NEBRASKA

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DEPT. OF HEALTH AND HUMAN SERVICES

PHENYLKETONURIA (PKU) Information

Phenylketonuria, or PKU, is caused by a recessively inherited enzyme defect in which the body cannot properly use the amino acid phenylalanine. All other metabolic processes are intact but phenylalanine, which comes from all dietary protein, accumulates in the blood. Excess phenylalanine cannot be converted to tyrosine due to a lack of phenylalanine hydroxylase, the enzyme that catalyzes the conversion of phenylalanine to tyrosine. Phenylalanine accumulates in the body and causes damage. Overall, PKU occurs in about 1 in 15,000 U.S. live births.

Clinical Features:
With appropriate treatment, the risk of any of these conditions is substantially reduced.

- **Classical phenylketonuria** is a disorder in which the blood phenylalanine, or phe, rises above 20 mg/dL on a normal diet (normal blood phe is less than 2.0 mg/dL). Without treatment, nearly all affected individuals develop severe mental retardation. Other symptoms include severe mental deficiency, microcephaly, eczematous or oily skin, cerebral palsy, convulsions, dysphasia, hyperactivity with purposeless movements, autistic-like behavior, and an abnormal EEG. In infants, vomiting may mimic pyloric stenosis. The skin and hair are usually fair, the eyes may be blue and a "mousey" odor of the baby's urine is frequent. The smell arises from phenylacetic acid.

- **Hyperphenylalaninemia** refers to any consistent elevation of phe levels, including classical PKU. If cases of classical PKU are excluded, this includes blood phe levels less than 20 mg/dL. These may be caused by liver damage, transient tyrosinemia of prematurity, mutation of the phenylalanine hydroxylase gene, disorders of cofactor synthesis or regeneration, or maternal PKU. In these cases, mental retardation may or may not be present. Blood levels may remain elevated throughout life or may gradually fall towards normal. In infancy, these patients can mimic the severe PKU condition, and even in mild cases there seems to be an increased risk of the maternal PKU syndrome, as described below.

- Much rarer causes of elevated phenylalanine are caused by defects of biopterin metabolism. Blood phenylalanine levels are variable. These patients have progressive neurological damage with seizures and steady deterioration which becomes noticeable sometime between 6 and 20 months of age despite early treatment with a low phenylalanine diet. In view of the severity of this group of diseases, all infants with persistently abnormal levels of phenylalanine should be tested by special blood or urine tests for biopterin abnormalities.

The cause of hyperphenylalaninemia must be determined if proper treatment is to be provided. Definitive tests can differentiate these variant forms of PKU. Treatment by dietary restriction alone is inadequate for a tetrahydrobiopterin cofactor defect. The cofactor is necessary not only

for normal activity of phenylalanine hydroxylase, but also for activity of the tyrosine and tryptophan hydroxylase which are involved in serotonin and dopamine synthesis.

Maternal PKU:
Pregnancy presents a special problem with PKU and other forms of hyperphenylalaninemia, as high blood levels of phe are teratogenic to the fetus. This is important in the context of newborn screening because early testing of an infant born to a mother with PKU or hyperphenylalaninemia can reflect the mother's phe levels. A positive test on a newborn who then has a normal repeat test, especially if the baby has growth retardation, microcephaly, or malformations, should raise the possibility of maternal PKU. These infants usually have a transient elevation of phenylalanine (3-20 mg/dL) reverting to normal within 24 hours. If maternal PKU is suspected, the mother should be appropriately tested and counseled. A medically supervised phenylalanine restricted diet begun before conception with phenylalanine levels maintained within a safe range throughout pregnancy may prevent damage to the fetus.

Laboratory Test:
The screening test for PKU amino acid analysis via tandem mass spectrometry is a dried blood spot specimen.

TEST RESULTS	LIKELY CAUSES	ACTIONS TO TAKE WHEN POSITIVE RESULT FOUND
Phe and Phe/Tyr ratios "borderline normal"	PKU Mild hyperphenylalanemia False positive	Telephone, fax and write submitter & MD to collect a repeat filter paper specimen Telephone and fax NNSP about results
Phe "abnormal", but Phe/Tyr ratios normal (or generalized elevation of several amino acids)	Newborn on hyperal/TPN PKU Mild hyperphenlalaniemia False positive	Telephone, fax and write submitter & MD to collect a repeat filter paper specimen in two weeks Telephone and fax NNSP about results
Concentration of Phe and Phe/Tyr ratios "abnormal"	PKU Mild hyperphe False positive	Telephone, fax and write submitter & MD to collect a repeat filter paper specimen within 48 hours. Recommend consult metabolic specialist. Telephone NNSP about results
Concentrations of Phe and Phe/Tyr "significantly" abnormal	PKU Hyperphenylalaninemia False Positive	Telephone, fax and write submitter & MD to collect urgent plasma for quantitative amino acid analysis, and recommend consult metabolic specialist. Telephone NNSP about results

Confirmation and Treatment:
Consultation with a pediatric metabolic specialist should be made for confirmation and diagnosis (see ACT sheet). Upon notification of a positive screening result ("abnormal" or "significantly abnormal", the physician should collect or cause to be collected 0.5 ml heparnized plasma for quantitative testing of phenylalanine and tyrosine. Serum is also acceptable. With early and proper treatment, mental retardation is normally preventable. Treatment should be started as

soon after birth as possible in any infant with phenylalanine levels over 8 mg/dL and should be continued for life.

Frequent monitoring and diet adjustment is required, especially in the first weeks, because infants with variant forms of hyperphenylalaninemia may be indistinguishable from true PKU **and improper nutritional therapy can produce brain damage or be fatal**. Specific formulas for the diet management and expert nutritional supervision are provided through University of Nebraska Medical Center.

If treatment is not started for some weeks, the results are more variable and the I.Q. tends to be lower. Patients who are not treated until after six months of age may show some improvement in I.Q., although they are likely to remain retarded. Older patients usually show little change in I.Q. with treatment, but a low phenylalanine diet may help to control serious behavior problems and other manifestations of untreated PKU.

Screening Practice Considerations:
Plasma phenylalanine is **not detectably elevated in cord blood**. It starts rising within 24 hours after birth and reaches 20 mg/dL or more within a few days. The screening test is often abnormal within 24 hours after birth and almost uniformly abnormal beyond 24 hours of birth in those infants with PKU.

The phe level of affected infants rises gradually after birth with little, if any, effect of the amount of protein ingested by the infant. The infant **must be at least 24 hours** of age to reliably detect PKU. Those with milder forms of hyperphenylalaninemia may need to be older to develop abnormal tests.

If an infant is tested "early" (less than 24 hours of age) a repeat test must be performed by seven (7) days of age, regardless of prior test results, as treatment started after 1 month of age may be less than optimal.

Dialysis or transfusion may temporarily lower phe levels**. ALWAYS OBTAIN A NEWBORN SCREENING SPECIMEN PRIOR TO A TRANSFUSION**. Children who develop retardation before one year of age should undergo testing for PKU even if a negative screening test is documented.

Prompt confirmatory testing is required even if there is evidence to suggest that one of the situations associated with false positive screens is present. These situations can include inadequate or early specimen collection, prematurity, heat-damaged specimen, hyperalimentation, or antibiotic therapy. The presence of any of these does **not** exclude the possibility of disease.