Approach to Phenylketonuria

Developed by Jennifer Butler, M.Sc, and Umairah Boodoo, B.Sc. and Dr. Hannah Geddie, MD FRCPC for PedsCases.com.
September 2021

Introduction:

Hello everyone! We are Umairah Boodoo and Jennifer Butler, two medical students at McMaster's School of Medicine in Ontario. This podcast on phenylketonuria was developed for pedcases.com, with guidance from Dr. Hannah Geddie, Assistant Professor and Pediatric Endocrinologist in the Division of Pediatric Endocrinology in the Department of Pediatrics at McMaster University.

Objectives:

By the end of this podcast, listeners will be able to:

1. Define PKU and explain its pathophysiology.
2. Describe the historical importance of PKU in modern medicine.
3. Explain the diagnosis and management options for patients with PKU.
4. List the potential complications of PKU into adulthood.

Case:[1]

We will start off by presenting a case.

Leo is a baby boy born at McMaster's Children's Hospital at 39 weeks, weighing 3.3kg. As part of the routine newborn screening, elevated Phe levels were found in Leo's blood. A repeat sample was obtained which showed Phe levels of 1260 umol/L. You are asked to see Leo's parents to discuss the results of the neonatal screening. The parents are devastated and ask you what this means for Leo and if he will be able to live a normal life. What are your next steps?

Definition:[2]

Phenylketonuria (PKU) is an autosomal recessive disorder involving the deficiency of phenylalanine hydroxylase (PAH), an enzyme that allows our bodies to break down amino acids.

Epidemiology:[2]

The incidence of PKU can vary between regions. In Canada the incidence is 1 in every 12, 000 live births. It is the most common inherited metabolic condition of amino acid breakdown. PAH deficiencies affect all ethnic groups but is most common in Turkish populations, northern European, Irish, and Indigenous populations. It is much less common in Hispanic, Asian, Ashkenazi Jewish and African populations.

Pathophysiology:[2]

Let's talk more about the pathophysiology of PKU before jumping into our case presentation. PKU is an inborn error of metabolism that follows an autosomal recessive inheritance pattern. Patients with PKU have a deficiency of the enzyme phenylalanine hydroxylase (PAH), found on chromosome 12. Thus, in order for an individual to be diagnosed with PKU, both alleles of the gene for PAH need to be mutated.

PAH is a hepatic enzyme that converts the essential amino acid phenylalanine to tyrosine. This pathway catabolizes the majority of Phe obtained through the patient's diet, and the remaining dietary Phe is used for protein synthesis. In 98% of PKU cases, there are defects or deficiencies in the PAH gene, leading to low levels of functioning PAH. In this situation, Phe from a patient's diet cannot be metabolized and converted to tyrosine effectively. This leads to a toxic buildup of Phe and Phe metabolites, known as phenylacetate and phenyllactate, in the blood and urine. Tyrosine concentrations are usually near normal although they can be low in some cases. In about 2% of PKU cases, a cofactor needed for Phe catabolism is not functional, as opposed to PAH.

To help us understand how a deficiency in PAH leads to an accumulation of phenylalanine, let's use the following analogy. Imagine an assembly line with 3 workstations: A, B, and C. Blocks enter the assembly line at station A and progress from stations B to C, where they are combined to form new products. If workstation B breaks down, the blocks from station A cannot get processed. This leads to a buildup of products at station A until they are falling off the assembly line and the whole factory comes to a halt. Meanwhile, there are almost no blocks at station C.

The degree of enzyme activity is related to the severity of symptoms. A complete PAH enzyme deficiency is seen in classic PKU. Phe levels in untreated, newly diagnosed newborns are over 1200 umol/L. Residual enzyme activity results in varying levels of disease severity.

Moderate PKU → 900 - 1200 umol/L
Mild PKU → 600 - 900 umol/L
Mild hyperphenylalaninemia (HPA) → 360 - 600 umol/L
Benign mild HPA → typically does not require treatment; 120 – 360 umol/L

History of PKU:[3]

PKU was discovered in 1935 by Asbjorn Fölling, a Norwegian physician and biochemist, and until the early 1960s, its diagnosis was initially made by detecting phenylpyruvic acid (an intermediate in phenylalanine synthesis) in urine. Although this test was accurate, it was not sensitive enough to detect phenylpyruvic acid until irreversible brain damage had already occurred. This was particularly troublesome because by the 1950s, clinicians knew that the neurotoxicity associated with PKU could largely be avoided by early administration of low-phenylalanine diets.

PKU is rare but it has garnered attention because it led to a historical victory for scientific medicine and public health. In the 1960s, Dr. Robert Guthrie, an American microbiologist, modified the tests he used in his cancer research to develop a bacterial inhibition assay that was successful in detecting PKU in newborns through a heel prick test.

As a result, PKU became the very first condition for which newborns were screened. In 1965, newborn screening began in Ontario and by the mid-1970s, newborn screening for PKU became routine in nearly every developed country. This simple screening test for PKU has now become the prototype for universal newborn screening programs.

This is a victory for modern medicine because PKU, as compared to other success stories of scientific medicine such as polio, smallpox, and typhoid fever, is rare and appropriate treatment requires screening of thousands of unaffected infants.

In addition, the fact that an environmental intervention could dramatically alter the course of a genetic disorder makes it a strong example of the importance of screening healthy infants for genetic disease.

Diagnosis:[2]

It is important to note that many children with PKU appear asymptomatic at birth. If undetected in screening, symptoms of PKU may not develop until early infancy when Phe levels become increasingly elevated via accumulation through dietary breast milk or standard commercial formula. If left untreated, this can lead to intellectual disability, abnormal gait and sitting posture and potentially epilepsy. However, when detected early and managed right away, severe symptoms can be mitigated. Thus, we can reassure the parents that detecting PKU in the neonatal period and swiftly enacting a management plan confers a positive prognosis. However, it is also important to keep in mind that many children born outside of the country may or may not have had screening at birth.

