Definition

Hypophosphatasia (HPP) is an inherited metabolic (chemical) bone disease that results from low levels of an enzyme called alkaline phosphatase (ALP). Enzymes are proteins that act in the body's chemical reactions by breaking down other chemicals. ALP is normally present in large amounts in bone & in the liver. In HPP, abnormalities in the gene that makes ALP lead to production of inactive ALP. Subsequently, several chemical – including Phosphoethanolamine, phridoxal 5'-phosphate (a form of vitamin B6) and inorganic phrophosphate- accumulate in the body and are found in large amounts in the blood and urine. It appears that the accumulation of inorganic pyrophosphate is the cause of the characteristic deficient calcification of bones in infants and children (rickets) and in adults (osteomalacia).

Nevertheless, the severity of HPP is remarkably broad-ranging from patient-to-patient. The most severely affected, fail to for a skeleton in the womb and are stillborn. The most mildly affected patients may show only low levels of ALP in the blood, yet never suffer bony problems.

In general, patients are categorized as having "perinatal", "childhood", or "adult" HPP depending on the severity of the disease which in turn is reflected by the age at which bony manifestations are first detected. *Odonto*hypophosphatasia refers to children and adults who have only dental, but not skeletal problems (premature loss of teeth).

The x-ray changes are quite distinct to the trained eye. Similarly, the diagnosis of HPP is largely substantiated by measuring ALP in the blood (a routine test) that is low in HPP together with measuring vitamin B6 that is high. However, it is important that the doctors use appropriate age ranges for normal when interpreting an ALP level. Now, gene testing for HPP is readily available.

Prevalence

It has been estimated that severe forms of HPP occur in approximately one per 100,000 live births. The more mild childhood and adult forms are more common. About one out of every 200 individuals in the United States may be a "carrier" for HPP.

Prognosis

The outcome following a diagnosis of HPP is variable. In general, the earlier the diagnosis is made the more severe the skeletal manifestations. Cases with severe deformity at birth almost always have a lethal outcome within days or weeks. Other patients with mild manifestation of HPP at birth can do very well. When the diagnosis is made before six months of age, some infants have a downhill and fatal course while others survive and may even do well. When diagnosed during childhood, there can by presence or absence of skeletal deformity from underlying rickets, but premature loss of teeth (less than five years of age) is common. Adults may be troubled by recurrent fractures in their feet & painful, partial fractures in their thigh bones.

Symptoms

Depending on the severity of the skeletal disease, there may be deformity of the limbs and chest. Pneumonia can result if chest distortion is severe. Recurrent fractures can occur. Teeth may be lost prematurely, have wide pulp (inside) chambers, and thereby be predisposed to cavities.

Inheritance Factors

The severe perinatal and infantile forms of HPP are inherited as autosomal recessive conditions. The patient receives one defective gene from each parent. Some more mild (childhood or adult) HPP cases are also inherited this way. Other mild adult and odontohypoposphatasia cases seem to be inherited in an autosomal dominant pattern (the patient gest just one defective gene, not two, transmitted from one of his/her parents). In this form, mild HPP can occur from generation-to-generation. The perinatal form of reoccurrences of HPP can often be detected during pregnancy by ALP gene mutation analysis.

Individuals with HPP and parents of children with HPP are encouraged to seek genetic counseling to explain the likelihood and severity of HPP recurring in their families.

Treatments

As yet, there is o cure for HPP and no proven medical therapy. Some medications are being evaluated, and a form of ALP replacement is promising as safe and effective in both infants and children. Treatment is generally directed towards preventing or correcting the symptoms or complications.

Expert dental care and physical therapy are recommended. An orthopaedic procedure called "rodding" may be especially helpful for adults with painful partial fracture in their thigh bones. Severely affected infants may manifest increased levels of calcium in their blood that may be treated with calcitonin and certain diuretics. Doctors should avoid the temptation to give calcium supplements or vitamin D unless there is a clear-cut deficiency.

HYPOPHOSPHATASIA

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