Journal Of Case Reports: Clinical & Medical

Case Report

# A Hypophosphatasia Patient with Multiple Stress Fractures

**Gultekin KE[1]*, Genc M[1], Onal A[1], Gungunes A[2] and Ceylan SD[2]**

[1]Department of Internal Medicine, Kirikkale University, Turkey

[2]Department of Endocrinology, Kirikkale University, Turkey

**ARTICLE INFO**

Received Date: November 16, 2019
Accepted Date: June 28, 2020
Published Date: July 03, 2020

**KEYWORDS**

Hypophosphatasia
Osteogenesis imperfect
Organic aciduria



**Citation for this article:** Gultekin KE, Genc M, Onal A, Gungunes A and Ceylan SD. A Hypophosphatasia Patient with Multiple Stress Fractures. Journal Of Case Reports: Clinical & Medical. 2020; 3(3):155

**Corresponding author:**
Korcan E Gultekin,
Faculty of Medicine, Department of Internal Medicine, Kirikkale University, Turkey,
Email: korcanemregultekin@gmail.com

## ABSTRACT

Hypophosphatasia (HPP) is a rare, genetic disease characterized by mutations in the Tissue Non-Specific Alkaline Phosphatase (TNSALP) gene, decreased activity of the TNSALP enzyme in target tissues. In this case we aim to introduce a patient who suffers from this very rare disease. A forty years-old woman applied to the orthopedic outpatient clinic with gait disturbance and leg pain. She was operated because of multiple stress fractures and was directed to the endocrinology outpatient clinic in terms of etiology.Gene analysis and organic acid analysis are performed in terms of hypophosphatasia, osteogenesis imperfecta and organic aciduria due to isolated low ALP levels determined in the patient's routine biochemistry and osteopenia detected in the bone mineral densitometer. COL1A1 gene mutation is not observed, organic aciduria is not detected. When ALPL gene is amplified, heterozygous p.V459M class 2 and heterozygous p.R335K class 3 mutations are detected. In conclusion, the diagnosis of hypophosphatasia in patients with multiple stress fractures should be considered and genetic analyzes should be performed.

## INTRODUCTION

Hypophosphatasia (HPP) is a rare, genetic disease characterized by mutations in the tissue non-specific alkaline phosphatase (TNSALP) gene, decreased activity of the TNSALP enzyme in target tissues, and accumulation of TNSALP substrates including inorganic pyrophosphate that is an inhibitor of mineralization. Clinical expression varies from stillbirth without mineralized bone to pathologic fractures developing only late in adulthood [1]. Low levels of alkaline phosphatase are detected in both serum and bone. In our case, we aim to introduce a female patient who suffers from this very rare disease.

## CASE PRESENTATION

A forty years-old woman applied to the orthopedic outpatient clinic with gait disturbance and leg pain. She was operated because of multiple stress fractures (Figure 1) and was directed to the endocrinology outpatient clinic in terms of etiology. Stress fracture was suspected because there was no finding on the physical examination to suggest presence of infection and the patient had no history of trauma. Her physical examination was normal except gait disturbance. In laboratory examinations; serum ALP level was 12 U/L (35-105), serum calcium was 9.7 mg/dL (8.8-10.6), serum phosphorus was 4.79 mg/dl (2.5-4.5), serum albumin 4.53 g/dl

(3,5-5,1), serum 25-OH Vit D level 9,43 ng/ml (25-80), serum parathormone 27,5 pq/dl (15-65) serum calcium was less than 2 mg/dl, urinary calcium excretion was 403 mg/24 h, and urinary phosphorus excretion was 381 mg/24 h. Liver and kidney function tests were within normal limits. Gene analysis and organic acid analysis are performed in terms of hypophosphatasia, osteogenesisimperfecta and organic aciduria due to isolated low ALP levels determined in her analysis. Osteopenia detected in the Bone Mineral Densitometry (BMD). COL1A1 gene mutation was not observed and organic aciduria was not detected. When ALPL gene was amplified, heterozygous p.V459M class 2 and heterozygous p.R335K class 3 mutations were detected. But, there was no family history.BMD revealed that the total hip BMD t score: -2.96; total spine (L1-L4) BMD t score: -1.07.

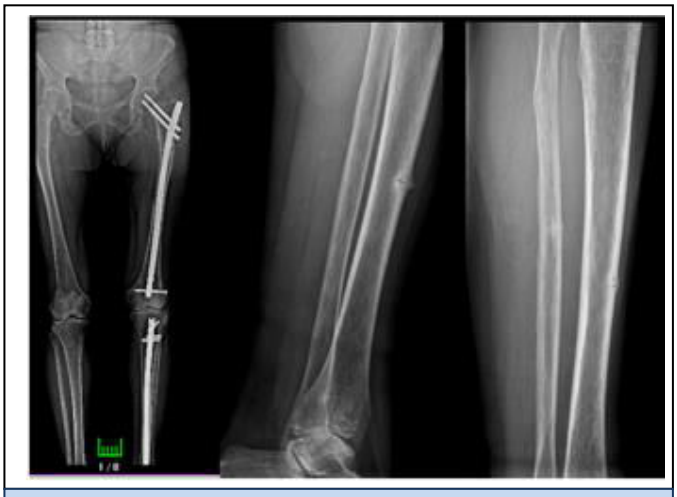

Figure 1: Multiple stress fractures and intrameduller nail application are seen.

