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Phenylketonuria: A Comprehensive Review of Pathophysiology, Diagnosis, and Management Strategies

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Abstract:

Introduction: Phenylketonuria (PKU) is a genetically determined congenital metabolic disorder characterized by the body's inability to properly metabolize the amino acid phenylalanine, which is ingested through food. This deficiency leads to the accumulation of phenylalanine in the blood. If untreated, this can result in neurological damage and cognitive impairments. Despite significant progress in understanding the disease, along with advancements in diagnostic methods, the fundamental approach to managing PKU has remained consistent: early detection and adherence to a diet low in phenylalanine are essential to preventing the adverse effects of the disorder.

Purpose of the work: The aim of the study is to analyze and present the current knowledge about phenylketonuria and the quality of life of patients suffering from this disease, as well as methods of its detection.

Materials and methods: An analysis of research papers available on PubMed and Google Scholar was undertaken using the following keywords: phenylketonuria; PKU diagnosis; phenylketonuria newborn screening; genetic testing for PKU; Quality of Life in PKU patients.

Results: There are various diagnostic methods used in newborn screening and to confirm diagnosis. Regardless of the method, early diagnosis and the introduction of an appropriate diet are crucial. Adherence to dietary restrictions and monitoring phenylalanine levels, along with managing the effects of elevated levels in the body, may negatively impact the quality of life for individuals affected by PKU.

Keywords: phenylketonuria; PKU diagnosis; phenylketonuria newborn screening; genetic testing for PKU; Quality of Life in PKU patients

History of PKU

The disease was first described by the Norwegian physician Asbjørn Følling. In 1936, the mother of two children with intellectual disabilities approached him, wanting to determine if it was related to the unusual musty odor of her children's urine. Følling concluded that this secondary metabolite originated from phenylalanine in the diet. He conducted tests on urine samples from 430 patients with intellectual disabilities. The urine samples were examined for several substances, including ketones. When ketones are present, urine usually turns reddish-brown upon the addition of ferric chloride. In the case of eight patients, the urine turned dark green. All eight patients presented with severe intellectual impairment, eczema, a stooping posture with broad shoulders, and a spastic gait. Dr. Følling published his findings and proposed the name ‘imbecillitas phenylpyruvica’, later changed to ‘phenylketonuria’. In 1939, Jervis was the first to suggest that the disease had genetic determinants. The same scientist demonstrated that the issue was the body's inability to metabolize phenylalanine into tyrosine, due to a lack of activity in the phenylalanine hydroxylating system. The breakthrough in treatment came in the 1950s with Dr. Horst Bickel, who first developed and implemented a low-phenylalanine diet. Then, in the 1960s, Guthrie devised a simple test for detecting hyperphenylalaninemia.

As a result, phenylketonuria became the first disorder to have newborn screening tests developed [1,2,3].

Etiology

Phenylketonuria is inherited in an autosomal recessive manner, involving a genetic mutation in the gene encoding the enzyme phenylalanine hydroxylase (PAH). Phenylalanine (Phe) is one of the exogenous aromatic amino acids, primarily sourced from dietary proteins. In humans, phenylalanine undergoes hydroxylation by the enzyme phenylalanine hydroxylase, converting phenylalanine into the next aromatic amino acid, tyrosine. This hydroxylation process occurs in the liver and is catalyzed by tetrahydrobiopterin (BH4). Phenylketonuria results from a partial or complete blockage of the hydroxylation of phenylalanine to tyrosine, caused by a deficiency or lack of the enzyme PAH [2,3,4].

The classification of PKU is based on blood phenylalanine concentration or dietary phenylalanine tolerance. There are three types of PKU distinguished. The reference range for blood phenylalanine levels is from 50 to 110 μmol/L. In severe (classic) PKU, the blood Phe level exceeds 1200 μmol/L with a dietary phenylalanine tolerance below 250 mg/day. In moderate PKU, the blood Phe level ranges from 900 to 1200 μmol/L. Meanwhile, in mild PKU, the blood Phe level ranges from 600 to 900 μmol/L with a dietary phenylalanine tolerance ranging from 250 to 400 mg/day. The lack of consensus regarding phenotype classification has led to patients with PAH deficiency being classified as either not requiring treatment or requiring diet, BH4, or both [5,6].

