R.C.P.U. NEWSLETTER

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R.C. Philips Research and Education Unit
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Phenylalanine Hydroxylase (PAH) Deficiency

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Introduction

Phenylalanine Hydroxylase (PAH) deficiency is an inborn error of metabolism that results in intolerance to the dietary intake of the essential amino acid, phenylalanine. The intolerance is due to decreased enzyme activity of phenylalanine hydroxylase, which converts phenylalanine to tyrosine (Figure 1). Excessive build-up of phenylalanine is toxic to nerve cells and can lead to brain damage. This intolerance produces a spectrum of disorders, with the most severe being profound and irreversible intellectual disability.

Prevalence ranges in frequency from 1:5,000 in those of Turkish and Irish descent to approximately 1:10,000 in those of northern European and East Asian origin. In the United States, the prevalence is approximately 1:10,000-1:20,000.

Thanks to efforts through the newborn screening program, we are able to detect PAH deficiency in babies and initiate medical management changes that have dramatically altered the long-term outcome for individuals with this condition. The article will review the standards for medical management of PAH deficiency.

Figure 1: Phenylalanine Catabolism by PAH

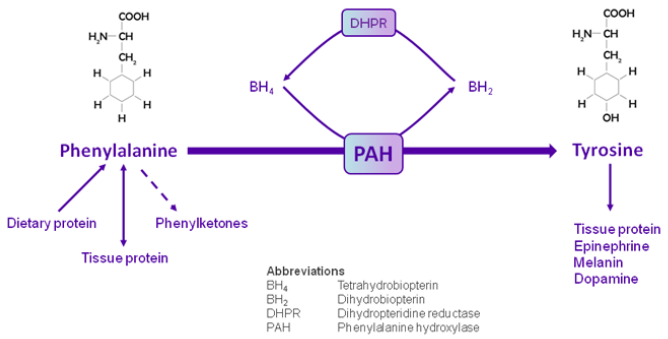

Photo Credit: Genetic Metabolic Dietitians International PKU tool kit

Diagnosis

In almost 100% of cases, PAH deficiency is now diagnosed through the newborn screening program by the detection of hyperphenylalanemia in a dried blood spot. Blood spots are collected on filter paper after the first 24 hours age of life and sent to the state laboratory for screening of PAH deficiency and other conditions. Early detection is important because there are usually no postnatal clinical findings in an infant with hyperphenylalanemia.

The diagnosis of PAH deficiency is then confirmed by persistently elevated plasma phenylalanine levels above 120umol/L. Further testing includes plasma amino acids, BH_4 cofactor testing and

molecular testing through sequencing or deletion/duplication analysis.

PAH deficiency is inherited in an autosomal recessive manner and is caused by genetic changes to the *PAH* gene. The gene is responsible for providing the instructions to make phenylalanine hydroxylase. There are more than 900 reported pathogenic variants which cause PAH deficiency. Genotype and phenotype correlations are complex, but identification of the specific genetic variants can help direct long-term management and responsiveness to BH_4.

Clinical Features

Common clinical findings in untreated adults with PAH deficiency include:

- Epilepsy
- Varying degrees of intellectual disability and behavior problems, including autism spectrum features
- Parkinson-like features (especially in adulthood)
- Musty body odor
- Eczema
- Decreased skin and hair pigmentation
- Females with a history of recurrent pregnancy loss and/or offspring with malformations including microcephaly, congenital heart disease, and small size. (Maternal PKU)
- Progressive white matter disease on brain MRI, regardless of neurologic deterioration. Usually those off diet or with poor compliance have most severe findings by MRI.

Individuals with severe PAH deficiency, known as classical Phenylketonuria (PKU), are at highest risk for developing profound intellectual disability. Milder PAH deficiencies, known as hyperphenylalanemias, vary in severity and degree of treatment. Some individuals do not require dietary interventions.

Those who are able to manage their PAH deficiency with dietary restriction of protein and supplementation, may have relatively normal cognitive abilities. Adults with classic PKU can have a small drop in IQ when there is poor adherence to diet and management. It is important to note that even with strict adherence, some individuals with classic PKU (treated from birth) may have difficulties with their learning abilities, memory, and executive function.

Figure 2: Classification of PKU
Adapted from Camp *et al*.

