Soft Bones Canada

Hypophosphatasia:
An Overview

Cheryl Rockman-Greenberg
MDCM, FRCPC, FCCMG

This publication is distributed by
Soft Bones Canada Inc. 2016

Hypophosphatasia [hi”po-fos”fah-ta´zhah]

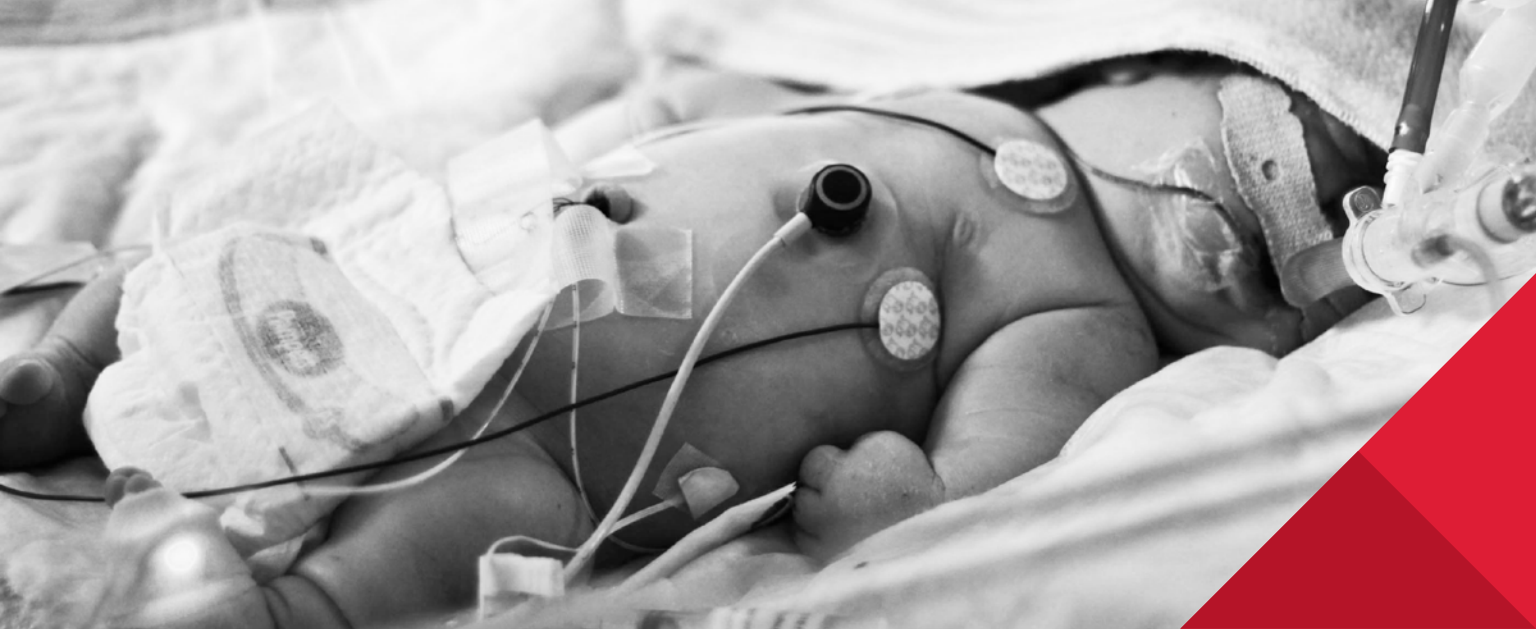
An inborn error of metabolism marked by abnormally low tissue nonspecific alkaline phosphatase (TNSALP) activity. The main manifestation is rickets in infants and children, and osteomalacia in adults.

