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There's Something in the Water: An Unusual Case of Hypophosphatasia

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Learning Objectives

1. Explain the mechanism of TNSALP in the pathogenesis of hypophosphatasia and the role of *ALPL* mutations in the severity of disease presentation.
2. Describe the clinical manifestations and diagnostic criteria of hypophosphatasia, as well as the rationale for utilizing enzyme-replacement therapy in the treatment of disease.
3. Explain the role of minerals in the enzymatic activity of ALP and understand why a mineral deficiency associated with drinking exclusively tap water could contribute to symptom severity in patients with hypophosphatasia.

Case Description

A 41-year-old male presented to the Endocrinology clinic with a 30-year history of severe musculoskeletal pain, cognitive dysfunction, and chronically loose teeth. Prior corticosteroid treatment increased his energy level but failed to improve myalgias or cognitive function. A physical exam revealed a well-nourished man with several missing teeth and a 4/10 pain score but no apparent joint swelling or spinal deformities. The patient was found to have osteopenia on bone densitometry and below normal serum alkaline phosphatase (ALP) at 33 IU/L (reference range: 40-130). He was started on asfotase alfa (200mg 3 times weekly) for presumed hypophosphatasia (HPP), which led to a significant improvement in symptoms. However, extensive genetic workup did not identify a mutation in the *ALPL* gene, which encodes the tissue-nonspecific isoenzyme of ALP (TNSALP). As the patient was not found to have mutations implicated in the pathogenesis of HPP, insurance coverage of asfotase alfa was denied after one year of treatment.

Interestingly, after discontinuation of asfotase alfa the patient began drinking tap water rather than exclusively bottled water. Following this change, he reported a remarkable improvement in symptoms, including fatigue, myalgias, and cognitive dysfunction. He also endorsed the ability to work more than 14 hours per day, increased from an average of 2 hours per day. Although he did continue to experience dental issues, his levels of both total and bone-specific ALP remained within normal limits one year after discontinuing medication, at 52 IU/L and 8.6 IU/L (reference range: 7-18.3), respectively. He also maintained normal levels of serum vitamin B6 (pyridoxine), pyridoxal 5' phosphate (PLP), and urinary phosphoethanolamine (PEA), three biochemical markers of disease. As no other dietary or medication changes were reported, this sustained clinical improvement was hypothesized to be secondary to the presence of minerals in tap water, including zinc and magnesium, which are often found in significantly lower levels in bottled water.[1]

Discussion

Hypophosphatasia is a rare inherited inborn error of metabolism characterized by low TNSALP activity that affects an estimated 1 in 100,000 individuals.[2-4] Over 300 known autosomal dominant and recessive mutations in the *ALPL* gene are implicated in the pathogenesis of HPP, contributing to a spectrum of clinical presentations ranging from lethal *in utero* to mild adult-onset forms of disease.[5] TNSALP is a cell-surface phosphohydrolase that is highly expressed in the bone, kidneys, liver, and teeth. An impaired function can result in the extracellular accumulation of ALP substrates, including inorganic pyrophosphate, an inhibitor of bone and tooth mineralization.[6]

Clinical manifestations of decreased ALP activity include osteomalacia, fractures, rickets, and tooth loss.[2] Patients with severe disease may also exhibit systemic symptoms, including kidney dysfunction, respiratory depression, and seizures. Seizures are typically responsive to pyridoxine treatment due to the role of TNSALP in both ATP dephosphorylation and hydrolysis of PLP, the primary circulating form of vitamin B6.[2,5] The diagnosis of HPP

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is dependent on both reduced ALP levels and a genetic defect in the *ALPL* gene, although 5% of patients have no identifiable mutation. Elevated serum levels of PLP and, to a lesser extent, elevated urinary levels of PEA, represent sensitive and specific markers of disease. However, patients often present with low or normal vitamin B6 levels, hypercalcemia, and hyperphosphatemia.[2] Treatment of HPP involves enzymatic replacement using asfotase alfa, a bone-targeted recombinant ALP, as well as nutritional support to maintain vitamin D and B6 levels.[2,7,8]

Deficiencies in either zinc or magnesium are known to contribute to decreased levels of ALP, which requires two Zn2+, one Mg3+, and one Ca2+ ion for enzymatic activity.[9] Although literature reports that imbalances in dietary mineral intake are associated with symptom severity in patients with HPP, the impact of minerals found in drinking water is unknown.[10] We hypothesize that increased mineral intake following the switch from bottled water to tap water led to clinical and biochemical improvement in this patient.[1] However, the mineral composition of this patient's tap and bottled water is unknown, so we cannot exclude the possibility that factors other than changes in drinking water-associated mineral intake contributed to his improved clinical status. This case highlights a unique presentation of HPP and suggests that further research into the association between mineral intake and symptomology is warranted.

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