Hypophosphatasia

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Hypophosphatiasis Case

- 57 y/o male with a hyperlipidemia and hypogonadism.
- Noted to have an alkaline phosphatase of <10 u/l on routine lab
- History follows:
  Teeth
  - Lost his four top front teeth and four bottom front teeth at the age of 18 months. He did not get front teeth until 8 years of age.
  - As a child, had numerous cavities. When he was 10 years of age, 8 cavities were found.
  - 10–15 tooth abscesses in his life time, all requiring root canals and caps. First in his late teens (age 16 or 17).
  - Cadaveric bone placed in his gums twice as an adult, the first time at age 40
  Bones
  - Fractured both 5th metacarpals and coccyx between the ages of 8–11 year old with minor trauma. At the age of 40 years, he broke his right 5th metatarsal with minor trauma. In his 40’s, he broke three metatarsals on the right (one twice), two metatarsals and a sesamoid bone on the left and two left metacarpals.
  - In 2016, a stress fracture left 2nd metatarsal present ~3 years – non-healing and persistent pain in this area.
Hypophosphatasia Case

Gait and Joints
- He hasn’t jogged for ten years due to knee pain. He notes a limp favoring the R leg due to knee pain
- As a child, he was told that he ran “funny” and had limited motion in wrists, ankles, and feet; limited range of motion in his hips and neck

Biochemical
- He has had a chronically low alkaline phosphatase (<10 u/L)
- In 12/15, the diagnosis of juvenile onset hypophosphatasia was considered and his relevant labs showed the following:
  - Pyridoxal 5-Phosphate 361 mcg/L (nl 5–50)
  - Phosphoethanolamine 301 nmol/mg Cr (nl <48)
  - Vitamin B6 >400 (nl 20–125)
  - PTH, Ca++, Phos, 25-D, Mg++, Cr all normal

- Hypophosphatasia diagnosed
Hypophosphatasia

- Rare (~1 case per 100,000 live births)—caused by mutations in the gene encoding tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP) leading to low alkaline phosphatase activity levels which in the severe form may lead to rickets, osteomalacia, or both

- Males and females are equally affected

- Clinical presentation from death in utero to cases in which pathologic fractures first present in adulthood.
Alkaline phosphatase is present as 4 isomers, each with its own gene locus.

- Three of these isoforms are tissue specific and are known as germ cell, placental, and intestinal alkaline phosphatase.
- The fourth isoform, TNSALP, is found in the bone, liver, kidney, and other tissues.
  - TNSALP cleaves phosphate-containing substrates

More than 250 distinct mutations have been described for this gene, 79% of which are missense mutations
Mechanism of HPP

Mutation in the gene encoding TNSALP → Deficient ALP Activity → Substrate Accumulation

- Inorganic pyrophosphate (PPI)
- Pyridoxal-5'-phosphate (PLP)
- Phosphoethanolamine (PEA)

→ Hypophosphatasia

High extracellular levels of inorganic pyrophosphate block hydroxyapatite crystal growth and may lead to decreased mineralization.
Hypophosphatasia: Inheritance

- The most severe forms of the disease have an autosomal recessive mode of inheritance. Analysis of the \textit{TNSALP} gene aids prenatal diagnosis.

- Compound heterozygosity and autosomal dominant mutations in the \textit{TNSALP} gene may cause childhood and adult hypophosphatasia.
At least 6 clinical forms of hypophosphatasia have been reported
  ◦ Less severe form may be missed for years, until a radiograph is obtained for chronic pain or a pathological fracture.

