Alkaline Phosphatase Activity Inconsistent with Patient's Clinical Presentation: A Cautionary Tale

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CASE DESCRIPTION

A 33-year-old White female was referred to the endocrine clinic for a decreased serum alkaline phosphatase (ALP) result. She had been suffering from daily generalized body aches since the age of 15 years. She had not sustained any fractures. A few months before the presentation, she was diagnosed with rapidly progressing advanced periodontal bone loss without the loss of teeth. On review of her laboratory results, serum ALP activities for the past 12 years were all below the reference interval. Notably, her serum vitamin B6 (pyridoxal 5′-phosphate) was increased together with a mildly increased ratio of urine phosphoethanolamine (PEP) to creatinine, raising suspicion for hypophosphatasia (HPP; Table 1). Genetic testing identified a heterozygous pathogenic variant, c.881A>C (p.Asp294Ala), in the alkaline phosphatase gene (*ALPL*) confirming a diagnosis of autosomal dominant HPP. Dual-energy X-ray absorptiometry reported normal bone density for age and gender. An X-ray of her ribs did not report rachitic changes. After a normal ophthalmic exam and renal ultrasound, asfotase alfa, a form of enzyme replacement therapy (ERT), was initiated. ERT resulted in an 80% improvement in her musculoskeletal pain with the expected decrease in serum vitamin B6 concentration (Table 1). However, ALP activities were undetectable on 2 occasions, an unexpected finding in the context of initiating ERT. Hence, the ordering physician contacted the laboratory regarding the inconsistent ALP activity measurements.

QUESTIONS TO CONSIDER	
1.	What are the key diagnostic criteria for hypophosphatasia?
2.	What is the effect of asfotase alfa treatment on ALP measurement?
3.	How does serum vitamin B6 concentration correlate with ALP in patients on asfotase alfa treatment?

Table 1. The patient's laboratory results.

Analyte	After asfotase alfa treatment	Before asfotase alfa treatment	RI
Alkaline phosphatase	<9 L	23 L	38–126 U/L
Vitamin B6 (Pyridoxal- 5′ Phosphate)	8.6 L	207.2 H	20–25.0 nmol/L
Phosphorus, inorganic	n/a	3.7	2.2– 4.5 mg/dL
PEP, urine	n/a	118 H	<60 µmol/g creatinine

Phosphorus, inorganic mg/dL to mmol/L x0.3329.
Urine creatinine g to mmol x88.4.
Abbreviations: H, above the upper reference limit; L, below the lower reference limit; n/a, Not applicable.

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Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the December 2024 issue of *Clinical Chemistry*. To view the case and comments online, go to https://academic.oup.com/clinchem/issue/70/12 and follow the link to the Clinical Case Study and Commentaries.

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