Abstract citation ID: bvad114.420

Bone And Mineral Metabolism

THU459

Hypophosphatasia With Normal ALPL Gene Test; A Case Report

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Disclosure: K. Alkwatli: None. **L.Z. Khan:** None.

Introduction: Hypophosphatasia is a rare hereditary disorder caused by loss of tissue nonspecific alkaline phosphatase activity, an essential enzyme in phosphate metabolism. Severe cases present perinatally and in early childhood. Mild cases can present in adulthood and can be misdiagnosed. We present an interesting patient who was clinically diagnosed with hypophosphatasia despite negative molecular genetic testing. **Case presentation:** 40 years-old female with a history of fibromyalgia and multiple bone fractures presented to the clinic with a long-standing history of multiple cavities, severe fatigue, headaches, muscle cramps, and arthralgia. The patient had numerous fractures throughout her life that started at age five without significant trauma, including wrist, forearm, and metatarsal bones. Her family history was negative. Laboratory testing showed low alkaline phosphatase levels on multiple occasions, 28,29,30 U/L (reference range 34-123). Her vitamin B6 was elevated at 309 nmol/L (20-125). Her zinc, calcium, vitamin D, and liver function tests were all within normal limits. Bone density scan showed a Z score of -1.0 at the lumbar spine and a Z score of -0.3 at the left femoral neck. Molecular genetic testing of the ALPL gene was negative. Hypophosphatasia was diagnosed based on her clinical and lab assessments, and she is being treated with Asfotase alfa. Her clinical course is yet to be determined. **Discussion:** ALPL gene is responsible for encoding the tissue nonspecific alkaline phosphatase (TNALP), the main enzyme affected in patients with hypophosphatasia. TNALP degrades inorganic pyrophosphate (PPi) to inorganic phosphate (Pi), an essential element for bone mineralization. It also facilitates vitamin B6 to cross the cell membranes. Therefore, loss of function mutations of the ALPL gene cause accumulation of PPi, which impairs the calcium-phosphate hemostasis and causes damage to multiple organs. In addition, the accumulation of the active form of vitamin B6 extracellularly can result in neurological damage.Patients present with a broad spectrum of musculoskeletal, renal, dental, and neurological symptoms. The variability of the phenotypic magnitudes is thought to be due to heterogeneity in the ALPL gene mutations. Over 400s of ALPL gene mutations have been identified in patients with hypophosphatasia. Novel variants are increasingly being reported.Negative genetic testing of the ALPL gene can still be seen in patients with hypophosphatasia due to either a variant that is undetectable by current testing methodology or if the causative gene/s are not on the ALPL gene panel. **Conclusion:** Genetic testing is helpful in confirming the disease and providing genetic counseling; however, treatment should still be considered if patients have sufficient clinical and laboratory findings.

Presentation: Thursday, June 15, 2023