Hypophosphatasia

Abstract
Hypophosphatasia is a genetic bone disease. There are six known forms of the disease and the symptoms, diagnosis, and prognosis can vary depending on the presentation and developmental stage when diagnosed. There are several surgical, medical, and therapeutic treatments. A case study will discuss the most deadly form of the disease known as Perinatal Lethal Hypophosphatasia, and the least lethal form known as Odontohypophosphatasia.

Introduction
Hypophosphatasia is a rare, genetic bone disease defined by a lack of development in the skeletal anatomy. The disease is recognized by soft or unformed bones and teeth. “[I]t is a hereditary disorder characterized by a deficiency of serum and bone alkaline phosphatase (ALP) activity and defective skeletal mineralization.”1(p.851) This disease presents itself in six known forms: lethal perinatal, prenatal benign, infantile, childhood, adult, and odontohypophosphatasia. The prevalence of the disease is area specific occurring in approximately 1/2,500 to 1/100,000 in Canada, with the most severe form being the most common, and 1/300,000 in Europe. The symptoms of Hypophosphatasia range from still birth, without mineralized bone, to pathologic fractures developing in late adulthood.

Perinatal Lethal Hypophosphatasia
Perinatal lethal Hypophosphatasia is one of the most severe and detrimental types of Hypophosphatasia. Perinatal lethal Hypophosphatasia occurs in approximately one in one-hundred thousand live births. It “is typically identified by prenatal ultrasound examination. Pregnancies may end in stillbirth. Small thoracic cavity and short, bowed limbs are seen in both liveborn and stillborn infants.”2(p.8) Carriers of the gene tissue non-specific alkaline phosphatase (TNSALP,) or those who have a mutation in the ALPL gene 1q36, may pass on this lethal form of Hypophosphatasia. Heterozygous patients may present completely normal or only show very mild signs and symptoms.
“Patients with [Perinatal lethal Hypophosphatiasia] tend to have short limb dwarfism (micromelia) with very soft calvaria.”\textsuperscript{3(p.1)} Furthermore, signs and symptoms may present as a blue sclera, bowdler spurs in the mid-portion of the forearms and lower legs, noticeable inconsistency in the amount of bone ossification, a lack in ossification of groups of vertebral bodies and neural arches of the spine, lack of ossification of bones in the hands, and “unusually dense, round, flattened, butterfly shaped; and sagittally clefted vertebral bodies.”\textsuperscript{3(p.1)} The main impediment of this form of Hypophosphatasia is Pulmonary hypoplasia. “Pulmonary hypoplasia refers to deficient or incomplete development of parts of the lung.”\textsuperscript{3(p.2)} The prognosis for Perinatal Lethal Hypophosphatiasia is likely death. Furthermore, there is a twenty-five percent chance of reoccurrence in future pregnancies.

**Prenatal Benign Hypophosphatiasia**

Perinatal benign Hypophosphatiasia is another form of Hypophosphatiasia. It “is typically identified by prenatal ultrasound examination. Postnatally, skeletal manifestations slowly resolve with an eventual childhood or adult Hypophosphatiasia.”\textsuperscript{2(p.1)} In the prenatal benign form, there is an unstructured enhancement of skeletal defects and symptoms. “Patients manifest limb shortening and bowing and often dimples overlaying the long bones deformities, and some ultrasounds revealed progressive improvement of the skeletal deformities and mineralization during the third trimester of the pregnancy.”\textsuperscript{4(p.2)}

**Infantile Hypophosphatiasia**

Infantile Hypophosphatiasia usually presents initial symptoms between birth and six months. “This form … has respiratory complications due to rachitic deformities of the chest…. Hypercalcemia also is present, explaining in part a history of irritability, poor feeding, anorexia, vomiting, hypotonia, polydipsia, polyuria, dehydratation, and constipation.”\textsuperscript{3 (p.1)} Additionally, due to the surplus of calcium excretion, renal damage and renal failure may present.\textsuperscript{4(p.2)} Infants who survive the first initial onset of the symptoms generally experience remission of the problems and the long term outlook is then termed as favorable.

**Childhood Hypophosphatiasia**
Childhood Hypophosphatasia presents with a wide variety of signs and symptoms. “[It] presents with premature loss of teeth and short stature and might be associated with a delay in walking, waddling gait, and skeletal deformities.”¹ (p. 851) Additionally, symptoms may include “skeletal deformities, such as dolichocephalic skull and enlarged joints, … signs of intracranial hypertension or failure to thrive, … a history of fractures and bone pain, … [and,] focal bony defects near the ends of major long bones may be observed.”⁴ (p.2) The symptoms experienced in this type of Hypophosphatasia may begin to regress and children will often live without symptoms for a period of time, however, oftentimes symptoms will return during adulthood.