Treatment and Management:[2]

The main treatment goal for PKU is to maintain blood Phe concentrations within a range of 120 – 360 umol/L (for classic PKU) to prevent the development of neurological complications. This is done through dietary restriction.

In general, Phe is found in all high protein foods and smaller amounts also occur in low protein foods, such as fruits, vegetables, and grains. Thus, the amount of Phe-containing foods an individual can consume depends on their Phe tolerance, i.e., the amount of Phe they can consume to remain within the therapeutic range of blood Phe levels. This treatment involves an interdisciplinary approach, with a team of nutritional, medical, and social work experts.

An individual's Phe tolerance is determined through careful observation and adjustment of Phe intakes by a registered dietitian. Individuals with classic PKU have too low a Phe-tolerance to achieve a nutritionally complete diet without supplementation from Phe-free medical formulas. For example: iron deficiency is common in protein restricted diets. These formulas provide individuals with high phenylalanine-free protein equivalents, vitamin, and mineral levels for appropriate growth and development. In addition, infants cannot rely solely on breastmilk because it contains Phe. Thus, they must alternate between breastmilk and Phe-free formula.

However, this tolerance level can change throughout life due to changes in age, BMI, and body composition. Thus, lifelong monitoring of blood Phe and tyrosine levels is required. During the first year of life, levels are measured weekly. From 1 - 12 years of age, levels are measured twice monthly and from 12 and onwards, levels are

measured monthly. Importantly, diet changes can reverse most signs of PKU, other than cognitive impairment if it has already occured.

Complications:[1,2]

When left untreated, PKU can lead to severe intellectual disability. The mechanism for this is largely unknown but several hypotheses exist. Phe is a precursor to Tyr, and dopamine is subsequently synthesised from Tyr, thus abnormal Phe metabolism may restrict dopamine synthesis. Additionally, white matter abnormalities may occur in the brain, leading to slower inter-neuron signal conduction and slower information processing.

Although early identification and treatment of PKU has greatly decreased the occurrence of cerebral damage and psychiatric manifestations, many PKU patients commonly struggle with attentional, behavioural, and mood disorders, which often go unrecognized. Patients may have decreased motivation, diminished social competence, irritability, hyperactivity, poor self esteem, and learning difficulties. In fact, recent studies have shown that even patients who maintain a low-phe diet may still struggle with poor self esteem and require psychotherapy.

In females, elevated serum phe during pregnancy can lead to a condition called Phenylalanine Embryopathy. Complications include intrauterine growth restriction, intellectual disability, microcephaly, and cardiac complications in the newborn. This condition can also be prevented through dietary restrictions during pregnancy.

Case Review:

Going back to the case above, you have now talked to Leo's parents about his diagnosis and management. They understand that it can be a challenging path living with a chronic illness, and the family will benefit from a primary health care provider (family physician or pediatrician) who can support and manage the family in a holistic manner. This includes monitoring for issues with mood, self esteem, coping with a chronic illness, and observing closely for learning disabilities and ADHD once Leo enters the school system. Additionally, adherence to diet generally decreases with increasing age, and adds complexity to the many developmental milestones experienced by adolescents. Ensuring that Leo feels well supported and informed is essential for his well being and dietary adherence!

Key Takeaways:

To summarize our main points, PKU is a rare inborn error of metabolism that can be detected through neonatal screening. If screening is not done, PKU symptoms generally appear in early infancy as Phe levels accumulate through dietary breast milk intake. When left untreated, PKU can lead to severe intellectual disability.

Individuals with PKU have varying degrees of deficiency of phenylalanine hydroxylase causing a toxic buildup of phenylalanine in the blood. Even with early treatment, patients may have some level of intellectual disability if Phe levels are not consistently maintained in the treatment range. It is imperative that pregnant women with PKU control their Phe intake during gestation to prevent the development of phenylalanine embryopathy, which can result in intrauterine growth restriction, cardiac problems and other congenital defects. Phe-restricted diets are the main treatment modality to ensure Phe levels remain near normal. Phe levels need to be monitored regularly throughout childhood and yearly into adulthood.

We hope this podcast has helped you better understand and manage a diagnosis of PKU in pediatric patients. Thank you to Dr. Geddie for all of her help throughout the making of this podcast and thanks for listening, everyone!

Developed by Jennifer Butler and Umairah Boodoo and Dr. Geddie for PedsCases.com.
September 2021

References:

1. Bailey, S. (2013). Phenylketonuria (PKU) and Hyperphenylalaninemia (HPA) - A Review. Nutrition Focus for Children with Special Needs, 28(4). Retrieved from http://depts.washington.edu/nutrfoc/webapps/wp-content/Focus28_4.pdf?fbclid=IwAR1kl82MGNSw0w2Jtocglvr_6KjCa9GrcpyWmEm2-ta8wGadyliGHeneM1I

2. Bodamer, O. A. (2020). Overview of phenylketonuria. UpToDate. Retrieved from https://www.uptodate.com/contents/overview-of-phenylketonuria/print?search=phenylketonuria&source=search_result&selectedTitle=1~136&usage_t…

3. Brosco, J. P., & Paul, D. B. (2013). The Political History of PKU: Reflections on 50 Years of Newborn Screening. Pediatrics, 132(6), 987-989. doi:10.1542/peds.2013-1441

Developed by Jennifer Butler and Umairah Boodoo and Dr. Geddie for PedsCases.com.
September 2021