Case Report

Hypophosphatasia with Coexisting Endocrinopathies: A Diagnostic Dilemma

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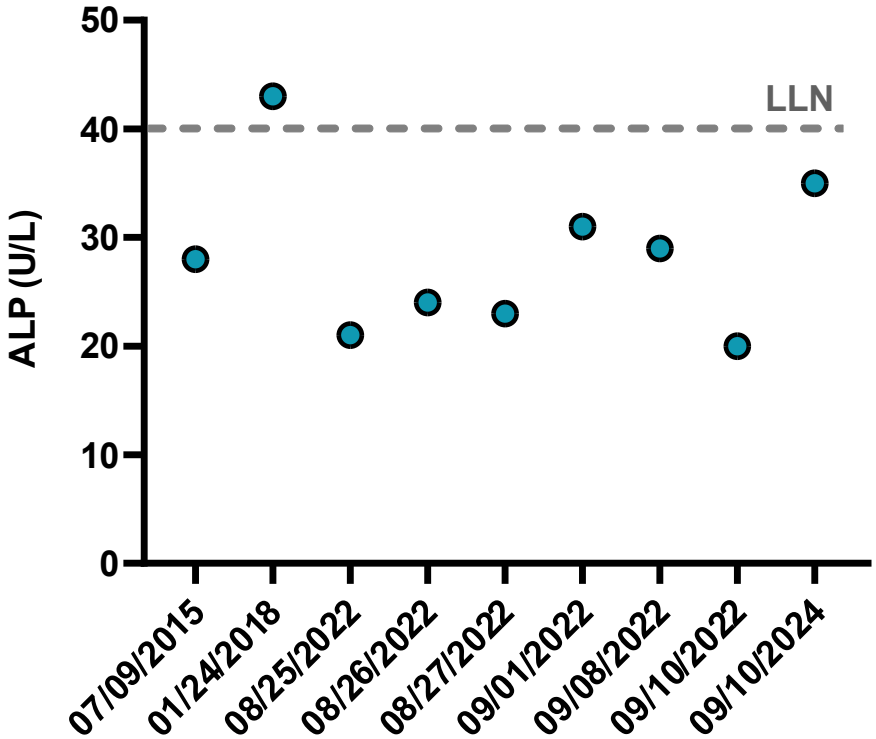
Abstract

Adult-onset hypophosphatasia presents a diagnostic challenge due to confounding clinical and analytical factors. Although rare, the consequence of missed diagnosis is significant, as it can potentiate skeletal mineralization defects. Despite the recent development of diagnostic criteria, integration into routine clinical practice remains limited, partly due to the variable course of disease progression. Effective management often requires a multidisciplinary team, including rheumatologists, orthopedic surgeons, endocrinologists, medical geneticists, dentists, physical and occupational therapists, pain specialists and clinical biochemists. Here, we present a case of adult-onset autosomal dominant hypophosphatasia, where diagnosis was complicated by coexisting endocrine disorders, Addison's disease and primary hypothyroidism. Persistently decreased alkaline phosphatase activity had been observed for over a decade and were initially attributed to hypothyroidism. However, an endocrinologist's clinical suspicion led to genetic testing, confirming hypophosphatasia. Although the patient exhibited no additional symptoms such as premature tooth loss, osteopenia, or osteoporosis, this incidental finding prompted a referral to medical genetics, carrier screening to support family planning, and cascade testing for family members.

Case Description

A 30-year-old female presents to the endocrinology clinic for follow-up and management of primary hypothyroidism and Addison's disease. At the time of initial diagnosis, thyroid-stimulating hormone increased at 15.08 µIU/mL (reference interval: 0.35-4.54 µIU/mL), free thyroxine decreased at 0.6 ng/dL (reference interval: 0.7-1.5 ng/dL), AM cortisol was undetectable at <1µg/dL (reference interval: 3.7-19.4 µg/dL), adrenocorticotropic hormone increased at 2050 pg/mL (reference interval: 7.2-63 pg/mL) and 21-hydroxylase antibodies were positive. Patient continues treatment with hydrocortisone 20 mg, fludrocortisone 0.1 mg and levothyroxine 75 µg. Notably, alkaline phosphatase (ALP) activity has been consistently decreased for past 10 years in the context of normal calcium, 25-hydroxy vitamin D and parathyroid hormone concentration (Figure 1). On average, ALP activity is decreased by 30% below the lower limit of normal. ALP activity is measured using the Abbott Alinity ci system between 2021-2024 and the Abbott Architect c4000 system between 2015-2021. In both assays, ALP catalyzes the hydrolysis of colorless p-nitrophenyl phosphate under alkaline conditions, producing p-nitrophenol (in its yellow phenoxide form) and inorganic phosphate and activity is quantified by measuring the increase in absorbance at 404 nm. Decreased ALP activity is known to be associated with hypothyroidism, predominantly due to impaired production of ALP (Paula Hoff, BMJ Open, 2025). However, ALP activity is expected to normalize after levothyroxine therapy. Despite normal free thyroxine (1 ng/dL) and thyroid-stimulating hormone concentrations (4.94 µIU/mL) post-treatment, her ALP activity remained decreased. ALP isoform testing was unsuccessful due to insufficient activity. Interestingly, bone density studies performed by dual-energy X-ray absorptiometry (DEXA) were unremarkable with z-scores of 1.2 for lumbar spine and 0.6 for right hip. Vitamin B12 concentrations were also normal at 695 pg/mL (reference interval: 213-816 pg/mL). Genetic testing identified a heterozygous pathogenic variant, c.517G>A(p.Glu191Lys), in the alkaline phosphatase (ALPL) gene confirming a diagnosis of adult-onset autosomal dominant hypophosphatasia (HPP). Patient denied symptoms of hypophosphatasia such as bone pain, abnormal dentition, short stature, muscle weakness, muscle pain, impaired mobility or abnormal gait. Due to lack of functional changes associated with HPP, treatment was deferred and patient was referred to medical genetics for further follow-up. A repeat DEXA scan is recommended in 4-5 years due to insidious nature of adult-onset HPP [4]. As the patient prepares for conception, education was provided on the significance of carrier screening to avoid autosomal recessive inheritance of severe forms of infantile or neonatal HPP. Additionally, genetic testing results were shared with family members to allow for cascade testing. To our knowledge, this is the first case report of a patient with HPP in the setting of two endocrine co-morbidities, Addison's disease and primary hypothyroidism.

