HEREDITARY HYPOPHOSPHATASIA IN A 30-YEAR-OLD FEMALE WITH CHRONIC BONE PAIN

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BACKGROUND

- Hereditary hypophosphatasia (HPP) is a rare autosomal recessive disorder, characterized by disrupted mineralization of bones and teeth.
- It is often caused by loss-of-function (LOF) mutations in the ALPL gene that encodes the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP).
- Accumulation TNSALP substrates
  - Inorganic pyrophosphate (PPi): inhibitor of bone mineralization
  - Phosphoethanolamine (PEA)
  - Vitamin B6/Pyridoxal 5-Phosphate
- Infantile (severe), childhood, adult (mild)
- Symptoms can vary, even with the same mutation
  - Defective mineralization of bone and teeth, leading to bone deformities, rickets, fractures, bone pain, loss of teeth, poor dentition, ↑ serum Ca^{2+}
  - Multiple systemic effects such as respiratory compromise, seizures, myopathy, and renal complications
- Diagnosis: Low ALP → genetic testing
  - Elevated PEA and Vitamin B6
- Adult onset HPP can be missed, given the uncommon and complex nature of disease.
  - Few reports of HPP presenting in adulthood mistaken for osteoporosis.

CASE PRESENTATION

- 30-year-old female, PMH of endometriosis and leg pain
- Presented to her family medicine physician with long history of chronic, progressive bone pain
- As a child and adolescent, her bone pain was classified as growing pain.
- Her alkaline phosphatase level at the time of the visit was 31 U/L (35-147 U/L).
- She previously had decreased alkaline phosphatase levels intermixed with levels on the low side of the normal range.
- Her physician noted bone pain, short stature, and decreased alkaline phosphatase levels and discussed possible genetic causes.

WORKUP AND TREATMENT

- Genetic testing identified an ALPL gene .571G>A (p.Glu191Lys) mutation, indicating HPP.
- Since diagnosis:
  - Renal ultrasound negative for stones
  - Normal DEXA scans
  - Normal tibial x-rays
- Treatments:
  - Pain management
    - Tapentadol 200 mg, gabapentin 300 mg, buprenorphine 10 mcg/hour weekly transdermal patch
  - Enzyme Replacement
    - Asfotase alfa (Strensiq)—recombinant glycoprotein active site of TNSALP, started January 2021, required extensive testing for insurance approval
  - Other treatment options: alkaline phosphatase replacement therapy, Teriparatide—modified parathyroid hormone that promotes bone growth

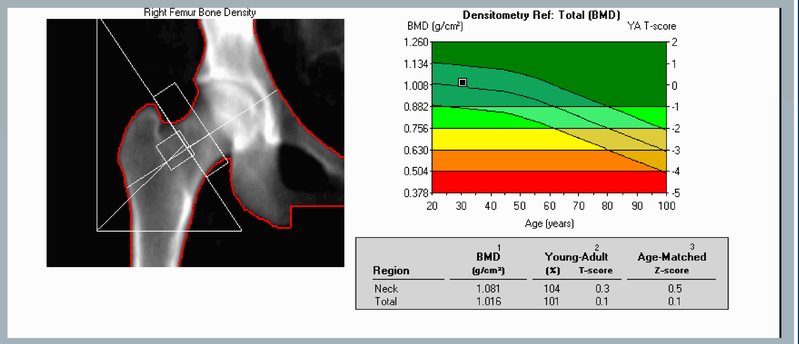

Figure 1: Results of a normal bone density DEXA scan

Table 1: Alkaline phosphatase levels (Range: 38-126 U/L) and serum calcium (Range: 8.4-10.2)

Days From Diagnosis Date	Alkaline Phosphatase Level	Calcium Levels
-465	40	10.1
-395	38	
-123	36 (L)	10.0
0	31 (L)	9.5
10	33 (L)	
42	38	9.0
153	35 (L)	9.3

Table 2: TNSALP substrate levels and reference for this patient. These levels were required for insurance coverage of enzyme replacement therapy with asfofase alfa.

Laboratory Test	Result	Reference
Urine PEA	36 nmol/mg (H)	0-27
Vitamin B6	67.1 nmol/L	20-125
Pyridoxal 5-Phosphate	13 mcg/L	5-50

CONCLUSIONS

- HPP is important to consider in patients with chronic bone pain
  - Low to low-normal alkaline phosphatase levels
- Distinguish bone pain compared to pain of muscular origin, as seen with fibromyalgia.
- Consider HPP in patients thought to have early-onset osteoporosis
  - Fragility fractures → ALP levels
- Diagnosis of HPP may provide more treatment options with asfofase alfa, teriparatide, and alkaline phosphatase replacement.
  - Pain management has not been enough for this patient
  - Insurance coverage is a barrier
  - Results of asfotase alfa (Stensiq) is unknown for this patient, as treatment started recently, but provides hope

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