

The MAGIC Foundation[®]

Hypophosphatasia

Definition

Hypophosphatasia 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 and liver. In hypophosphatasia, abnormalities in the gene that makes ALP lead to production of inactive ALP. Subsequently, several chemicals -including phosphoethanolamine, pyridoxal 5'-phosphate (a form of vitamin B6) and inorganic pyrophosphate - 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 defective calcification of bones in infants and children (rickets) and in adults (osteomalacia).

Nevertheless, the severity of hypophosphatasia is remarkably variable from patient-to-patient. The most severely affected fail to form 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" hypophosphatasia depending on the severity of the disease, which in turn is reflected by the age at which bony manifestations are first detected. Odontohypophosphatasia 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 hypophosphatasia is largely substantiated by measuring ALP in the blood (a routine test) that is low in Hypophosphatasia. However, it is important that the doctors use appropriate age ranges for normals when interpreting an ALP level.

Prevalence

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

Prognosis

The outcome following a diagnosis of hypophosphatasia is very variable. In general, the earlier the diagnosis is made the more severe the skeletal manifestations. Cases detected in the womb or with severe deformity at birth almost always have a lethal outcome within days or weeks. When the diagnosis is

made before six months of age, some infants have a downhill and fatal course, others survive and may even do well. When diagnosed during childhood, there can be presence or absence of skeletal deformity from underlying rickets, but premature loss of teeth (less than five years of age) is the most common manifestation. Adults may be troubled by recurrent fractures in their feet and 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 hypophosphatasia are inherited as autosomal recessive conditions. The patient receives one defective gene from each parent. Some more mild (childhood or adult) hypophosphatasia cases are also inherited this way. Other mild adult and odonto hypophosphatasia cases seem to be inherited in an autosomal dominant pattern (the patient gets just one defective gene, not two, transmitted from one of his/her parents). In this form, mild hypophosphatasia can occur from generation-to-generation. The perinatal form of hypophosphatasia can often be detected during pregnancy by ultrasound and by measuring ALP activity in chorionic villus samples from amniocentesis.

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

Treatments

As yet, there is no cure for hypophosphatasia and no proven medical therapy. Some medications are being evaluated. 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 fractures 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 clear-cut deficiency.

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