**Adult Hypophosphatasia**

Adult Hypophosphatasia is usually diagnosed in middle age. “The cardinal features being stress fractures and pseudofractures of the lower extremities.”⁴ (p.2) Additionally, affected adults may experience tooth loss and other dental problems, foot pain, and thigh and hip pain. Moreover, “Adult Hypophosphatasia is sometimes associated with a history of transient rickets in childhood and/or premature loss of deciduous teeth.”² (p.8) Adult Hypophosphatasia is distinguished from Odontohypophosphatasia by the Osteomalacia symptoms that it presents.

**Odontohypophosphatasia**

“Odontohypophosphatasia can be seen as an isolated finding without additional abnormalities of the skeletal system or can be variably seen in the above forms of Hypophosphatasia.”² (p.9) The signs and symptoms of Odontohypophosphatasia include an absence of some teeth or a premature loss of teeth. This form “affects the normal stability of teeth and may cause them to fall out.”⁵ (p. 4) While other forms of the disease may include problems with the teeth, Odontohypophosphatasia only includes the teeth and does not include other tribulations such as rickets, broken bones, or bone length abnormalities. ⁵ (p.4)

**Diagnosis**

“Hypophosphatasia is characterized by defective mineralization of bone and teeth in the context of low activity of serum and bone alkaline phosphatase.”² (p.2) There are a variety of symptoms that doctors look for in addition to the low activity and low enzyme levels that include

- Prenatal long-bone bowing
- Infantile rickets with or without elevated serum alkaline phosphatase activity
- Hypercalcemia and hypercalciuria
- Pathologic fractures
- Premature loss of deciduous teeth
- Family history \(^2\) (p. 2)

In addition to these medical and family evaluated signs, there are a number of radiographic signs. “The radiographic signs of Hypophosphatasia vary with age and type, and may be quite distinctive.” \(^2\) (p.3) In the Perinatal Lethal form, radiographs have shown images of fetuses with very little to no skeletal formation at all as shown in Figure 1. \(^6\) (p.4) Other radiographic signs include

- Osteopenia, osteoporosis, or low bone mineral content for age
- Infantile rickets
- Alveolar bone loss
- Focal bony defects of the metaphyses
- Metatarsal stress fractures
- Osteomalacia with lateral pseudofractures (Looser zones) \(^2\) (p.3) (see Figure 2).

**Treatment and Managing Symptoms**

The treatment plan for Hypophosphatasia is based on the age of the patient, the type of disease, and the symptoms the patient is experiencing. Treatment of the disease can be as mild as therapies and relaxation training or as severe as medical or surgical management. Either way, the treatment plan will be based on a rigorous and very carefully thought out plan involving both the patient and the physician.

Treatment therapies for Hypophosphatasia include transcutaneous electrical nerve stimulation (TENS,) acupuncture and acupressure, massage therapy, mind and body therapies, and relaxation training. Many of these therapies include mind and body relaxation and training to reduce pain. In acupuncture and acupressure “trained professionals use pressure or special needles that are placed gently into the skin.” \(^5\) (p. 3) Massage therapy uses hand movements to stimulate and relax the muscles although special care must be given to not put too much pressure on weak bones. \(^5\) (p. 3)
Medical treatment of the disease is very limited and experimental. Medically “supported care is generally aimed at decreasing morbidity associated with the disease.” Dr. Plotin of the University of Nebraska School of Medicine claims that children with Hypophosphatasia, or in suspicion of having the disease, should be regularly examined and injuries should be monitored closely. Adults with pseudofractures should be cared for accordingly, including receiving the required orthopedic care. Plotkin continues to say that dentists should monitor their patients with Hypophosphatasia very closely. The most encouraging medical advancements seen with the disease have included enzyme replacement therapies and donor bone fragments and marrow.

Surgical treatments and internal fixation (also known as rodding) may also be used to treat Hypophosphatasia. Surgical rodding may aid in the healing process for “fractures, pseudofractures, and bone deformities.” Additionally, “patients may need neurosurgery for craniosynostosis.”

While many of these treatments aid in pain relief for patients with Hypophosphatasia, often times they do not alleviate the symptoms and ailments of the brutal disease. “There is no cure for hypophosphatasia and no proven medical therapy…. expert dental care and physical therapy are recommended…. [the disease] is complex with different forms and a wide range of symptoms. Each patient is unique…. But being informed …can help [patients] understand when [they] need to be vigilant and what [they] might need to be prepared for.”

**Case Studies**

**Perinatal Lethal Hypophosphatasia**

Doctors at Washington University School of Medicine have identified a promising new treatment for children and infants with the most deadly forms of Hypophosphatasia. Since there is no approved medical treatment for the disease, the children were all given an experimental treatment known as ENB-0040 or asfotase alfa. The trial was small, but the results were promising.

