DR. JEFF C.H. DONOVAN

DERMATOLOGIST, SPECIALIZING IN HAIR LOSS

4370 Lorimer Road
Suite 334B
Whistler, BC, Canada
V8E 1A6

Tel: 604.283.1887
Fax: 604.648.9003
Email: office@donovanmedical.com
Web: www.donovanmedical.com

Hypophosphatasia (HPP)

Hypophosphatasia (HPP) is an inherited metabolic disease caused by mutations in a gene known as the tissue non-specific alkaline phosphatase (*TNAP*) gene. The result of this mutation is low activity of tissue non-specific alkaline phosphatase (TNAP). This is sometimes simply called alkaline phosphatase (ALP).

As a result of this enzyme not functioning properly, there is an accumulation of "substrates" that would normally have been broken down or changed by the body. Due to the poorly functioning ALP, these substrates build up in the body. One of the important issues that happens in HPP is the inability to breakdown a chemical known as inorganic pyrophosphate. ALP is the enzyme that normally breaks down inorganic pyrophosphate into inorganic phosphate. This step is so important because inorganic phosphate is needed to form bones. As a result of this process not happening properly, calcium and phosphate can't be properly combined to form hydroxyapatite – the key ingredient in bone. Bone strength comes from the deposition of hydroxyapatite crystals. This leads to an impairment in bone formation and weak bones. Many children and adults with HPP have bone fractures.

Severe forms of HPP are uncommon. Some studies have suggested incidence rates of 1 in 100,000 newborns to 1 in 300,000. However milder forms of HPP are known to be underdiagnosed and some have suggested rates as high as 1 in 6000. Although experts can't agree on exactly how common HPP is, there is one thing they can agree on: there are a lot of people out there in the world who are not being diagnosed.

There are many different way that HPP can present, including perinatal forms, childhood forms and adults forms. Presentation are diverse and can range from death in utero (during pregnancy) to patients who are completely asymptomatic. It's important to be aware that there is not just one form of HPP or one classical patient that serves as an example for HPP. There are many, many forms. In adults, HPP can range from a patient with many fractures to a patient with a few dental problems and consistently poor sleep or muscle pain.

A High Index of Suspicion is Needed for HPP

HPP does not directly cause hair loss. However, we have helped diagnose a 4 patients with HPP simply by an awareness of a simple rule "*patients with persistently low ALP often benefit from further investigation by an endocrinologist, genetics specialist or specialist in these metabolic issues.*"

Most often in our clinic, we come to wonder about patients with mild forms of HPP who have never been diagnosed but share common features. These include a low ALP level in the blood plus one or more of the following:

1. A history of bone fractures – wrist, ankle, hip
2. A history of dental issues including premature bone loss, abnormal dentition and periodontitis
3. A history of musculoskeletal issues including rickets/osteomalacia, bowed legs, muscle weakness or muscle pain, joint pain, fatigue, and fibromyalgia like presentations
4. A history of short stature
5. A history of CPPD and pseudogout
6. A history of kidney stones (nephrocalcinosis) and renal damage

Other features are also supportive including:

1. a history of depression, anxiety
2. A history of neuropathy
3. A history of hearing loss
4. A history of sleep disturbances

Bone and Dental Problems are The Most Common Symptoms of HPP

It's easy to see that HPP has a variety of manifestations. Bone problems are the most common followed by dental problems and muscle problems.

In one study by Colazo JM et al 2019 Seventy-four percent had a family history of bone disease, while 17% had a family history of neurologic disease. Bone problems occurred in 89%, dental problems in 77%, and muscle problems in 66%. Fatigue occurred in 66%, headache in 61%, sleep disturbance in 51%, gait change in 44%, vertigo in 43%, depression in 39%, anxiety in 35%, neuropathy in 35%, and hearing loss in 33%.

CLASSIFICATION of HPP

HPP has six main forms. These are based on age of onset, severity and clinical manifestations. The forms include 1) a benign perinatal HPP, 2) perinatal HPP 3) infantile HPP 4) childhood HPP 5) adult HPP and 6) OndonalHPP.

Adult Hypophosphatasia (HPP)

We will focus here on adult HPP. *It's often the find finding of low ALP with concerns such as musculoskeletal pain and/or bone fractures and/or dental issues that trigger the clinician to at least consider HPP.*

Musculoskeletal pain is a common complaint and may be present in 40-75% of patients. The site of pain include feet, ankle, knee, thigh, hip, and back. There may be joint swelling and pain or even diffuse pain. Some patients have a long history of just not being able to participate in sports and leisure activities like others. *Foot pain is common.*

Many patients with HPP have a history of broken bones. In fact, this findings is present in up to 50% of patients with HPP and some even have a history of more than one fracture. The sites of fracture include the feet (a specific type of fracture called a metatarsal stress fracture), femur/hip, wrist, and vertebrae - but other sites can occur as well. A particularly important point to note about HPP is that the fractures often heal slowly and poorly. These patients often find that their surgeries to fix the fractures (such as fracture fixation, screws, plates) often fail and sometimes joint replacement surgery ends up now being a success. Patients with low ALP and a history of unexpectedly poor surgical outcomes or unexpectedly poor healing of fractures must raises the suspicion for HPP.

Patients with HPP have weak bones. We're reviewed above that calcium and inorganic phosphate must can't combine properly to form hydroxyapatite. However, what is surprising is that bone mineral density can be low, normal or high. The key is that the quality of the bone is not always ideal.

Teeth are commonly affected in HPP so dentists come to be aware of HPP too. Some patients experience an early loss of adult teeth. Other features like periodontitis may be present. Patients with low ALP and a history of gum grafts must trigger suspicion.

