

PHENYLKETONURIA (PKU)

Hyperphenylalaninemia (OMIM database No. 261600),¹⁵⁰ an abnormal increase in the concentration of the amino acid phenylalanine (Phe) in the blood, may be a benign condition with little clinical significance. When the concentration of Phe is very high (>20 mg/dL or 1210 $\mu\text{mol/L}$) and there is accumulation of phenylketones, the condition is called classic phenylketonuria (PKU).

Incidence

Despite the fact that newborn screening has been underway for more than 40 years in the United States, data only allow estimates of the incidence and prevalence of this disorder. This is partly because of the fact that states vary in their definitions of hyperphenylalaninemia and PKU. For PKU, the reported incidence ranges from 1 in 19000 to 1 in 13500 newborn infants. For non-PKU hyperphenylalaninemia, the estimated incidence is 1 in 48000 newborn infants. There are large variations in the incidence of PKU by ethnic and cultural groups, with individuals of Northern European ancestry and American Indian/Alaska Native individuals having a higher incidence than black, Hispanic, and Asian individuals.¹⁵¹

Clinical Manifestations

PKU is rarely diagnosed before 6 months of age without newborn screening, because the most common manifestation without treatment is developmental delay followed by mental retardation. Untreated individuals may also develop microcephaly, delayed or absent speech, seizures, eczema, and behavioral abnormalities.

Pathophysiology

PKU results from a deficiency of activity of a liver enzyme, phenylalanine hydroxylase (PAH), leading to increased concentrations of Phe in the blood and other tissues. Certain mutations of the *PAH* gene usually result in non-PKU hyperphenylalaninemia, and others result in classic PKU. Because siblings with the same mutation at the *PAH* locus may have different clinical findings, it is likely that other genetic and environmental factors influence the severity of the disorder.¹⁵² In fact, a few individuals with PKU have no evidence of mental retardation, even without dietary treatment.¹⁵¹ However, there is evidence that certain genotypes are associated with higher increases of Phe concentration.¹⁵³ It is likely that Phe itself leads to the mental retardation and other findings of PKU. In excess, Phe disturbs transport of other amino acids across the blood-brain barrier and impairs synthesis of neurotransmitters.¹⁵¹ For the enzyme PAH to be active, the cofactor tetrahydrobiopterin (BH4) is required. Impaired synthesis or recycling of BH4 results in increased concentrations of Phe and certain other amino acids. This condition does not respond to routine dietary management of PKU, and hence, states have instituted additional screening programs to identify infants with these rare disorders so that appropriate treatment can be initiated.

Inheritance

PKU is an autosomal recessive disorder, with the *PAH* locus on chromosome 12q24.1. More than 400 different mutations have been described, including deletions, insertions, missense mutations, splicing defects, and nonsense mutations. Most individuals with PKU are compound heterozygotes, meaning that a single individual will have different mutations of each copy of the *PAH* gene.¹⁵¹ The numerous possible combinations of gene mutations undoubtedly contributes to the variable clinical findings in PKU.

Benefits of Newborn Screening

Children with PKU who are treated appropriately after positive newborn screening results have average intelligence as measured by IQ tests, although their scores are somewhat lower than expected when compared with parent and sibling IQs. There is an inverse relationship between the age at which treatment is begun and the IQ level, even in PKU that is treated early.¹⁵⁴ Tremor of unknown origin has been reported in 10% to 30% of early-treated individuals with PKU.¹⁵⁵ Adolescents and young adults who are treated early and continuously seem to have no increased incidence of psychiatric, emotional, or functional disorders, and there is no increase in problems of self-concept.^{156,157} Although children with PKU are not at increased risk of developing dental caries, children with PKU may exhibit increased signs of tooth wear because of the erosive potential of the amino acid supplements in the diet.¹⁵⁸ Therefore, it is important for children and adolescents with PKU to have regular dental care.

Screening

There are 3 main methods used for screening newborns for PKU in the United States: the Guthrie BIA, fluorometric analysis, and MS/MS. The Guthrie BIA is inexpensive and reliable. Fluorometric analysis and MS/MS are quantitative and can be automated; both of these methods also produce fewer false-positive results than BIA.¹⁵¹ Preliminary data indicate that MS/MS produces fewer false-positive results than the fluorometric method in samples obtained in the first 24 hours of life.¹⁵⁹ Newborn screening laboratories in the United States use cutoff values from 2 mg/dL (125 μ mol/L) to 6 mg/dL (375 μ mol/L). A positive screening result should lead to rapid evaluation of the newborn for clinical status, age, and diet at the time of sample collection. Severe deficiency of PAH will usually result in an increased concentration of blood Phe within the first 24 hours of life; however, infants with a less severe deficiency may take longer to develop an abnormal Phe concentration. It is for this reason that a repeat test for all infants initially screened in the first 24 hours of life has been recommended by some authorities.¹⁶⁰ Few states, however, currently require a second screen.

Follow-up and Diagnostic Testing

Early treatment of PKU is associated with improved intellectual outcome. Therefore, an infant with a positive newborn screening result should receive the benefit of rapid diagnostic testing. Diagnostic testing includes quantitative determination of plasma Phe and tyrosine concentrations. If the Phe concentration is increased, additional studies are indicated to determine if the infant has an abnormality in synthesis or recycling of BH4.

Brief Overview of Disease Management

Once the diagnosis of hyperphenylalaninemia is confirmed, metabolic control should be achieved as rapidly as possible. This is achieved through the use of medical foods, including medical protein sources that are low in Phe; small amounts of Phe must also be provided, which is achieved through the use of small amounts of natural protein. The infant with PKU can be given breast milk along with Phe-free formula under the direction of a metabolic dietitian. The response to dietary treatment is monitored through periodic measurement of blood Phe concentrations, assessment of growth parameters, and review of nutritional intake. There is no consensus concerning the optimal blood Phe concentration or the duration of strict dietary management. The most commonly reported blood Phe concentration recommendations for US centers are 2 to 6 mg/dL for individuals 12 years or younger and 2 to 10 mg/dL for persons older than 12 years.¹⁵¹ Most US centers recommend lifelong dietary treatment. This is particularly important for women, because fetuses exposed to increased concentrations of Phe are at significant risk of microcephaly, congenital heart disease, and reduced IQ.¹⁵¹ It is recommended that a woman with PKU achieve Phe concentrations of less than 6 mg/dL at least 3 months before conception and that concentrations be maintained between 2 and 6 mg/dL throughout pregnancy.¹⁵¹ The importance of management throughout the reproductive years illustrates the critical role of long-term follow-up in this disorder.

Current Controversies

As noted previously, there is no national or international consensus regarding the optimal concentration of Phe across the life span. Similarly, there is no consensus regarding discontinuation of dietary therapy. Although appropriately treated young adults with PKU lead normal and productive lives, there are no meaningful data regarding the incidence of long-term sequelae in individuals who remain on dietary therapy into middle and old age. Recent evidence suggests that some individuals with hyperphenylalaninemia and classic PKU may benefit from BH4 treatment in addition to dietary Phe restriction.¹⁶¹

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