The phenylalanine hydroxylase enzyme is encoded by the PAH gene, located on chromosome 12 in the q22-24.1 region. Currently, there are over 1000 mutations causing phenylketonuria. The human PAH gene exhibits significant allelic variability. Mutations can either be neutral with respect to phenotype or pathogenic due to disruption of enzyme structure and function. These mutations come in various types [3]:

- missense mutations: 62% of PAH alleles
- small or large deletions: 13%
- splicing defects: 11%
- silent polymorphisms: 6%
- nonsense mutations: 5%
- insertions: 2%

The most common mutation replaces arginine (Arg) with tryptophan (Trp) at position 408 (i.e., Arg408Trp) [2]. [4] Mutations in the PAH gene vary in their impact on enzyme activity. The Arg408Trp mutation is responsible for "classic" PKU. Other mutations of the gene lead to mild and moderate phenylketonuria, where blood phenylalanine levels range from 600 to 1200 micromoles. Some mutations result in hyperphenylalaninemia, where blood phenylalanine levels are lower than 600 micromoles. Most patients with phenylketonuria have 2 different PKU variants, meaning they are compound heterozygotes. A much less common form of the disease is the absence of enzymatic reaction cofactors - biopterins [1,2,5,7].

Epidemiology

The prevalence of PKU varies depending on the geographic region and ethnic group. Worldwide, the estimated incidence of PKU is 1 in 23,930. It is estimated that 0.45 million people are affected by it, with at least two-thirds requiring treatment [1]. In terms of ethnicity, PKU predominantly affects White and East Asian populations. PKU is one of the most common inherited disorders among Europeans, with an incidence of approximately 1 in 10,000 live births. This prevalence mainly applies to Germany, Spain, Ireland, Scotland, and Estonia. PKU occurs much less frequently in Finland, with a prevalence of 1 in 100,000 live births. In Turkey, the incidence rate is particularly high, at 1 in 4,000 live births. Similarly high rates, i.e., 1 in 5,000 live births, are observed in the Middle East, including Egypt, Jordan, and Iran. Such a high incidence of PKU in certain regions is associated with a high degree of consanguinity within the population. In the United States, PKU affects 1 in 15,000 live births. In South America, the prevalence of PKU is lower in the north compared to the south of the continent, ranging from 1 in 25,000 to 1 in 50,000 live births [1,4,7,8].

Pathophysiology

Phenylalanine metabolism disorders caused by its hydroxylase deficiency lead to excessive accumulation of this amino acid and its toxic metabolites in the blood and brain - primarily phenylpyruvic and phenyllactic acid, as well as increased urinary excretion of phenylketone bodies. Hydroxylation of phenylalanine requires BH4 as a cofactor. Moreover, the cause of hereditary HPA, giving symptoms similar to BH4 deficiency, may be a deficiency of the co-chaperone DNAJC12, which leads to incorrect folding of PAH by disturbing the folding, degradation and translocation of hydroxylases.

Excess phenylalanine has a toxic effect on the body and causes secondary disturbances in the metabolism of tyrosine and tryptophan by inhibiting the hydroxylation of these amino acids. The concentration of tyrosine and therefore thyroxine in the blood is reduced, although hypothyroxinemia is usually not severe due to the consumption of tyrosine with food. Phenylalanine metabolites also inhibit another enzyme involved in the metabolism of neurotransmitters- aromatic L-amino acid decarboxylase, also known as DOPA decarboxylase, tryptophan decarboxylase and 5-hydroxytryptophan decarboxylase.

Tyrosine is used by the body for the biosynthesis of biogenic amines (norepinephrine, adrenaline), dopamine, thyroid hormones (thyroxine, triiodothyronine) and pigment substances (melanins), while tryptophan is a precursor of serotonin. Phenylalanine, tyrosine and tryptophan share a common transport system - the large neutral amino acid transporter type 1 (LAT1). In the case of hyperphenylalaninemia, as a result of its competition with the transporter, too little tyrosine, tryptophan and other large neutral amino acids reach the brain. The resulting deficiencies are responsible for reduced synthesis of brain proteins in sick adults, reduced availability of these amino acids for neurons, and impaired synthesis of neurotransmitters, primarily dopamine and serotonin. There are separate, sodium-dependent Large neutral amino acid transporters that can transport amino acids out of the brain back into the circulation and may regulate any disturbances in amino acid homeostasis. Thus, oral supplements of large neutral amino acids other than phenylalanine may be useful in treatments to correct amino acid imbalances in the brain.

