Phenylketonuria

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Synonyms of Phenylketonuria

- classical phenylketonuria
- hyperphenylalanemia
- phenylalanine hydroxylase deficiency
- phenylalaninemia
- PKU

General Discussion

Phenylketonuria (PKU) is an inborn error of metabolism that is detectable during the first days of life via routine newborn screening. PKU is characterized by absence or deficiency of an enzyme called phenylalanine hydroxylase (PAH), responsible for processing the amino acid phenylalanine. Amino acids are the chemical building blocks of proteins, and are essential for proper growth and development. With normal PAH activity, phenylalanine is converted to another amino acid, tyrosine. However, when PAH is absent or deficient, phenylalanine accumulates and is toxic to the brain. Without treatment, most people with PKU would develop severe intellectual disability. To prevent intellectual disability, treatment consists of a carefully controlled, phenylalanine-restricted diet beginning during the first days or weeks of life.

Signs & Symptoms

Infants with PKU typically appear normal at birth. With early screening and dietary treatment, affected individuals may never show symptoms of PKU. However, untreated newborns not diagnosed in the first days of life may be weak and feed poorly. Other symptoms may include vomiting, irritability, and/or a red skin rash with small pimples. Developmental delay may be obvious at several months of age. The average IQ of untreated children is usually less than 50. Intellectual disability in PKU is a direct result of elevated levels of phenylalanine in the brain which causes the destruction of the fatty covering (myelin) of individual nerve fibers. It can also cause depression by reducing brain levels of dopamine and serotonin (neurotransmitters).

Untreated infants with PKU tend to have unusually light eye, skin, and hair color due to high phenylalanine levels interfering with production of melanin, a substance that causes pigmentation. They may also have a musty or “mousy” body odor caused by phenyl acetic acid in the urine or sweat.

Neurological symptoms are present in some untreated patients with PKU, including seizures, abnormal muscle movements, tight muscles, increased reflexes, involuntary movements, or tremor.

Untreated females with PKU who become pregnant are at high risk for having a miscarriage or problems with fetal growth (intrauterine growth retardation). Children of women with untreated

PKU may have an abnormally small head (microcephaly), congenital heart disease, developmental abnormalities, or facial abnormalities. There is a strong relationship between the severity of these symptoms and high levels of phenylalanine in the mother. As a result, all women with PKU who have stopped treatment should resume treatment before conception and continue on it throughout pregnancy, managed by a metabolic geneticist and dietician.

Causes

PKU is inherited in an autosomal recessive pattern. Recessive genetic disorders occur when an individual inherits an abnormal gene from each parent. If an individual receives one normal gene copy and one abnormal gene copy, they will be a carrier for the condition, but will not have symptoms. The risk for two carrier parents to both pass the abnormal gene and, therefore, have an affected child is 25% with each pregnancy. The risk is the same for males and females.

More than 300 different changes (mutations) in the PKU gene have been identified. Because the different mutations result in varying degrees of PAH enzyme activity, and therefore varying degrees of phenylalanine elevation in blood, the diet of each child must be adjusted to the individual's specific phenylalanine tolerance.

Affected Populations

The reported incidence of PKU from newborn screening programs ranges from one in 13,500 to 19,000 newborns in the United States. PKU affects people from most ethnic backgrounds, although it is rare in Americans of African descent and Jews of Ashkenazi ancestry.

Standard Therapies

Treatment

The goal of treatment for PKU is to keep plasma phenylalanine levels within 120-360 umol/L (2-6 mg/dL). This is generally achieved through carefully planned and monitored diet. Limiting the child's intake of phenylalanine must be done cautiously because it is an essential amino acid. A carefully maintained diet can prevent intellectual disability as well as neurological, behavioral, and dermatological problems. Treatment must be started at a very young age or some degree of intellectual disability may be expected. However, even some late-treated children have done quite well. Studies have repeatedly demonstrated that children with PKU who are treated with a low phenylalanine diet before the age of three months do well, with an IQ in the normal range.

If people with PKU stop controlling their dietary intake of phenylalanine, neurological changes usually occur. IQs may decline. Other problems that may appear and become severe once dietary regulation is stopped include difficulties in school, behavioral problems, mood changes, poor visual-motor coordination, poor memory, poor problem-solving skills, fatigue, tremors, poor concentration, and depression.

After years of controversy, there now is nearly universal acceptance among clinicians that the diet needs to be continued indefinitely, and that adults with PKU who stopped the diet in childhood or beyond should return to the diet. Many young adults have restarted the diet and found improvement in mental clarity as a result of lowered blood phenylalanine levels.

Because phenylalanine occurs in practically all natural proteins, it is impossible to adequately restrict the diet using natural foods alone without compromising health. For this reason, special

phenylalanine-free food preparations are helpful. Foods high in protein, such as meat, milk, fish and cheese are typically not allowed on the diet. Naturally low protein foods such as fruits, vegetables, and some cereals are allowed in limited quantities.

In 2007, Kuvan (sapropterin hydrochloride) was approved by the U.S. Food and Drug Administration (FDA) to treat PKU. Kuvan is an oral pharmaceutical formulation of BH4, the natural cofactor for the PAH enzyme, which stimulates activity of the residual PAH enzyme to metabolize phenylalanine into tyrosine. Kuvan is to be used in conjunction with a phenylalanine restricted diet. Kuvan is manufactured by BioMarin Pharmaceutical Inc.

In 2018, Palynziq (pegvaliase-pqpz) was approved by the FDA for adults with PKU. Palynziq is an injectable enzyme therapy for patients who have uncontrolled blood phenylalanine concentrations on current treatment. Palynziq is manufactured by BioMarin Pharmaceutical Inc.

Investigational Therapies

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Toll-free: (800) 411-1222
TTY: (866) 411-1010
Email: prpl@cc.nih.gov

Some current clinical trials also are posted on the following page on the NORD website:
https://rarediseases.org/for-patients-and-families/information-resources/news-patient-recruitment/

For information about clinical trials sponsored by private sources, in the main, contact:
www.centerwatch.com

For information about clinical trials conducted in Europe, contact:
https://www.clinicaltrialsregister.eu/