine analysis were normal. The patient was treated several times with vitamin D, calcium, and phosphorus. Evidences

indicated that bone fracture correlated with increase in alkaline phosphatase, but this enzyme was decreased (hypophosphatasia) in the current patient. In this setting, along with the other clinical features, hypophosphatasia should be suspected (All laboratory findings are shown in Table 1).

In several members of her family, HPP-like symptoms history was positive (Figure 4). Two siblings (IV.6 and IV.7); a sister and a brother lost their teeth at the age of 12 in the absence of skeletal symptoms also there is an 18-year-old female nephew (V.6) with mental retardation and no ability to talk or walk since childhood. There were no symptoms in the patient's parents (III.1 and III.2). However, they carried a single allele of disease which is demonstrating AR inheritance and because of natural selection, recessive genes are more frequent in people of the race.[27-29] Existing of common clinical presentation of HPP in descending generations, implying of genetic inheritance because of consanguineous marriage.[30] Most of the marriages in this family have been between cousins which were led to gene sharing. Also, a 40-year-old female lost her teeth when she was 12 and had a disability in walking (III.6) and a man with teeth complications (I.4).

3 | DISCUSSION

Hypophosphatasia is an inherited disease with highly variable clinical features from in utero death in the perinatal lethal form to moderate symptoms including musculoskeletal pain, lower limbs fracture, and premature loss of teeth in adulthood.[31,32] All types characterized enzymatically by insufficient TNSALP activity at the setting of low ALP serum level which is the initial suspicion of HPP was described by J.C. Rathbun in 1948 for the first time.[26,33-35] Forty years later in 1988, the first ALPL mutation which is an exchange of guanine to adenine at position 711th nucleotide of cDNA reported by Harry Harris and team.[33] The adult form presents during middle age with PPi arthropathy such as pseudogout, frequent metatarsal fracture, and dental abnormalities.[6,31,35-38] One of the characteristic feature is laterally and proximally fracture in femur bones.[38] In heterozygous mutations, mild HPP forms could be in result of a dominant-negative effect; however, severe forms occur with homozygous mutations.[25,39,40] In this context classification of rare heterozygous ALPL mutations as photogenic factors in adults is challenging.[41] Along with gene analysis, documentation of radiological findings, Z-score assessed by DXA, laboratory tests, and family history are helpful to HPP diagnosis.[3] In humans, at least four genes account for encoding the ALP isoenzymes including intestinal (IALP), placental (PALP), germ-cell (GCALP), and liver/bone/kidney.[42] The last one is named TNSALP which is encoded by ALPL and essential for the bone and teeth mineralization process located on chromosome 1 while the first three (tissue-specific) are located on the second chromosome.[43] Measuring serum ALP level is an affordable and reasonable parameter in HPP screening moreover low levels of ALP may be observed in other non-HPP conditions such as magnesium or zinc deficiency, Wilson disease, hypothyroidism, or hyperparathyroidism that must be considered and ruled out during the diagnostic procedure.[20,37,42,44] The prevalence of a moderate form of hypophosphatasia was estimated at 1/6370 which is 50 times more than severe form (1/300,000).[20]

Hypophosphatasia could be detectable without gene analysis, although different mutations of it are located on