Myelination disorders are also observed in phenylketonuria - phenylalanine may impair cholesterol synthesis by inhibiting the activity of HMG-CoA reductase, thus interfering with myelin production. In addition to reduced cholesterol levels, patients with phenylketonuria have altered levels of high-density lipoprotein (HDL), low-density lipoprotein (LDL) and apolipoprotein A-I/A-II and B, as well as reduced levels of oxysterols and vitamin D. Due to the lack of appropriate myelin synthesis and its faster breakdown, demyelination occurs, loss of some neurons and conduction disorders. Additionally, it has been shown that there is a reduced concentration of docosahexaenoic acid (DHA), an essential long-chain omega-3 polyunsaturated fatty acid, in plasma phospholipids and blood samples of patients with phenylketonuria, and such a deficit may be involved in the neuronal damage occurring in this disease.

The main neurotoxic factor responsible for the above abnormalities is an increased level of phenylalanine. Clinically, untreated patients develop profound mental retardation, various psychiatric and neurological disorders, and also often suffer from eczema and have light pigmentation of the skin, hair and eyes [1,9,10,11].

Maternal phenylketonuria

Maternal phenylketonuria (MPKU) is a syndrome of congenital anomalies and mental retardation in the offspring of women with phenylketonuria. It arises from exposure of the fetus to high levels of phenylalanine in the mother's blood. During pregnancy, phenylalanine tolerance increases due to fetal enzymatic activity. Phenylalanine is actively transported from the mother to the fetus through the placenta. Phenylalanine concentrations in the fetal blood can be up to twice as high as in their mothers'. There are many factors that influence phenylalanine tolerance in pregnant women, such as age, variability in weight and body composition, protein catabolism, fetuses affected or unaffected by phenylketonuria, single or twin pregnancy. Low phenylalanine tolerance in the third trimester of pregnancy may indicate fetal phenylketonuria [1,12,13].

In pregnant women with phenylketonuria, it is important to maintain phenylalanine intake in balance between the minimum amount preventing Phe deficiency in the fetus and mother, and the maximum amount within safe limits for the mother and fetal brain. The recommended blood Phe level for a pregnant woman is 120-360 μmol/L or a Phe level <240 μmol/L. Maternal phenylketonuria occurs if the mother's Phe concentration rises above 360 μmol/l during pregnancy. In such cases, high levels of this amino acid impair organogenesis. Characteristic symptoms in the child include microcephaly, growth retardation, intellectual disability, and congenital defects [12,13,14,15]. The recommendations issued by both the World Health Organization (WHO) and the European Food Safety Agency indicate a protein intake of 0.83 g/kg ideal body weight and an additional amount of 1 g, 9 g, and 28 g (31g for WHO) protein during the first, second, and third trimester, respectively, and an additional 19 g during exclusive breastfeeding [16,17].

Newborn screening

Although PKU is a rare disease, the possibility of its effective treatment with diet has caused worldwide prevalence of newborn screening for this disease. Currently, these tests are conducted in the United States, Canada, Australia, New Zealand, Japan, the nations of Western and most of Eastern Europe, and many other countries. The test is relatively simple and minimally invasive. It involves pricking the newborn's outer or inner side of the heel and collecting blood onto a filter paper card (Guthrie card) so that the marked circles on the card are filled in. This sample is called a dried blood spot (DBS). The timing of collecting DBS samples is different among countries and varies from 24 hours to 72 hours after birth.

Right after birth, the newborn's body still contains enzymes supplied from the mother's body, which enable the proper metabolism of phenylalanine. The level of phenylalanine increases only after feeding the baby with nourishment containing phenylalanine, which usually means breast milk or standard formula milk for newborns. Therefore, taking blood too early may result in a false negative test result. [9,18,19,20].

The screening method originally used was the Guthrie test. It involved placing a cut-out disk of paper with blood on a medium containing an inhibitor and Bacillus subtilis spores. Phenylalanine present in the blood of children with phenylketonuria allowed the bacteria to grow. The diameter of the formed colony correlated with the concentration of phenylalanine in the blood. Currently, several methods are used depending on the country and region. The most common method is tandem mass spectrometry. Although the Guthrie test is still used in some areas, other methods include, for example, fluorometric or enzymatic tests [21,22,23].

Molecular diagnosis

PKU diagnosis includes a variety of methods that allow both early detection of the disease in newborns and regular monitoring of phenylalanine levels in people already diagnosed with phenylketonuria. The key diagnostic techniques have their own specific uses and advantages, allowing for a comprehensive approach to diagnosing and monitoring PKU.

