AMINO ACID DISORDERS

Phenylketonuria (PKU)

What is Phenylketonuria (PKU)?

Phenylketonuria (PKU) is a disorder of aromatic amino acid metabolism in which phenylalanine cannot be converted to tyrosine due to a deficiency or absence of the enzyme phenylalanine hydroxylase.[1] Phenylalanine hydroxylase requires the co-factor 6-pyruvoyltetrahydropterin or BH4 for activity in the hydroxylation to tyrosine, absence of this co-factor may present with an increase in plasma phenylalanine similar to phenylketonuria but is considered a separate disorder.[2]

CLINICAL MANIFESTATIONS

Patients affected with PKU appear normal at birth.[2, 3] The most important and sometimes the only manifestation of PKU is mental retardation.[2] Patients may present with constitutional, intellectual, and neurologic abnormalities and signs as well as hypopigmentation of the skin and hair and iris rapidly develop due to impaired metabolism of melanin.[3] Seizures occur in a fourth of patients.[2]

The odor of the phenylketonuric patient is that of phenylacetic acid described as mousy, barny, or musty.[2]

PATHOPHYSIOLOGY

PKU results from a deficiency of activity of a liver enzyme, phenylalanine hydroxylase leading to increased concentrations of phenylalanine in the blood and other tissues. Elevated phenylalanine interfere with myelination, synaptic sprouting, and dendritic pruning; and in addition, it competitively inhibits the uptake of neutral amino acids in the blood-brain barrier causing reduced tyrosine and tryptophan concentrations thereby limiting the production of neurotransmitters.[3]

Inheritance: autosomal recessive[2,3]

CONFIRMATORY TESTING

Plasma amino acids, urine proteins, DHPR enzyme assay. Further confirmatory testing (i.e. BH4 loading) may be required after referral to a metabolic specialist.

Overview of Disease Management

Dietary management is key to treatment. The diet of patients has four components: (1) complete avoidance of food containing high amounts of phenylalanine; (2) calculated intake of low protein/ phenylalanine natural food; (3) sufficient intake of fat and carbohydrates to fulfill the energy requirements of the patient and; (4) calculated intake of phenylalanine free amino acid mixture supplemented with vitamins, minerals and trace elements as the main source of protein.[3] Initiation of management should be done in consultation with an attending physician/metabolic specialist.

Prognosis

When treatment is started early and performed strictly, motor and intellectual development can be expected to be near normal.[3,4]

Preliminary / Initial Management During Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

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WHAT TO DO

If unwell and cannot tolerate oral intake:

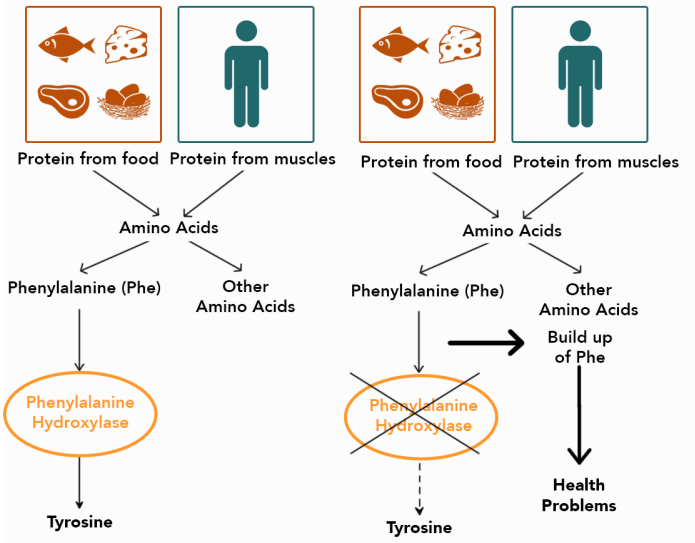
- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Collect dried blood spot for phenylalanine levels. May request for investigations (i.e. CBC, blood gas, etc.) as needed.
- May give fluid boluses if the patient requires it.
- Start D12.5% 0.3NaCl at full maintenance. Assess the patient and clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with PKU milk formula or protein free formula at maintenance rate
- Insert IV access. Collect dried blood spot for phenylalanine levels. May request for investigations (i.e. CBC, blood gas, etc.) as needed.
- Start D12.5% 0.3NaCl at 5-10 cc/hr
- Monitor input and output strictly (q6 hours)

**Children should not be protein restricted for longer than necessary (24-48 hours)*
**Inform the metabolic doctor on call for further guidance regarding on-going management*
**If the patient is well, coordinate with a metabolic specialist regarding further management*

Normal break-down of protein vs PKU patient's breakdown of protein



[1] *Nyhan WL, Barshop BA and Ozand P. Chapter 20: Phenylketonuria. Atlas of Metabolic Diseases 2nd ed. Great Britain: Oxford University Press, 2005 pp 127-133.*
[2] *Nyhan WL, Barshop BA and Ozand P. Chapter 21 Hyperphenylalaninemia and defec ve metabolism of tetrahydrobiopterin. Atlas of Metabolic Diseases 2nd ed. Great Britain:Oxford University Press, 2005 pp 136-145.*
[3] *Kaye CI and the Committee on Genetics. Newborn screening fact sheets. Pediatrics 2006;118:934-963.*
[4] *Schulze A, Matern D, Hoffmann GF. Chapter 2: Newborn screening in Sarafoglou K, Hoffman GF and Roth KS (eds). Pediatric Endocrinology and Inborn Errors of Metabolism. New York:McGraw Hill, 2009 pp 17-32.*
[5] *Burgard P, Lui X, Hoffmann GF. Chapter 13: Phenylketonuria in Sarafoglou K, Hoffman GF and Roth KS (eds). Pediatric Endocrinology and Inborn Errors of Metabolism. New York:McGraw Hill, 2009 pp 163-168.*