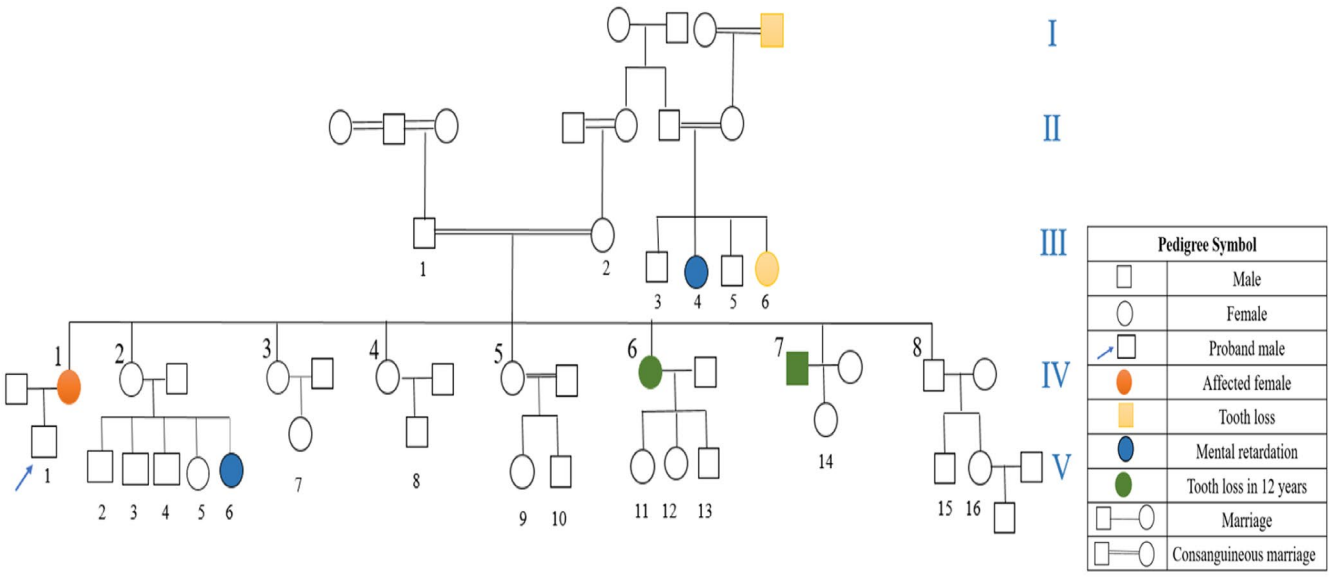

FIGURE 4 Pedigree of a consanguineous family showed the affected members

chromosome 1 p36.1 which is caused by extracellularly subtracts accumulation and reduced TNSALP activity. All patients who suffered from HPP at least have one mutation in the ALPL gene. Our patient has strong symptoms in support of suspicion of HPP, persistently low ALP level, bone fracture, teeth complications, and positive family history.[37]

There is no exact medical treatment for HPP, especially in adult forms. Most of the management in adult patients includes symptomatic and supportive therapies such as physiotherapy, mechanical ventilation, dental monitoring, and fracture treatment, also need a multidisciplinary team to provide proper management and follow-up to the patients and their families.[37,45,46] However, enzyme replacement therapy (ERT) called asfotase alfa with the bone target was approved in 2015 to pediatric-onset forms treat, improve survival of infants with severe forms, and quality of life in other types. This study aimed to evaluate causes of frequent low ALP levels, excluding secondary causes of HPP.[47]

4 | CONCLUSION

In this study, we described a patient who has been affected with typically adult HPP complications, such as pseudofractures, early loss of several permanent teeth, repeated ALP measurement below the reference range, and osteoporosis in BMD.[48] Accumulation of three natural substrates of TNSALP in extracellular space is the reason for deleterious clinical features which had developed over time.[9] HPP is a multisystem disease that is frequently misdiagnosed in adult's leads to delayed diagnosis and futile medical treatments that could exacerbate symptoms. In conclusion, early diagnosis and proper treatment, depending on the clinical symptoms along with laboratory tests, can be effective in reducing the suffering of the disease and side effects.

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CONFLICT OF INTEREST
None.

AUTHOR CONTRIBUTIONS
Shahin Besharati Kivi conceived and analyzed the case report. Haleh Siami drafted the manuscript. Negin Parsamanesh and Shahin Besharati Kivi drafted and revised the manuscript. Haleh Siami, Negin Parsamanesh, and Shahin Besharati Kivi collected data and analyzed the case report.

ETHICAL APPROVAL
This case collection was approved by the Ethics Committee of the Affiliated Zanjan University of Medical Sciences.

CONSENT
Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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