
NORTHSTAR HEALTHCARE CONSULTING

CLINICAL COMPASS

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PHENYLKETONURIA

BACKGROUND

Phenylketonuria (PKU) is the most common and most severe type of hyperphenylalaninemia (HPA), a group of genetic disorders in which individuals have elevated blood phenylalanine levels.¹ Classic PKU results from deficiency (total or nearly total) of phenylalanine hydroxylase (PAH). Phenylalanine hydroxylase is the enzyme

responsible for hydroxylation of phenylalanine to tyrosine. Other forms of HPA may be caused by partial deficiency of PAH or the absence of other enzymes required to metabolize phenylalanine. The normal level of phenylalanine in a healthy patient is 1 mg/dL. A patient with PKU may have levels from 6 to 80 mg/dL, but usually the levels are between 30 and 80 mg/dL.² The classifications of blood phenylalanine levels are summarized in Table 1.³



Table 1: Classifications of Blood Phenylalanine Levels³

Blood Phenylalanine Classifications	Blood Phenylalanine Level
Normal	60 $\mu\text{mol/L}$ (1 mg/dL)
Mild Hyperphenylalaninemia (HPA)	<600 $\mu\text{mol/L}$ (<10 mg/dL)
Phenylketonuria (PKU)	>1,200 $\mu\text{mol/L}$ (>20 mg/dL)
Variant or Atypical PKU	600-1,200 $\mu\text{mol/L}$ (10-20 mg/dL)

Phenylketonuria affects 1 in 10,000 to 15,000 infants in the US.^{4,5} Phenylketonuria occurs more in Caucasians and Native Americans, and less commonly in African-American, Hispanics and Asians. Ireland and Turkey have the highest prevalence worldwide: 1 in 4,500 and 1 in 2,600, respectively.^{6,7} Phenylketonuria is an autosomal recessive disorder; thus, the child must receive a mutated gene from each parent in order to be affected by the disease. If only one parent gives a mutated gene to the child, the child will be a carrier.⁸

SYMPTOMS

At birth, a child with PKU will not display any signs or symptoms; however, the infant will develop encephalopathy after a few months and high phenylalanine levels during the first two weeks of life can lead to vision problems. Additional signs and symptoms of untreated PKU include abnormal electroencephalopathy with seizures, hyperactive behavior, autistic or schizophrenic characteristics, fair skin with eczema and musty odor. Treatment is necessary to prevent permanent mental disability.⁵

DIAGNOSIS

Every state requires screening for hyperphenylalaninemia during the first few days of life. This screening process began in the 1960's. Since phenylalanine levels are already high at birth, it is very important to prevent neurologic damage as soon as possible. A blood sample is taken from the infant's heel, placed on a special paper card and analyzed for elevated phenylalanine levels. If positive, these results are verified with additional diagnostic evaluations. Generally, patients with levels greater than 10mg/dL are started on therapy; however, some clinicians will start treatment at 7 mg/dL.⁴

TREATMENT

The goal of treatment for patients with phenylketonuria is to maintain blood phenylalanine levels from 2 to 10mg/dL depending on age, as summarized in Table 2.⁴

Table 2: Goals for Blood Phenylalanine⁴

Age	Blood Phenylalanine Goal
≤12 years old	120-360 μmol/L (2-6 mg/dL)
>12 years old	120-600 μmol/L (2-10 mg/dL)

A multidiscipline approach is needed to provide optimal care to patients with PKU. The patient and family will need life-long monitoring, counseling, treatment and education from physicians, dieticians and social workers to achieve successful management of the disease. Treatment should be initiated as soon as possible after diagnosis. Starting treatment early in

life reduces the risk for intellectual deficiencies. Therapy should be followed closely while the child's brain is developing. Current goals allow for slight relaxation of restrictions at age 12 even though cognitive development is still occurring through adolescence. Even adults who discontinue therapy can see mental deterioration; thus, life-long therapy is highly recommended.⁴

Phenylalanine levels are measured regularly to assess the effectiveness of therapy. During the first year of life, phenylalanine levels should be drawn once a week. From age 1 to 12, the patient is monitored twice a month and after age 12, monthly monitoring is recommended.⁴

The current treatment options for PKU are phenylalanine-restricted diet and sapropterin dihydrochloride (KuvanTM). Both therapies are discussed below.

Phenylalanine-Restricted Diet

A phenylalanine-restricted diet is the primary treatment in the management of PKU. The patients must only intake enough phenylalanine to promote normal development. The diet includes fruits, vegetables, and low-protein carbohydrate products. The diet is supplemented with phenylalanine-free milk substitutes to provide the patient with enough vitamins and minerals. Foods to avoid include red meat, chicken, milk, eggs and nuts. Patients that begin this diet shortly after birth can develop normally without neuronal damage.⁹

Sapropterin Dihydrochloride (KuvanTM)

Sapropterin was approved by the Food and Drug Administration (FDA) in 2007 to reduce phenylalanine levels in patients with tetrahydrobiopterin-responsive PKU along with a phenylalanine-restricted diet. Sapropterin is the synthetic form of tetrahydrobiopterin (BH4), which is a cofactor for PAH. Patients that respond to sapropterin have partial phenylalanine hydroxylase activity that is increased by the presence of the medication.^{10,11}

The starting dose of sapropterin is 10 mg/kg/day. The tablets are dissolved in 4 to 8 ounces of water or apple juice and taken once daily. Phenylalanine levels should be measured one week into therapy and repeatedly at the physician's discretion during the first month. The dose may be increased to 20 mg/kg/day if adequate results are not achieved. If this dose does not produce desired results, the therapy should be discontinued as the patient is considered a non-responder. Approximately 20 to 56% of patients in clinical trials responded to sapropterin treatment; thus, approximately, 44 to 80% of patients could potentially be non-responders. Laboratory testing (e.g., genetic testing) cannot predict response to sapropterin treatment and response can only be determined by a trial of sapropterin.¹⁰

The most common adverse reactions of sapropterin are headache, diarrhea, abdominal pain, upper respiratory tract infection, pharyngolaryngeal pain, nausea and vomiting.¹⁰

LONG-TERM EFFECTS AND SURVIVAL

Life-long adherence to therapy is essential in managing phenylketonuria. Several studies have shown that higher brain function deteriorates when phenylalanine levels are above 10 mg/dL and show improvement in brain function at values less than 10 mg/dL.^{1,4} A correlation between phenylalanine level and intelligence has been made by measuring the Intelligence Quotient (IQ) of patients with PKU. For every 1.67 mg/dL increase in phenylalanine levels, the IQ can decrease by 1.3 to 4.1 points.¹² This is true for young children and adolescents. Case reports demonstrate that adults experience cognitive deterioration after discontinuing dietary restrictions of phenylalanine. Another reason for life-long dietary adherence is that resuming a restricted diet is very challenging. A support team to encourage patient compliance is key in managing PKU.^{1,4}

CONCLUSION

Phenylalanine levels must be monitored and controlled with dietary restrictions throughout the patient's life. This is best achieved with a multidisciplinary approach. Further research needs to be conducted to determine the relationship between a patient's phenotype and blood phenylalanine levels for new treatments to degrade phenylalanine.⁴

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