

Introduction:

Phenylketonuria (PKU) is an inborn error of metabolism (IEM) in which metabolism of the essential amino acid phenylalanine is defective. It is inherited in an autosomal recessive fashion, and occurs in about **1 in 15,000** live births in the U.S.

In **classic PKU**, patients are **completely deficient** in functional phenylalanine hydroxylase (**PAH**), the hepatic enzyme that converts phenylalanine into tyrosine (**Figure 1**). This results in hyperphenylalaninemia (serum **phenylalanine >20 mg/dL**) and accumulation of phenylalanine metabolites, including phenylacetate and phenyllactate (phenylketones). PKU patients may be deficient in PAH to varying degrees, resulting in variable severity in clinical manifestations.

Approximately 2% of patients with hyperphenylalaninemia are deficient in tetrahydrobiopterin (**BH4**), an essential cofactor for PAH and other enzymes. This deficiency results in progressive **neurological dysfunction** due to impaired synthesis of neurotransmitters. Also on the differential for PKU is tyrosinemia.

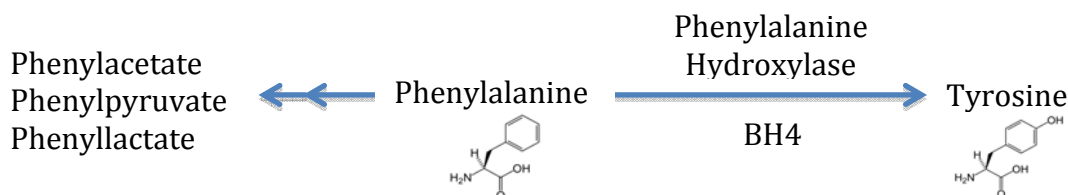


Figure 1 Phenylalanine metabolism

Clinical Manifestations

As PKU is now included in routine newborn screening panels **in all states and Canada**, it is treated early, halting progression and limiting clinical manifestations. As PKU most often manifests as neurocognitive dysfunction, other causes of mental retardation and neurological deficits must be considered on differential diagnosis.

Below are the most common findings found in varying degrees in untreated PKU:

- **Intellectual disability.** Elevated phenylalanine levels are thought to result in progressive reduction in IQ (average IQ <30 in untreated PKU). The mechanism by which hyperphenylalaninemia results in progressive decrease in brain growth, myelination, and neurotransmitter synthesis is as yet unclear.
- **Neurological deficits.** Spastic cerebral palsy is seen in roughly one third of patients, with one third exhibiting some hypertonia and one third neurologically intact. Seizures are seen in about 25% of cases. Brain MRI may exhibit white matter injury even in patients receiving screening and early treatment, but may be reversible.

- **Skin manifestations.** Untreated patients may exhibit fair skin and hair (**Figure 2**) due to decreased melanin synthesis. Eczema and keratosis pilaris are seen at a higher rate in PKU, and a “musty” or “mousy” odor to the skin, hair, sweat, and urine may be noted due to accumulation of phenylalanine metabolites.



Figure 2 PKU patient exhibiting fair skin and hair. Taken from <http://emedicine.medscape.com/article/947781-clinical#a0256>.

Screening

Screening for PKU in the U.S. began in the early 1960s, and PKU is currently included as a part of the newborn screening panel in all states. However, states vary in their policies regarding the parental right to decline testing as well as in funding and the provision of follow-up services.

Screening is performed via one of three methods: (1) Guthrie Bacterial Inhibition Assay (BIA), (2) fluorometric analysis, and (3) tandem mass spectrometry. BIA is the cheapest and simplest method, but produces more false positives and provides less information than the alternative methods.

Treatment

- **Diet.** The mainstay of PKU treatment is dietary modification—a **phenylalanine-restricted diet** must be instated as early as possible. This rigorous diet entails elimination of high-protein foods (meat, dairy, etc.) as well as starchy foods (**Figure 3**), and supplementation of calories, other essential amino acids, vitamins, and minerals. Aspartame-sweetened foods must also be eliminated from the diet, as they are high in phenylalanine. Care must be taken to ensure some natural phenylalanine in the diet to prevent deficiency, especially in younger children in whom the amino acid is required for growth. It is recommended that the PKU diet be continued **throughout life** into



Figure 3 Dietary guide for PKU patients. Taken from <http://depts.washington.edu/transmet/The%20process/essential.htm>

adulthood to prevent cognitive decline. Given the strictness of this diet, it is important to acknowledge patient barriers to adherence, especially in older children and young adults.

- **Pharmacologic treatment.** Though dietary restriction is the first line, given the difficulties in diet adherence, several pharmacologic treatments are being explored. Some studies have suggested that large neutral amino acid (LNAA) supplementation may block phenylalanine transport into the brain. Sapropterin, a BH4 analog, may be beneficial in patients with some residual PAH function. An injectable PAH analog, phenylalanine ammonium lyase, is being studied, as well as gene therapy.
- **Monitoring.** Patients must be routinely monitored to ensure blood phenylalanine levels between **2-6 mg/dL** (2-12 mg/dL for children >12 years). Levels are monitored twice a week in neonates, tapering off to monthly monitoring in adulthood. Monitoring includes ensuring levels in target range as well as observing for variability in phenylalanine levels, suggestive of the degree of control. Long-term follow up should include psychology, nursing, social services, nutrition therapy, and genetic and family services.
- **Pregnancy.** Maternal PKU is not a contraindication for pregnancy—however, mother with PKU must strictly adhere to the PKU diet and consistently maintain phenylalanine levels in the 2-6 mg/dL range. Hyperphenylalaninemia during pregnancy may result in IUGR, microcephaly, mental deficiency, and congenital heart disease. Twice weekly phenylalanine level monitoring is recommended in pregnant women with PKU.

Support

PKU requires significant changes not only in the life of the patient but their families as well. Providing sufficient emotional support and networking with other affected families is key. There are various support organizations that may be helpful, including:



The National Society for Phenylketonuria
www.nspku.org



Children's PKU Network
[www.pkunetwork.org/Childrens PKU Network/Home.html](http://www.pkunetwork.org/Childrens_PKU_Network/Home.html)



A collection of PKU & Allied Disorders Regional and State Organizations
http://medicalfood.com/metabolic_groups.php

REFERENCES

1. Meglio, GD. Phenylketonuria. *Pediatrics In Review*. Vol. 19 No. 6. June 1, 1998
2. Hellekson, KL. Practice Guidelines: NIH Consensus Statement on Phenylketonuria. *Am Fam Physician*. 2001 Apr 1;63(7):1430-1432.
3. Phenylketonuria: Screening and Management. National Institutes of Health Consensus Development Conference Statement.
<http://consensus.nih.gov/2000/2000phenylketonuria113html.htm>
4. Steiner, RD. Phenylketonuria. Medscape Reference.
<http://emedicine.medscape.com/article/947781-overview>
5. Overview of phenylketonuria. UpToDate.
http://www.uptodate.com.proxy.uchicago.edu/contents/overview-of-phenylketonuria?source=search_result&search=phenylketonuria&selectedTitle=1~143