Clinical Types of HPP

HPP can be classified into six subtypes based on age at onset of signs or symptoms:

1. Perinatal Hypophosphatasia
2. Infantile Hypophosphatasia
3. Childhood Hypophosphatasia
4. Adult Hypophosphatasia
5. Odontohypophosphatasia
6. Benign Prenatal Hypophosphatasia

The severity of the disease and the clinical manifestations are on a continuum with variation within and between families ranging from death in utero due to skeletal hypomineralization to poor dentition and loss of teeth in adulthood with no skeletal involvement. HPP is often classified according to age at onset of symptoms which usually inversely correlates with severity i.e. as a general rule the younger the age of onset the more severe the disease.



Physical Signs and Symptoms of Hypophosphatasia

1. Perinatal Hypophosphatasia

Perinatal hypophosphatasia can typically be identified in utero with prenatal ultrasound, right at the time of birth, or very soon after. This is the most severe form of HPP and has traditionally not been compatible with life. Although HPP can be suspected in utero on a routine ultrasound, additional tests would need to be done in pregnancy to confirm the diagnosis as there are many causes of abnormalities in the developing skeleton of a fetus that can be confused with HPP. A baby with the perinatal form of HPP could be stillborn or, until recently, was able to live sometimes only a few hours or days succumbing to respiratory compromise caused by hypoplastic lungs and very small chest. At birth, shortened bent limbs, soft skull, and osteochondral (Bowdler) spurs protruding from the long bones may be present. The infant may present with pyridoxine (B6)-dependent seizures because of an inability to form the active form of vitamin B6 due to the lack of TNSALP activity. The presence of B6-responsive seizures has been a very poor prognostic sign for survival and, overall, long-term survival is rare.

Physical Signs and Symptoms (CONTINUED)

2. Infantile Hypophosphatasia

If HPP does not present in the perinatal period, it can present before the age of 6 months. This is known as infantile HPP. Babies with infantile HPP may seem normal at birth but gradually there is the onset of poor feeding, failure to thrive, hypotonia, signs of rickets and sometimes seizures. Muscle weakness and delayed motor development are often seen and fractures may occur which may lead to pneumonia when they involve the ribs and the chest wall. Often patients with infantile HPP manifest seizures which specifically respond to high dose of pyridoxine/vitamin B6. But even though seizures respond to high dose vitamin B6, the prognosis of infantile HPP has been dismal. Initially the cranial sutures appear wide due to hypomineralization of the skull, however patients with infantile HPP, in spite of being a disorder of bony mineralization, sometimes develop premature fusion of the cranial sutures (craniosynostosis). Neurosurgical procedures to open the bony sutures of the skull are sometimes necessary if there are symptoms and signs (severe vomiting and headache or a changing level of consciousness) of increased intracranial pressure with abnormal appearance of the optic nerves and distinct changes on skull X-ray. A flail chest, due to fracture from rachitic deformity, predisposes an infant to respiratory compromise and pneumonia. Infants with HPP may also suffer from hypercalcemia and hypercalciuria causing malaise, severe vomiting, nephrocalcinosis, and renal compromise. Radiographs show transition from relatively normal appearing diaphyses (shafts of the long bones) to uncalcified metaphyses (ends of long bones), indicating a metabolic change characteristic of rickets. Global statistics indicate the onset of HPP in infants less than 6 months of age has traditionally been associated with mortality between 50-100%.

3. Childhood Hypophosphatasia

Childhood (juvenile) onset HPP occurs after 6 months of age, and prior to 18 years of age. Initial diagnosis often occurs after premature loss of deciduous teeth, usually well before the age of five. Because of the lack of acellular cementum covering tooth roots, the teeth painlessly slide out from tooth sockets with the root intact, and without bleeding. Typically the anterior teeth are most affected. Dental radiographical findings show enlarged pulp chambers and root canals ("shell teeth"). The progress for permanent dentition is better, though problems continuing into adulthood are common.

Other physical characteristics can include short stature, delayed walking, and a characteristic waddling gait due to muscle weakness (myopathy). Stiffness, swelling, and pain in joints and muscles is common. Signs of rickets are often present; bowed legs, knock knees, enlarged wrists, knees, and ankle joints, as well as beading of the costochondral junctions on the ribs. Defects of the cartilage at the end of long bones present as radiolucent "tongues" projecting from the rachitic growth plates into the metaphyses.