Figure 1: ALP activity is consistently below the lower limit of normal reference interval (LLN).



Introduction

Hypophosphatasia (HPP) is a rare inborn error of metabolism caused by loss of function mutation in the ALPL gene encoding tissue non-specific ALP, which is predominantly expressed in bone, liver and kidneys [1]. Prevalence is estimated to be ~1 in 100,000 individuals, and >480 ALPL variants are characterized [2]. Hypomineralization is the pathological hallmark of HPP, driven by the accumulation of inorganic pyrophosphate, a natural substrate of ALP and a potent inhibitor of hydroxyapatite crystal formation [3]. Clinical severity is determined by the age of onset and is highly variable ranging from mild tooth loss or periodontal disease to severe bone demineralization, pulmonary hypoplasia, respiratory failure and vitamin B6-responsive seizures [4]. Perinatal and infantile HPP often display severe phenotypes, whereas adult-onset HPP shows mild-to-moderate phenotype [5].

Diagnosis of HPP is made based on combination of signs and symptoms, biochemical findings (persistently decreased ALP activity, elevation of ALP natural substrates such as pyridoxal-5′-phosphate, phosphoethanolamine, or inorganic pyrophosphate), imaging (DEXA) and genetic studies (ALPL variant analysis) [6]. In 2023, the international working group on HPP comprised of experts from Europe and North America provided recommendations for clinical diagnosis in adults and children using 2 major or 1 major and 2 minor criteria [5]. For adults, major criteria include pathogenic or likely pathogenic ALPL variants, elevation of natural ALP substrates, atypical femoral fractures, recurrent metatarsal fractures, whereas minor criteria include poor healing fractures, chronic musculoskeletal pain, early traumatic loss of teeth, chondrocalcinosis and nephrocalcinosis [5]. For children, major criteria include pathogenic or likely pathogenic ALPL variants, elevation of natural ALP substrates, early nontraumatic loss of primary teeth, presence of rickets, whereas minor criteria include short stature or linear growth failure over time, craniosynostosis, nephrocalcinosis, B6-responsive seizures and delayed motor milestones [5]. Currently, human recombinant enzyme replacement therapy for ALP called Asfotase Alpha is the only FDA approved treatment for patients with perinatal/infantile and juvenile-onset HPP but not adult-onset HPP in the United States [7].

Discussion

Decreased ALP activity is seen in a plethora of clinical settings, including anti-resorptive drug therapy, endocrine disorders such as hypothyroidism, hypoparathyroidism, hypercortisolism and renal osteodystrophy, hematological conditions such as pernicious anemia and myeloproliferative disorders, and nutritional deficiencies such as magnesium, zinc, copper, vitamin C, vitamin B6 and vitamin B12 [5] . Due to this overlap, HPP diagnosis is estimated to be delayed by ~5.7 years after onset of symptoms [8]. For instance, the current patient exhibited decreased ALP activity as early as 2015, but a definitive diagnosis was only established in 2024 following genetic confirmation. This delay is partly attributed to co-existing primary hypothyroidism.

In the absence of clinical symptoms, persistently decreased ALP below the lower limit of normal reference interval served as the primary trigger for initiating genetic testing in our case. It is essential to consider preanalytical, analytical, and post-analytical factors that may influence ALP results. Pre-analytically, the use of an incorrect collection tube containing EDTA preservative can lead to chelation of magnesium and zinc ions, resulting in falsely decreased ALP activity [9]. Analytically, ALP test is prone to instrument errors due to insufficient absorbance reads and can lead to misinterpretation of falsely decreased value [10]. ALP assay from multiple vendors were confirmed to detect Asfotase Alpha in the patient samples upon dilution [10]. Hence, it is important to troubleshoot the absorbance errors rather than reporting as undetectable [10]. Post-analytically, it is crucial to interpret ALP activity using the age and sex-partitioned reference intervals. Our current assay has a single reference interval of 40-150 U/L for adults based on the manufacturer's package insert. Before opting for expensive genetic testing, one could assess the concentration of tissue nonspecific ALP natural substrates such a pyridoxal-5′-phosphate, phosphoethanolamine, or inorganic pyrophosphate. However, access to these tests within our geographical location is limited. Both clinical and analytical factors can complicate the diagnosis of HPP. Given the broad spectrum of phenotypes across the HPP disease continuum, genetic testing plays a critical role in confirming the diagnosis. Patients diagnosed with HPP benefit from a multidisciplinary care team, an approach that remains limited in rural healthcare settings worldwide.

Ethical approval

Patient consent submitted to Sanford Health Information Management.

Declaration of conflicts

The authors declare no conflict of interest.

Funding and Data Availability

Not applicable.

CRediT author statement

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