Journal of Clinical Nutrition and Metabolism

Editorial

A SCITECHNOL JOURNAL

Phenylketonuria (PKU)

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Phenylketonuria (PKU) is an inborn defect of metabolism that results in decreased metabolism of the amino acid phenylalanine. Untreated, PKU can lead to intellectual disability, seizures, behavioural problems, and mental disorders. It may also result in a musty smell and lighter skin. A baby born to a mother who has poorly treated PKU may have heart problems, a small head, and low birth weight.

Phenylketonuria is a genetic disorder inherited from a person's parents. It is due to mutations in the PAH gene, which results in low levels of the enzyme phenylalanine hydroxylase. This results in the build-up of dietary phenylalanine to potentially toxic levels. It is autosomal recessive, meaning that both copies of the gene must be mutated for the condition to develop. There are two main types, classic PKU and variant PKU, depending on whether any enzyme function remains. Those with one copy of a mutated gene typically do not have symptoms. Many countries have new-born screening programs for the disease.

Signs and Symptoms

Abnormally small head (microcephaly)

Untreated PKU can lead to intellectual disability, seizures, behavioural problems, and mental disorders. It may also result in a musty smell and lighter skin. A baby born to a mother who has poorly treated PKU may have heart problems, a small head, and low birth weight.

Because the mother's body is able to break down phenylalanine during pregnancy, infants with PKU are normal at birth. The disease is not detectable by physical examination at that time, because no damage has yet been done. New-born screening is performed to detect the disease and initiate treatment before any damage is done. The blood sample is usually taken by a heel prick, typically performed 2–7 days after birth. This test can reveal elevated phenylalanine levels after one or two days of normal infant feeding.

If a child is not diagnosed during the routine new-born screening test and a phenylalanine restricted diet is not introduced, then phenylalanine levels in the blood will increase over time. Toxic levels of phenylalanine (and insufficient levels of tyrosine) can interfere with infant development in ways which have permanent effects. The disease may present clinically with seizures, hypopigmentation (excessively fair hair and skin), and a "musty odor" to the baby's sweat and urine (due to phenylacetate, a carboxylic acid produced by the oxidation of phenyl ketone). In most cases, a repeat test should be done at approximately two weeks of age to verify the initial test and uncover any phenylketonuria that was initially missed [1-5].

Genetics

Phenylketonuria is inherited in an autosomal recessive fashion

PKU is an autosomal recessive metabolic genetic disorder. As an autosomal recessive disorder, two PKU alleles are required for an individual to experience symptoms of the disease. For a child to inherit PKU, both the mother and father must have and pass on the defective gene. If both parents are carriers for PKU, there is a 25% chance any child they have will be born with the disorder, a 50% chance the child will be a carrier, and a 25% chance the child will neither develop nor be a carrier for the disease.

PKU is characterized by homozygous or compound heterozygous mutations in the gene for the hepatic enzyme phenylalanine hydroxylase (PAH), rendering it non-functional. This enzyme is necessary to metabolize the amino acid phenylalanine (Phe) to the amino acid tyrosine (Tyr). When PAH activity is reduced, phenylalanine accumulates and is converted into phenylpyruvate (also known as phenylketone), which can be detected in the urine.

Carriers of a single PKU allele do not exhibit symptoms of the disease but appear to be protected to some extent against the fungal toxin ochratoxin A. This accounts for the persistence of the allele in certain populations in that it confers a selective advantage—in other words, being a heterozygote is advantageous.

The PAH gene is located on chromosome 12 in the bands 12q22-q24.2. As of 2000, around 400 disease-causing mutations had been found in the PAH gene. This is an example of allelic genetic heterogeneity.

Pathophysiology

When phenylalanine (Phe) cannot be metabolized by the body, a typical diet that would be healthy for people without PKU causes abnormally high levels of Phe to accumulate in the blood, which is toxic to the brain. If left untreated (and often even in treatment), complications of PKU include severe intellectual disability, brain function abnormalities, microcephaly, mood disorders, irregular motor functioning, and behavioural problems such as attention deficit hyperactivity disorder, as well as physical symptoms such as a "musty" odor, eczema, and unusually light skin and hair coloration.

Treatment

PKU is not curable. However, if PKU is diagnosed early enough, an affected new-born can grow up with normal brain development by managing and controlling phenylalanine ("Phe") levels through diet, or a combination of diet and medication.

Diet

People who follow the prescribed dietary treatment from birth may (but not always) have no symptoms. Their PKU would be detectable only by a blood test. People must adhere to a special diet low in Phe for optimal brain development. Since Phe is necessary for the synthesis of many proteins, it is required for appropriate growth, but levels must be strictly controlled.

For people who do not have phenylketonuria, the U.S. Institute

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Received: May 10, 2021 **Accepted:** May 21, 2021 **Published:** May 26, 2021

of Medicine set recommended at least 33 mg/kg body weight/day phenylalanine plus tyrosine for adults 19 years and older.For people with PKU, a recommendation for children up to age 10 years is 200 to 500 mg/d; for older children and adults below 600 mg/day. Where in the range depends on body weight and age, and on monitoring blood concentration.

Epidemiology

The average number of new cases of PKU varies in different human populations. United States Caucasians are affected at a rate of 1 in 10,000. Turkey has the highest documented rate in the world, with 1 in 2,600 births, while countries such as Finland and Japan have extremely low rates with fewer than one case of PKU in 100,000 births. A 1987 study from Slovakia reports a Roma population with an extremely high incidence of PKU (one case in 40 births) due to extensive inbreeding. It is the most common amino acid metabolic problem in the United Kingdom.

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