The types include:
  ◦ Perinatal (lethal)
  ◦ Infantile
  ◦ Childhood
  ◦ Adult – may have had signs of the disease earlier in life
  ◦ Odontohypophosphatasia (no clinical changes in long bones are present, only biochemical and dental manifestations)
  ◦ Pseudohypophosphatasia.
    • Clinically indistinguishable from infantile hypophosphatasia, but serum alkaline phosphatase (ALP) activity is normal
Severe cases are lethal. Mortality in infants is 50% if manifest within 6 months of birth.
  ◦ Most common cause of death is respiratory complications

Individuals with less severe disease can reach adulthood, often with significantly increased morbidity

Adults may have increased morbidity from poorly healing stress fractures and may be severely affected and not able to ambulate
  ◦ Premature loss of dentition.
  ◦ Patients may also present with nephrocalcinosis, neurological damage secondary to vitamin B–6–responsive seizures, increased intracranial pressure secondary to craniosynostosis, and joint problems secondary to calcium deposits

Adults may present with severe mobility impairment (about 23% require a wheelchair; about 25% require a walking device)
Adult Form

- Adult form presents with signs and symptoms during middle age.
  - As with the childhood form, premature loss of deciduous teeth due to disturbed cementum formation is common.
  - Mineralization of dentin is less likely to be under the influence of the inhibitory action of pyrophosphate than mineralization of cementum.

- Diagnosis often made after a low alkaline phosphatase level detected during routine blood work, or when tested after a direct family member was diagnosed with the condition.

- Adults may also have a history of foot pain due to stress fractures and joint pain due to deposition of calcium pyrophosphate dihydrate.

- Affected adults may manifest osteomalacia, with slowly healing or nonunion stress fractures (commonly metatarsal) and proximal femur pseudofractures.
Assess alkaline phosphatase levels
Measure calcium, phosphorus, magnesium, creatinine, parathyroid hormone (PTH), 25(OH) vitamin D, and 1,25(OH)2 vitamin D.
Levels of PLP, PPi in plasma, and PEA in urine determine the diagnosis.
- Patient's intake of vitamins (particularly vitamin B-6) may affect results.

- Elevated serum calcium and phosphorus levels may be present, but are not necessary
- Genetic testing is not always required, but may be helpful, depending upon your patient's situation

Inorganic pyrophosphate (PPI)
Pyridoxal-5'-phosphate (PLP)
Phosphoethanolamine (PEA)
Imaging Studies

- In lethal cases, there is frequently a near absence of skeletal mineralization. Fractures and rachitic changes are often present.
- Pseudo-fractures—hallmarks of hypophosphatasia in adults.
  - Increased incidence of poorly healing stress fractures, especially of the metatarsals
- Renal ultrasound may reveal nephrocalcinosis.
Bisphosphonates contra-indicated and teriparatide results inconsistent

The FDA approved asfotase alfa (Strensiq) in 2015 as the first therapy for hypophosphatasia
- Recombinant, fusion protein comprising the TNSALP ectodomain, the constant region of the human IgG1 Fc domain, and a terminal deca-aspartate motif for bone targeting

Asfotase Alfa is a tissue nonspecific alkaline phosphatase indicated for the treatment of patients with perinatal/infantile- and juvenile- onset hypophosphatasia
Treatment

- Approval based on 4 prospective, open-label studies—99 patients who developed hypophosphatasia in utero, as an infant, or as a juvenile.
  - Received the drug up to 6.5 years. Patients with either perinatal or infant onset of the disease showed improvement in overall survival, as well as ventilator-free survival.
  - 97% receiving the drug were alive at age 1 year compared with 42% of control patients. Ventilator-free survival rates for both groups followed much the same pattern.
  - Patients with juvenile-onset hypophosphatasia also experienced improved growth and bone health compared with patients in a natural history database.

Back to the Hypophosphatasia Case

- Given 6–8 months of Forteo in early 2016 without clear bone healing benefit and no change in alkaline phosphatase

- Started Asfotase alfa on 12/24/16

- Since then, his feet and ankle pains and knee have improved 90% with ambulation

- Radiographically, metatarsal fractures are healing

- Labs: Alkaline Phosphatase: >6000 (U/L) (04/25/2017) with a normal Ca++ and Cr
Before, (1/17) and on Rx, (7/17)