Classification of PKU

Severity of PAH Deficiency	Blood PHE Concentration Pre-treatment	Dietary PHE Tolerance	PAH Genotype
Classical PKU	>1200 umol/L	250-350 mg	2 classic mutations (often null)
Moderate PKU	900-1200 umol/L	350-400 mg	1 classic+ 1 moderate or 2 moderate mutations
Mild PKU	600-900 umol/L	400-600mg	1 classic, moderate or mild mutation +1 mild HPA mutation
Mild HPA	360-600 umol/L	No data	1 classic, moderate or mild mutation +1 mild HPA mutation

Management

Nutrition therapy was introduced six decades ago and remains the primary treatment for PAH deficiency. Nutritional therapy requires a decrease in the intake of natural protein through diet and replacement by using an amino acid mixture that has all the other amino acids except phenylalanine (since protein is necessary for normal growth and development). These dietary changes need to be monitored by a team of experienced metabolic geneticists and registered metabolic dietitians.

The dietary restrictions and decrease in natural protein is usually quite drastic, and can be as low as 3g protein or 150mg phenylalanine. This means that those with PAH deficiency must adhere to a strict vegan diet that also omits nuts, seeds, and beans. Limitation of dietary phenylalanine is an effective treatment for PAH deficiency, however, the diet is very restrictive and long-term adherence is difficult. This often leads to suboptimal control in older children and adults.

The restrictive nature of the diet by omitting meats and dairy can increase the risk for multiple vitamin deficiencies due to the synthetic make-up of the diet. Dietitians have the important role of keeping in touch with PAH deficiency patients and adjusting diet based on their blood phenylalanine. Blood phenylalanine is monitored every week to every month using small drops of blood, usually from a finger or heel when patients are under one-year old. Dietitians communicate with their patients weekly to review their lab results, dietary intake and manage their formula to ensure it is adequate and appropriate for their age and development. Diet and formula are changed in accordance with blood phenylalanine levels.

Since the diet is so strict, this leads to issues with long-term compliance and often many individuals with PAH deficiency stray from their diet during their teenage years and into adulthood. Medically modified low protein foods are commercially available online but can be extremely expensive, being markedly higher than their regular counterparts in the grocery stores. For example, one box of specialized low protein pasta costs close to $10.00. By comparison, a regular box of pasta costs about $1.00. Therefore, these low protein foods can be so cost prohibitive that families are not able to benefit from either the standpoint of better long-term compliance nor as an additional dietary option to keep phenylalanine levels low.

To assist with diet and medical formula compliance, Kuvan is a medication that is available to some patients with PAH deficiency. Kuvan is a pharmaceutical form of tetrahydrobiopterin (BH_4), which is a natural substance that helps the PAH enzyme convert phenylalanine to tyrosine. This helps reduce overall phenylalanine levels in the body. Kuvan is very beneficial to those that are considered ‘responders’. Unfortunately, only 30-50% of those who try Kuvan actually respond and find that it helps to lower their blood phenylalanine.

Maternal PKU

A major concern in the management of PAH deficiency is that of women with the condition who are of childbearing age. High maternal phenylalanine concentrations have teratogenic effects on the developing fetus. These features include facial dysmorphism, microcephaly (small head size), developmental delay, learning difficulties and congenital heart disease.

Studies have shown that a reduction in phenylalanine levels before or soon after conception, have a significant effect on fetal outcomes. Maternal PKU syndrome is preventable by keeping blood phenylalanine levels within 120-240 umol/L prior to conception and maintaining these phenylalanine levels throughout pregnancy.

To achieve optimal phenylalanine control, natural sources of protein must be tightly restricted. Protein requirements are provided through synthetically manufactured phenylalanine free amino acid mixes. However, these protein restrictions place pregnant women at a high risk for developing multiple nutritional deficiencies. Therefore, these amino acid mixes contain a high concentration of micronutrients, which are above the currently set Reference Nutrient Intake values. This helps to decrease the likelihood of malnutrition.

Patient Resources

Support organizations serve an important role for families to connect to other families who have PAH deficiency. Major support groups include:

National PKU Alliance: https://npkua.org/

National Organization for Rare Disorders (NORD) : https://rarediseases.org/

National PKU News: http://www.pkunews.org/

Genetic and Rare Disease Information Center: https://rarediseases.info.nih.gov/

Conclusion

From the early detection of babies with PAH deficiency identified through the newborn screening programs to dietary management with low protein foods, medical formula and Kuvan supplementation, few genetic conditions have had such a dramatic change in their long-term outlook and quality of life over the past few decades.

PAH deficiency is, deservedly so, a reminder of the importance of early detection, management, and continued research to prevent intellectual disabilities and other medical complications in future generations born with this and other metabolic conditions.

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About the RCPU

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health. The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate mental retardation through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects. Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes. Pediatric Genetics University of Florida Box 100296 Gainesville, FL 32610. The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health professionals and for the community at large.

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