Physical Signs and Symptoms (CONTINUED)

4. Adult Hypophosphatasia

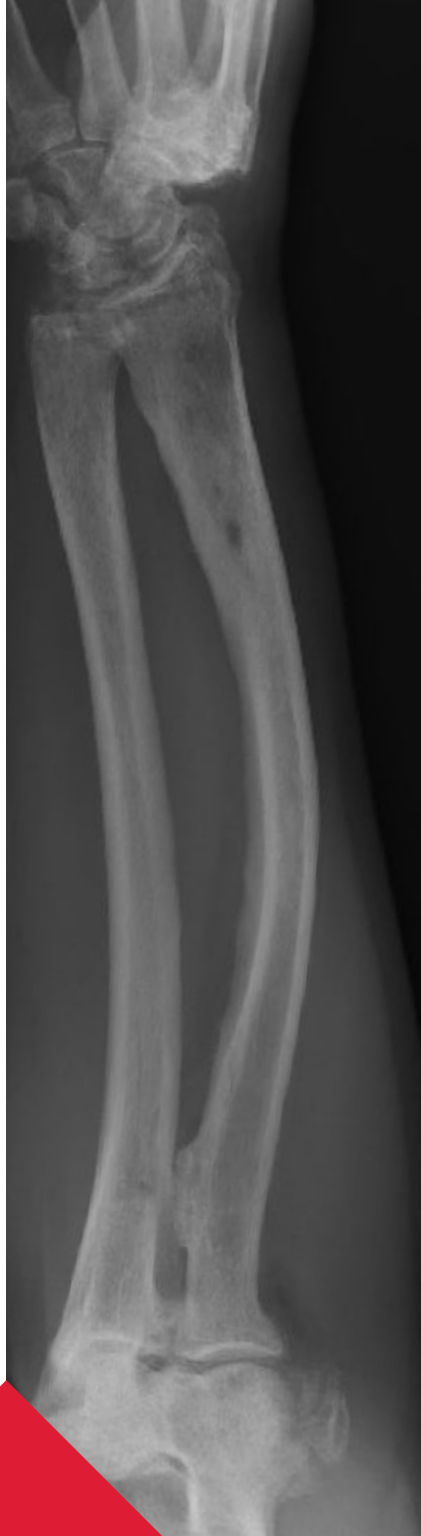
If the disease does not present in childhood it can present in adulthood, typically during middle age where adults can develop recurring metatarsal stress fractures and femoral pseudofractures in the thighs and hips. Fractures tend to heal poorly and orthopaedic surgery with intramedullary fixation - load sharing rods or nails - is almost always necessary for stabilization. Significant bone pain, arthritis caused by calcium phosphate crystal deposition, and frequent poorly healing fractures can lead to immobility. Often an adult patient will recall premature loss of deciduous teeth as a child.

5. Odontohypophosphatasia

This is the least severe form of HPP, and affects only the teeth. As in childhood HPP, the premature, spontaneous loss of fully rooted deciduous teeth results from failure of the cementum to form on tooth roots. Teeth also present with severe carries, enlarged pulp chambers and root canals.

6. Benign Prenatal Hypophosphatasia

Differing from perinatal HPP, benign HPP is not fatal. These patients show bowing deformity *in utero*, but postnatally show spontaneous skeletal improvement. Initially it may be difficult to differentiate from severe perinatal hypophosphatasia, but there is often a positive family history of a parent being affected and serial ultrasounds may show spontaneous improvement.



