

## Phenylketonuria

### Information for Health Professionals

#### Description

Individuals with phenylketonuria (PKU) cannot properly utilize the amino acid phenylalanine. Phenylalanine is derived predominately from dietary protein. Other metabolic processes function as they should, but the body is unable to convert phenylalanine to tyrosine due to a lack of the converting enzyme, phenylalanine hydroxylase. Phenylalanine accumulates, giving rise to symptoms.

#### Incidence

Classic PKU and other causes of hyperphenylalaninemia occur in about 1:10,000 to 1:25,000 live births in the United States. These disorders occur with equal frequency in males and females. It is important to note that PKU, although rare in black children (1:500,000 births), does occur, as well as in other dark skinned individuals.

#### Clinical Features

Infants with PKU appear normal at birth. While in utero, phenylalanine is maintained in the normal range by the mother's system. Cord blood tests are normal in these infants. About 24 hours after the first protein feeding the level of phenylalanine begins to rise to abnormally high levels. Without treatment, nearly all affected individuals develop severe mental retardation.

In untreated cases, symptomatology, such as developmental delay, may not be manifested for months. Vomiting may be a prominent early symptom of untreated PKU, mimicking pyloric stenosis. Other symptoms include irritability, eczematous or oily skin and possibly a musty odor to the body and to the urine, which is due to phenylacetic acid. Neurological manifestations such as convulsions, hyperactivity with purposeless movements, autistic-like behavior and an abnormal EEG may occur along with cerebral palsy-like symptoms. Some individuals with PKU may have lighter hair and skin color than other family members due to inadequate production of tyrosine (a precursor to melanin pigment formation).

Other reasons for increased phenylalanine on newborn screening:

- There are several intermediate forms of hyperphenylalaninemia in which the phenylalanine levels are moderately elevated (3-15 mg/dL). Many of these children still require diet restrictions to maintain their blood phenylalanine level in the 2-6 mg/dL range.
- Biopterin deficiency is a defect in the production of a co-factor, tetrahydrobiopterin, which results in a PKU-like disorder. Although elevation

of phenylalanine is characteristic in these infants, the medical management is different than that for infants with PKU.

- Maternal PKU (MPKU) and hyperphenylalaninemia: Untreated MPKU causes damage to the fetus due to high phenylalanine in the intrauterine environment (amniotic fluid). It can result in mental retardation, microcephaly, congenital heart defects and low birth weight. A woman who has PKU or hyperphenylalaninemia must be on a medically supervised phenylalanine-restricted diet prior to conception and maintain her blood phenylalanine levels within treatment goals (2-6 mg/dl) throughout pregnancy for optimum outcome.

### **Screening**

The screening test for PKU is done by the IEM laboratory as part of the standard newborn biochemical screening. Tandem mass spectrometry (MS/MS) is applied to this process.

### **Confirmatory testing**

It is important to remember that newborn biochemical screening is just a screening test, and a diagnosis must be confirmed using an independent analysis of serum phenylalanine and tyrosine. It is essential to confirm or exclude the diagnosis of PKU in a timely fashion and with a high degree of accuracy to avoid unnecessary testing, to provide appropriate interventions, prognostic and genetic counseling, and to ensure access to specialized medical services.

The diagnosis of PKU should be made in the neonatal period. Plasma phenylalanine is not detectably elevated in cord blood. It starts rising within 24 hours after birth and can reach levels of 20 mg/dL or more within a few days to a week. Despite the presence of newborn screening programs, 10% of phenylketonuric/hyperphenylalanemic infants miss being detected in the newborn-infancy period.

Prompt confirmatory testing is required even if there is evidence to suggest that one of the situations associated with false positive screening is present. False positive results can be caused by: inadequate or early specimen collection, heat damaged specimen, prematurity, hyperalimentation, or antibiotic therapy. The presence of any of these factors does not exclude the possibility of disease.

### **Treatment**

Treatment must begin early and should be continued for life for optimum effect. Phenylalanine is present in all dietary protein; therefore the treatment of PKU is the provision of a diet sufficiently low in phenylalanine to maintain serum concentrations within a reasonable range and to keep body fluids free of metabolites.

Treatment also requires frequent quantitative assessment of the concentration of phenylalanine in the blood. Growth and development should also be followed closely, in conjunction with monitoring of the diet by a trained nutritionist.

**Treatment for PKU should not be started before confirmatory testing is completed and consultation with a metabolic/genetic specialist is initiated.**

### **Implications for Genetic Counseling**

PKU is inherited in an autosomal recessive manner. Approximately 1 in 50 persons is a carrier of the gene. Carriers are healthy, but two carrier parents have a one in four (25%) chance to have an affected child with each pregnancy. Unaffected siblings of a child with PKU have a 66% chance of being carriers. Carriers are asymptomatic but can often be identified through genetic testing.

### **Interpretations/Recommendations**

#### **Expected Results:**

- Phenylalanine  $<180 \mu\text{M}$  plus Phenylalanine/ Tyrosine ratio  $<2.5$
- Recommend: No action - Within Acceptable Limits.

#### **Borderline Results:**

- Phenylalanine  $\geq 130-179 \mu\text{M}$  plus Phenylalanine/Tyrosine ratio  $\geq 2.5$
- Recommend: Repeat filter sample within two days

#### **Borderline Results:**

- Phenylalanine  $\geq 180-239 \mu\text{M}$  plus Phenylalanine/Tyrosine ratio  $<2.5$
- Recommend: Repeat filter sample within two days.

#### **Any repeat borderline or any repeat presumptive**

- Immediate assessment of baby's health; consultation strongly recommended

#### **Presumptive-Positive Results:**

- Phenylalanine  $\geq 180-239 \mu\text{M}$  plus Phenylalanine/Tyrosine ratio  $\geq 2.5$  or Phenylalanine  $\geq 240 \mu\text{M}$  regardless of any ratio
- Recommend: Immediate assessment of baby's health; consultation strongly recommended

**Note: Newborn screening is an adjunct to clinical assessment, which is paramount. Therefore, PKU should be considered in infants and children with any of the signs/symptoms.**

Additional Information:

Illinois Department of Public Health Newborn Screening Program

<http://www.idph.state.il.us/HealthWellness/fs/pku.htm>

GeneTests/GeneClinics

<http://www.genetests.org>

Nebraska Health and Human Services System

<http://www.hhs.state.ne.us/nsp/pmpku.htm>

Texas Department of Health Newborn Screening Practitioner's Guide

[http://www.tdh.state.tx.us/newborn/p\\_pku.htm](http://www.tdh.state.tx.us/newborn/p_pku.htm)

For questions, contact:

Inborn Errors of Metabolism Laboratory at (609) 292-3090

Newborn Screening and Genetic Services at (609) 292-1582

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