## DISCUSSION

There are five major clinical types of HPP. The disorder is more severe and may be lethal when expressed in utero or perinatal in infants. However, when symptoms first occur at older ages, as in childhood or in adults, the expression of the disease, although variable, tends to be less severe. Adult form occurs during middle age. Delay of diagnosis of adult forms is estimated to 4 and 6 years for women and men [2]. In our case, the diagnosis has been made at 40 years. The first symptom may be foot pain caused by stress fractures of the metatarsals. Femur may also have thigh pain due to pseudo fractures. In addition, prominent osteoarthropathy may develop in later life [3,4]. Inherited as either an autosomal recessive or autosomal dominant trait, HPP is characterized by marked variability in clinical expression, even within affected families. The diagnosis of the adult form of HPP is rather difficult because the phenotype varies greatly in severity depending on the degree of residual enzyme activity [5]. In adults, HPP should be considered in patients with low serum ALP established in routine laboratory tests or in patients who have been investigated for osteoporosis and bone fractures. If low serum ALP is confirmed on repeat testing and other causes of low ALP are excluded, elevation of serum pyridoxal-5'-phosphate (vitamin B6) supports the diagnosis [6]. The finding of a mutation in the ALPL gene is a requirement for the diagnosis [7]. In our case, ALP values were deeply low. The primary clinical benefit of ALP assessment is the diagnosis of bone diseases with elevated ALP values due to high bone turnover (osteomalacia, Paget's disease) and generally little attention is paid to the low values of ALP [8]. There is no defined certain treatment for HPP in adult but symptomatic treatments are starting to be used. Treatments with zinc and magnesium (catalytic ions of the enzyme), and pyridoxal 5'-phosphate were reported to not significantly improve the course of disease. Preliminary results suggest that dietary phosphate restriction could be helpful in hypophosphatasia [9]. Teriparatide has been used with variable success. Recombinant human alkaline phosphatase (asfotasealfa) was approved by the US Food and Drug Administration (FDA) in October 2015 for treatment in adults where evidence of the disease was present in childhood. But there are no current data regarding effectiveness or optimal treatment regimen in adult HPP.

## CONCLUSION

In conclusion, the diagnosis of hypophosphatasia in patients with multiple stress fractures should be considered and genetic analyzes should be performed.

## REFERENCES

1. Whyte MP. (1994). Hypophosphatasia and the role of alkaline phosphatasein skeletal mineralization. Endocr Rev. 15: 439-461.
2. Berkseth KE, Tebben PJ, Drake MT, Hefferanet TE, E Jewison DE, et al. (2013). Clinical spectrum of hypophosphatasia diagnosed in adults. Bone. 54: 21-27.
3. Whyte MP, Murphy WA, Fallon MD. (1982). Adult hypophosphatasia with chondrocalcinosis and arthropathy.

Variable penetrance of hypophosphatasemia in a large Oklahoma kindred. Am J Med. 72: 631-641.

4. Maman E, Briot K, Roux C. (2016). Atypical femoral fracture in a 51-year-old woman:Revealing a hypophosphatasia. Joint Bone Spine. 83: 346-348.
5. Iqbal SJ, Brain A, Reynolds TM, Penny M, Holland S. (1998). Relationship between serum alkaline phosphatase and pyridoxal-5'-phosphate levels in hypophosphatasia. Clin Sci (Lond). 94: 203-206.
7. Luis MJ, Whyte MP. (2016). "Alkaline Phosphatase and Hypophosphatasia." Calcified Tissue International. 98: 398-416.
8. Maman E, Borderie D, Roux C, Briot K. (2016). Absence of recognition of low alka-line phosphatase level in a tertiary care hospital. Osteoporos Int. 27: 1251-1254.
9. Wenkert D, Podgornik MN, Coburn SP, Ryan LM, Mumm S, et al. (2007). Dietary phosphate restriction therapy for hypophosphatasia: preliminary observations. Fifth International Alkaline Phosphatase Symposium: "Understanding alkaline phosphatase function – Pathophysiology and treatment of Hypophosphatasia and other AP-related diseases" 2007, Huningue, France 2007. https://www.researchgate.net/publication/285501253_Dietary_phosphate_restriction_therapy_for_hypophosphatasia_Preliminary_observations