On account of the inability to break down pyrophosphate, some patients develop a condition called "pseudogout." This is a condition that occurs due to deposition of calcium pyrophosphate dihydrate (CPPD) crystals in joints. Patients may have reduced mobility in the ankles or other ligaments due to ossification of ligaments (syndesmophytes). Enthesopathy and calcific periarthritis can occur. Patients with low ALP along with joint pain and 'tendon issues" and "ligament issues" must be evaluated for HPP.

Patients with HPP may also have a range of other symptoms. These include headaches, fatigue, abnormal gait, poor sleep. Some patients with poor sleep and fatigue and joint pain go many years diagnosed as the condition fibromyalgia before someone recognizes the low ALP levels and pieces together the diagnosis.

The Low ALP Blood Test: What Else Can Cause Low ALP?

HPP is not the only condition that causes low ALP. That's a very important point for patients and physicians. Evaluating HPP can be complex. That's why proper evaluation by a physician with expertise in diagnosis of HPP is so important. Here are some conditions that cause low ALP levels:

1. Endocrine diseases
    - Cushing, hypothyroidism
2. Dietary issues
    - Starvation, vit C, D, zinc, magnesium deficiency
    - Vit D intoxication
    - Others
3. Metabolic bone diseases
    - Osteogenesis imperfecta (type2), hypophosphatasia
    - Others
4. Hematological Conditions
    - Severe anemia, pernicious anemia,
    - Multiple myeloma
    - Massive blood transfusion
    - others
5. Improper blood collections

6. Other conditions
    - Wilson disease, hemochromatosis, celiac disease, heavy metal intoxication
7. Drugs
    - Bisphosphonates, chemotherapy
    - Tamoxifen, clofibrate, glucocorticosteroids
    - Denosumab

Source: **Tournis et al. Hypophosphatasia. J Clin Med 2021 Dec; 10(23):5676**

BLOOD TESTS

Blood tests are probably best ordered by a specialist with expertise in HPP. However, I often order a variety of tests myself to help facilitate the referral and increase the suspicion that HPP may actually be present. For otherwise healthy adults, it's sometimes difficult to get anyone to believe that this could actually be diagnosis. Without these tests, it's often difficult to convince others that HPP may be a diagnosis worth looking into.

Here are the tests I order. I have patients stop all vitamins for 1-2 weeks before having these tests done.

1. ALP
2. AST, ALT bilirubin
3. Ferritin and anti TTG
4. Vitamin B6 and vitamin B12
5. Calcium and 25 hydroxyvitamin D, Phosphate
6. PTH, if indicated
7. TSH
8. Ascorbic acid
9. Magnesium and Zinc
10. AM cortisol
11. Glucose
12. Hemoglobin A1c
13. Creatinine
14. Urinary calcium (if needed) – not usually helpful.
15. *Copper and ceruloplasmin (if appropriate)*
16. *Tests such as* PLP · *Pyridoxal 5-Phosphate may be ordered in specialty centers but not typically available to most physicians.*

In general, a persistently low ALP level on two or more occasions (less than 40 U/L) <u>with</u> the right clinical story along with confidence that other diseases have been <u>ruled out</u> increases the likelihood that HPP may be present.

In children, evaluation for conditions like rickets is quite important. Parameters of calcium metabolism, including blood tests for calcium, phosphate, PTH and vitamin D (both 25-hydroxy and 1,25-dihydroxy) are usually within normal range in patients with HPP but provide help in the differential diagnosis from rickets. Hypercalciuria is often discussed in HPP and sometimes there can be hypercalcemia and hyperphosphatemia with hypophosphaturia but levels of these largely vary and are not helpful for diagnosis.

GENE TESTING

HPP is most commonly caused by heterozygous or compound heterozygous mostly missense (about 74%) mutations at the *ALPL* gene . This testing is left up to the specialist and not something that I order.

TREATMENT

Diagnosis of HPP is important for several reasons.

First, proper diagnosis may help get patients connected with the right experts in the event of poorly healing fractures or if osteoporosis is present. It's now appreciated that typical treatments for osteoporosis like bisphosphonates are not the ideal treatment for HPP associated osteoporosis and may worsen outcomes.

There is much research on fracture healing strategies for patients with HPP. These include bone-targeted therapies such as teriparatide (TPTD), a recombinant parathyroid hormone. This drug is approved for the treatment of osteoporosis and may help reduce bone pain and speed up the healing of fracture and pseudofractures in adults with HPP.

Enzymes treatment with asfotase alfa is more common in pediatric patients but is being studied in adults with severe fractures.

Second, many adults with HPP have been misdiagnosed with other conditions and having a diagnosis of HPP offers validation for their symptoms. Some patients with HPP are diagnosed with depression, sleep disorders, joint problems, fibromyalgia and more. Getting an accurate diagnosis helps people heal in many aspects of the disease.

Third, HPP is thought by experts to be more common than realized. It's possible that HPP gets passed down from one generation to another and manifestations may be different from generation to generation. In autosomal recessive forms, it's possible that two parents with HPP who don't know they have HPP could have a child with severe forms of perinatal, infantile or childhood HPP. Getting the diagnosis of HPP as early as possible in an adult, will help allow for appropriate genetics counseling in the event that a patient with HPP wishes to have children.

REFERENCES

Colazo JM et al. Neurological symptoms in Hypophosphatasia. Osteoporos Int. 2019 Feb;30(2):469-480.

Conti F et al. Hypophosphatasia: clinical manifestation and burden of disease in adult patients. Clin Cases Miner Bone Metab. 2017 May-Aug; 14(2): 230–234