



Phenylketonuria (PKU) Information for Healthcare Professionals

Phenylketonuria (PKU) is a disorder of amino acid metabolism that results in excess levels of phenylalanine in body fluids. Elevated levels of phenylalanine can become neurotoxic; early detection and treatment of hyperphenylalaninemia is necessary to prevent intellectual disabilities.

✓ **Clinical Symptoms**

Infants with classic PKU appear normal until they are a few months old. Early symptoms can include skin rash, seizures, excessive restlessness, irritable behavior and a musty odor of the body or urine. Later signs include developmental delays, psychiatric disorders and intellectual disabilities. Without treatment, these children develop permanent intellectual disabilities. Children with classic PKU tend to have lighter skin and hair than unaffected family members due to low tyrosine levels, and are also likely to have skin disorders such as eczema.

✓ **Incidence**

In the United States, PKU occurs in 1 in 25,000 newborns. The incidence varies according to ethnic background of the child, with a higher incidence in White and Native American populations and lower incidence in African American, Hispanic, and Asian populations.

✓ **Genetics of PKU**

Mutations in the PAH gene cause phenylketonuria. The PAH gene codes for phenylalanine hydroxylase. Phenylalanine hydroxylase is responsible for the conversion of phenylalanine to tyrosine. PAH mutations reduce the activity of phenylalanine hydroxylase, preventing it from processing phenylalanine effectively. As a result, this amino acid can build up to toxic levels in the blood and other tissues. Because nerve cells in the brain are particularly sensitive to phenylalanine levels, excessive amounts of this substance can cause brain damage.

Classical PKU occurs when phenylalanine hydroxylase activity is severely reduced or absent. People with untreated classic PKU have levels of phenylalanine high enough to cause severe brain damage and other serious medical problems. Mutations in the PAH gene that allow the enzyme to retain some activity result in milder versions of this condition, such as variant PKU or non-PKU hyperphenylalaninemia.

✓ **Inheritance Patterns**

PKU is inherited in an autosomal recessive pattern. Parents of a child diagnosed with PKU are unaffected. These individuals are carriers of the condition and have one normal PAH gene and one abnormal PAH gene. Each pregnancy between carrier parents has a 25% chance of producing a child affected with PKU, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier.

✓ **Treatment**

Early diagnosis and treatment is essential to prevent developmental delays. Treatment is life-long and consists of a low phenylalanine diet, which includes a specialized medical formula, in combination with regular foods that are low in phenylalanine.

Tetrahydrobiopterin (BH4) deficiency occurs in a subset of children with PKU due to defects in pterin metabolism. This causes early severe neurologic disease (developmental delay/seizures) and requires replacement therapy with tetrahydrobiopterin.

Babies born to mothers with poorly controlled PKU have a significant risk of intellectual disabilities due to their exposure to very high levels of phenylalanine before birth. These infants may have a low birth weight and grow more slowly than other children. Other characteristic medical problems include heart defects, microcephaly, and behavioral problems. These babies have "Maternal PKU syndrome". Women with poorly controlled PKU also have an increased risk of miscarriage. Strict dietary control prior to conception and throughout pregnancy is essential to prevent the "Maternal PKU syndrome".

✓ **Screening Methodology**

Newborn screening for PKU is by tandem mass spectrometry. This technology allows for measurement of phenylalanine. Elevated phenylalanine levels in conjunction with an increased phenylalanine to tyrosine ratio is indicative of PKU. **Infants with a high risk positive screening test (significantly elevated phenylalanine level) require prompt follow-up.**

✓ **What other conditions can cause elevated levels of phenylalanine?**

Intermediate forms of hyperphenylalaninemia, in which the levels of phenylalanine are lower than what is usually found in classical PKU, can cause variable intellectual disabilities and, in some cases, can be completely benign. Biopterin is a cofactor for PAH. Defects in biopterin metabolism can cause hyperphenylalaninemia and will also require treatment. Maternal PKU, hyperalimentation (TPN), and liver disease can also lead to the finding of increased phenylalanine levels in newborn screening blood spots.

✓ **What to do After Receiving Presumptive Positive PKU Screening Results: TAKE THE FOLLOWING IMMEDIATE ACTIONS:**

- 1) **Contact family immediately to inform them of the newborn screening result.**
- 2) **Consult with pediatric metabolic specialist.**
- 3) **Evaluate the newborn and refer as appropriate.**
- 4) **Initiate confirmatory/diagnostic tests in consultation with metabolic specialist.**
- 5) **Provide the family with basic information about PKU and dietary management.**
- 6) **Call KS Newborn Screening Program at 785-291-3363 with questions about results**
- 7) **Report Clinical Findings to Newborn Screening Program at 785-291-3363.**

✓ **Confirmation of Diagnosis**

Once the initial screen is positive, diagnostic tests must be performed:

- Plasma amino acid analysis which shows increased **phenylalanine** without increased **tyrosine** (increased phenylalanine: tyrosine ratio).
- Urine pterin analysis and red blood cell DHPR assay will identify pterin defects. Once these blood samples have been collected, a low phenylalanine diet is started.
- Consider PAH mutation testing.

✓ **Communication of Results to Parents**

If a baby has a presumptive positive PKU newborn screening result, additional testing needs to be performed to confirm a diagnosis. In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

If a baby is diagnosed with PKU, the following points should be conveyed to parents:

- ***Parents should understand that treatment is life-long and that compliance with dietary management is imperative to the child's health, growth and development.***
- ***Infants and children with PKU or hyperphenylalaninemia should have regular follow-up appointments with a metabolic disease specialist.***
- ***Parents should understand that treatment is not curative. Long-term management, monitoring and compliance with treatment recommendations are essential to the child's well-being. A multidisciplinary approach is recommended and should include the following specialties: pediatrics, genetics, and nutrition.***
- ***Parents who have a child with PKU have a 25% chance with each pregnancy of having another affected child.***

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