The treatments used in the study were a man made form of the deficient enzyme in the children’s bodies. “ENB-0040 … is a manufactured form of normal alkaline phosphatase, but enhanced so that it is targeted to bone.” Studies were performed using a normal form of the enzyme, but the studies were unsuccessful. Dr. Whyte, of Washington University School of
Medicine, and his colleagues found the missing link. “Adding a short protein chain that adheres to bone allowed the alkaline phosphatase to be targeted to the skeleton.” The physicians first completed many successful tests on mice, proving that, with daily injections, the mice could live full and normal life spans.

Eleven children with confirmed cases of the disease from Shriners Hospital for Children were treated with the new compound. The children ranged in age from twenty days to three years old. “At the beginning, nine of the 11 patients had severe or extremely severe rickets; two were classified as moderate.” Most of the children were unable to breathe on their own. Additionally, the majority of children had delayed motor development and could not turn their heads without assistance or while lying down. The older children in the study, between two and three years old, were able to sit up, but not crawl, stand, or walk. “At the beginning of the study, one patient’s hand [had] almost no visible bone in an X-ray.” However, twenty-four weeks into the study the child had produced extensive bone formation in his or her hand (See figure 3.)

In conclusion of the study, nine of the eleven children had finished one year of treatments. Sadly, one child passed away due to a sudden and untreatable fever and sepsis. This was not credited to the treatments, but to other unanticipated reasons. One child withdrew from treatments. The remaining nine children all had drastic improvements of their symptoms. “One progressed to moving all limbs against gravity, one to sitting unsupported, two could crawl, one pulled to standing, and two started taking steps. Of the two older children who could only sit, both progressed to walking after a year of treatment.” The remaining nine children continue to receive treatments in an extension study.

**Odontohypophosphatasia**

In a case report of a child with odontohypophosphatasia, a four-year-and-eight-month-old girl presented with exfoliation of the anterior incisors and canine’s only months after her teeth came in. Reportedly, she was the second child of healthy parents. The child’s developmental checkups were within normal ranges, but her height on her physical examination was slightly less than normal. She had no history of a delay in walking, and there were no presence of waddling, bone pain, or fractures to be noted. “The physical examination was unremarkable, other than the absence of the upper and lower anterior incisor and canine teeth without any bone and joint deformity.” Upon further medical evaluation, it was found that she had a very
low ALP level, which is indicative of hypophosphatasia. Further noted, both of her parents were heterozygous for the same abnormally low ALP levels. A bone age x-ray of the child’s wrist also indicated a child of three years old, not four. Additionally, “dental x-rays showed a reduced alveolar bone and enlarged pulp chambers and root canals.”

Differing classifications of hypophosphatasia, and differing severities of the disease, range from benign to lethal depending on the symptoms patients present with. While the patient in this study presented with a much more mild form of odontohypophosphatasia, the resulting prognosis proved to be one of the more severe cases. The severity increased due to the presence of a mild metaphyseal bone defect, osteopenia, short stature, and the “mild phenotype of [the patient] may reflect the role of other factors such as modifier genes and epigenetics and/or environmental factors.”

Additionally, while not as severe as the perinatal lethal, infantile, childhood, or adult forms, her case proved to be more severe than originally considered due to the presence of the disease in both her parents genes. Further studies could still prove helpful.

Conclusion

Hypophosphatasia and its devastating symptoms affect one in every hundred thousand babies born. In Canada the disturbing disease effects as many as one in every twenty-five hundred babies born. While there are promising new advancements in the search to find a cure, the cure itself is still just out of reach.

Hypophosphatasia attacks in many forms. The worst form of the disease presents itself as Perinatal Lethal Hypophosphatasia, in which a child will likely not even survive long enough to be born. This is due to a lack of ability for the body of the child to produce or absorb the enzyme alkaline phosphatase. “Based on clinical presentation, [Hypophosphatasia] can be mistakenly diagnosed as other skeletal diseases, but a low alkaline phosphatase is an important, distinguishing sign of this condition.”

Alkaline phosphatase enables bones to mineralize, and a lack of it, is a fundamental characteristic of all forms of the disease. Other forms, while not as severe, emerge at any age. Children may form Rickets from birth to six months, adults may begin to sporadically lose bone density at any age, or middle aged persons may begin to have stress and pseudofractures of the lower extremities. The least severe form of the disease only affects the teeth of adults and children alike. Although there are many forms that present
symptoms of many kinds, they are all devastating. More research must be done and more tests must be performed, but a cure to this rare disease would be miraculous.
References


Figures and Captions

Figure 1. Image of a baby aborted during the third trimester of pregnancy. The features of the image are 1) An absence of ossification of the facial and skull bones 2) small triangular scapulae and small irregular pelvic bones 3) short thin ribs and metaphyseal ossification defects. All features of the image caused by Perinatal Lethal Hypophosphatasia. Image courtesy of Hong Kong Journal of Medicine: Lam ACF, Lam CW, Tang MHY, Chu JFY, Lam STS, et al. A case of perinatal lethal form of hypophosphatasia; and review of literatures. Hong Kong J Pediatr. 2006;11:341-346.