Hypophosphatasia at a Glance

FEATURE	PERINATAL	INFANTILE	JUVENILE	ADULT
Age of Onset	*In utero/at birth*	*<6 months of age*	*6 months-18 years*	*>18 years*
Clinical Signs & Symptoms	Apnea	Craniosynostosis	Muscle/bone pain	Abnormal dentition
	Fractures	Failure to thrive	Hypomineralization	Adult tooth loss
	Hypomineralization	Fractures	Low bone mineral density	Chondrocalcinosis
	Long bone deformity	Hypercalcemia/ hypercalciuria	Missed motor milestones	Muscle/bone pain
	Osteochondral spurs	Hypomineralization	Muscle weakness	Hypomineralization
	Poorly ossified epiphyses	Hypotonia	Poorly healing/ recurrent fractures	Osteoarthropathy
	Radiolucencies into metaphysis	Nephrocalcinosis	Premature tooth loss	Osteomalacia
	Severe chest deformity	Poor feeding/weight gain	Rachitic disease	Pseudofractures/ fractures
	Stillbirth	Premature deciduous tooth loss	Short stature	Pseudogout
	Vitamin B6-responsive seizures	Pulmonary insufficiency	Skeletal deformity	

Adapted from: Simmons (2013, p2).

Diagnostic Testing

TNSALP

A diagnosis of HPP can reliably be made when taking into account the clinical history, radiographic changes, and physical findings in conjunction with serum TNSALP activity that is below normal for patient's age and gender. It should be emphasized that the lab values must be age- and gender-adjusted for accuracy. The TNSALP level of unaffected infants, children, and adolescents is higher than that of an adult, so when an abnormally low result is found it can be misread as normal if compared to the normal adult range of TNSALP. Low serum TNSALP levels can be detected from umbilical cord blood when diagnosing perinatal and infantile HPP.

Lowest Normal Range for Gender & Age Total Serum or Plasma ALP Activity (U/L)

AGE	MALE	FEMALE
<1 month	60	60
1-11 months	70	70
1-3 years	125	125
4-11 years	150	150
12-13 years	160	110
14-15 years	130	55
16-19 years	60	40
>20 years	40	40

Adapted from: ARUP Laboratories. Alkaline phosphatase isoenzymes, serum or plasma: 0021020. Available at: http://ltd.aruplab.com/tests/pub/0021020

Elevated Plasma PLP/B6 levels

The most sensitive substrate marker for hypophosphatasia is an increased pyridoxal 5'-phosphate (PLP) plasma level. Often the lower the TNSALP level, the higher the PLP level will be.

Elevated Serum or Urinary PEA

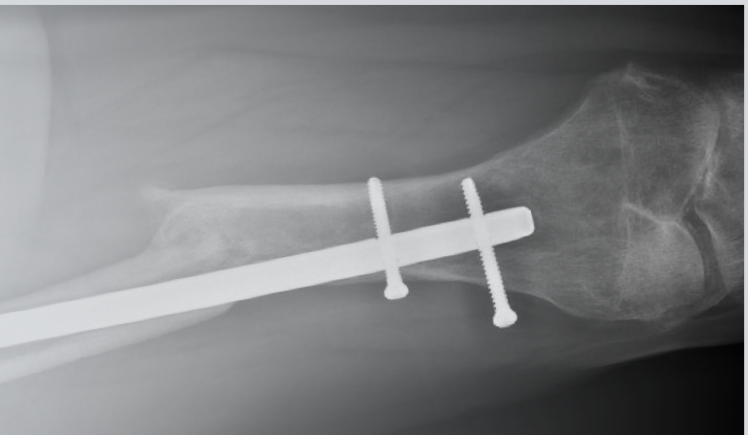
As phosphoethanolamine (PEA) is also an endogenous substrate for TNSALP, increased serum and urinary levels of phosphoethanolamine (PEA) are also observed in most HPP patients, and can be found on a random urine sample. An abnormally high finding can be indicative of several other metabolic disorders and should not be used in isolation to diagnose HPP and a normal level does not exclude the diagnosis.

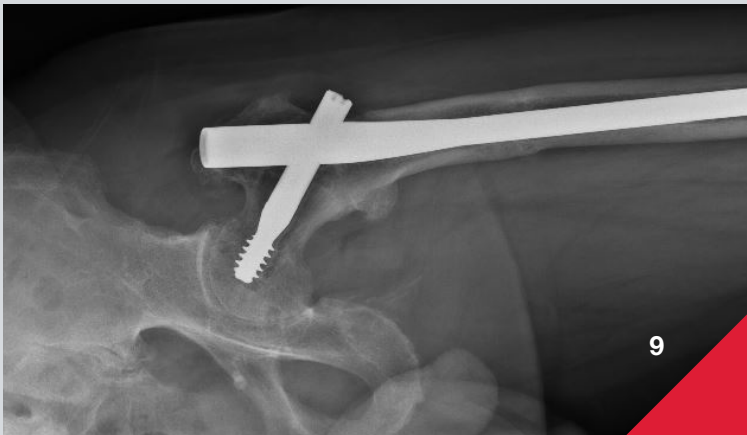
Elevated Pyrophosphate (PPi)

Elevated levels of PPi are also characteristic of HPP but most labs do not offer this as a diagnostic test.

Radiographs

Radiologic evidence of skeletal defects is found in nearly all patients and includes hypomineralization, rachitic changes, incomplete vertebrate ossification and occasionally, lateral bony spurs on the ulnae and fibulae.





Genetic Testing

If a diagnosis of HPP is suspected, a health care professional who has experience with the disease should be consulted. This often includes a geneticist and a genetic counselor. If the history, physical examination, blood, urine, and X-ray results suggest this diagnosis, blood tests may be recommended for the parents or other family members. DNA testing looking for diagnostic mutations in the ALPL gene may also be recommended, but DNA testing is not essential to make the diagnosis of HPP.

Medical Treatment

Recently enzyme replacement therapy with human recombinant bone-targeted alkaline phosphatase, known as asfotase alfa, has been authorized by Health Canada for treatment of pediatric-onset HPP. In clinical trials, after 3 to 5 years of treatment, patients with early onset HPP have shown marked improvement with asfotase alfa with a very good safety profile. For further information please refer to the Health Canada website **www.hc-sc.gc.ca.**

Prior to this there was no approved medical treatment for hypophosphatasia. Some physicians have prescribed, “off label”, a medication (teriparatide) used to treat osteoporosis in the hope that the HPP patient may benefit by producing more ALP in their bones. However, teriparatide is restricted for use in adults, it is not used in children, and results have not been promising. As well, drugs like the bisphosphonates used to treat osteoporosis (alendronate, risedronate, ibandronate, pamidronate, zolendronate) may actually unmask or worsen the osteomalacia of adults with HPP and are contraindicated.

Referrals

If you suspect one of your patients has HPP you can make a referral to:

Cheryl Rockman-Greenberg
MDCM, FRCPC, FCCMG

Program in Genetics and Metabolism, WRHA
Phone: 204.787.4681
Fax: 204.787.1419
Email: cgreenberg@exchange.hsc.mb
Cooperation: Winnipeg Children's Hospital

Sources

Plotkin, H. B. (2015). *Hypophosphatasia*. Medscape. Retrieved from *http://emedicine.medscape.com/article/945375-overview*

Rockman-Greenberg C. Hypophosphatasia. *Pediatr Endocrinol Rev.*2013;10(Suppl 2):380-388

Simmons, JH. (2013) Best Practices in: Recognizing and Diagnosing Hypophosphatasia. *Clinical Endocrinology News.* Retrieved from *www.clinicalendocrinologynews.com/resources/best-practices.html*

Whyte, M. (2013). Hypophosphatasia: An Overview. *Soft Bones Canada*. 2-12.

Soft Bones
Canada

Soft Bones Canada
PO Box 23520 Prairie Mall
Grande Prairie, AB T8V 7G7
TOLL FREE 1.844.255.8477

EMAIL **contactus@softbonescanada.ca**
www.softbonescanada.ca