The following diagnostic methods can be used in the diagnosis of phenylketonuria:

- Sanger sequencing:

This is a classical DNA sequencing method involving dideoxy-sequencing. It involves selective incorporation of chain-terminating dideoxynucleotides during DNA replication. In this method DNA to be sequenced is amplified and denatured into single strands. A primer is annealed to the single-stranded DNA, and DNA polymerase extends the primer by adding nucleotides. Four separate reactions are performed, each containing one of the four dideoxynucleotides (ddATP, ddTTP, ddGTP, ddCTP) along with standard nucleotides. Incorporation of a dideoxynucleotide causes chain termination. The resulting fragments are separated by size using capillary electrophoresis. The sequence is read by detecting labeled dideoxynucleotides. Sanger sequencing is used for precise identification of known mutations in the PAH gene that cause PKU. It is particularly useful in confirmatory diagnostics when specific, known mutations are being investigated [24].

- Next Generation Sequencing (NGS):

This advanced technique allows simultaneous sequencing of multiple genes or the entire genome. In this method DNA is fragmented, and adapters are attached to the ends of the fragments.

The fragments are then amplified and sequenced in parallel on a sequencing platform. Sequencing data are collected and analyzed using bioinformatics tools to reconstruct the DNA sequence. NGS is used in cases where comprehensive examination is required, such as when a patient has complex or unknown mutations in the PAH gene. It enables the discovery of new mutations associated with PKU by sequencing multiple genes or the entire genome. This is particularly useful when classical methods fail to identify the cause of the disease [25].

- SNP (Single Nucleotide Polymorphisms) analysis:

This technique allows rapid detection of specific mutations. It is used in population screening and non-invasive prenatal testing. In this method specific regions of DNA are amplified using PCR. The amplified DNA is then hybridized with SNP-specific probes that can detect the presence of specific SNPs. Detection methods may include fluorescence, mass spectrometry, or other techniques that allow identification of specific SNPs in the DNA sample. SNP analysis is used for rapid detection of specific mutations in the PAH gene. It is commonly employed in population screening programs and non-invasive prenatal tests to identify individuals carrying specific mutations associated with PKU [26].

- real-time PCR (qPCR):

It is a technique used to amplify and simultaneously quantify a targeted DNA molecule. DNA is amplified using specific primers and a DNA polymerase enzyme. During each cycle of PCR, a fluorescent dye or probe binds to the DNA, allowing the accumulation of the product to be measured in real-time. The amount of fluorescence is directly proportional to the amount of amplified DNA, allowing quantification. qPCR is used for rapid detection of known mutations in the PAH gene by quantifying specific PAH alleles. It is also used to monitor the gene copy number, which is useful in diagnosing deletions or duplications of the gene associated with PKU [27].

Sanger sequencing and NGS are key methods used to identify mutations in the PAH gene. Studies have shown that different mutations can lead to varying phenotypes of PKU, from the classic form of the disease to milder forms of hyperphenylalaninemia. Identifying these mutations is crucial for correct diagnosis and treatment. Understanding the correlation between genotype and phenotype is essential for personalizing PKU treatment. For example, patients with milder mutations may respond better to dietary therapies, while patients with more severe mutations may require more intensive treatment. Molecular diagnostics enable early detection of PKU, which is crucial for effective disease management. Mutation information allows the personalization of therapy, including diet, supplementation and potential gene therapies.

When suffering from phenylketonuria, blood levels of phenylalanine are measured. The frequency of phenylalanine level monitoring may vary depending on the patient's age, severity of the disease and effectiveness of dietary management. PKU is a genetic metabolic disorder that requires careful monitoring and management to prevent severe health complications. A key element of effective PKU management is the regular monitoring of blood phenylalanine levels and adjusting treatment and diet based on these results.

Monitoring Blood Phenylalanine Levels

Regular blood phenylalanine level tests are essential to assess treatment effectiveness and prevent the harmful effects of high phenylalanine levels. The frequency of these tests varies depending on the patient's age and the effectiveness of dietary management:

- Newborns and infants: Phenylalanine levels can change rapidly at this age, so monitoring is often done weekly or even more frequently to effectively control the disease and adjust the diet as needed.
- Children and adolescents: As phenylalanine levels stabilize, tests are usually conducted every 2 weeks to 1 month. The frequency of monitoring depends on the stability of phenylalanine levels and the effectiveness of the diet.
- Adults: For adults who adhere well to their diet, tests are recommended every few months. However, depending on individual needs and specialist recommendations, more frequent monitoring may be necessary.

Methods of Measuring Phenylalanine

- Blood Spot Testing: The most commonly used method for monitoring phenylalanine levels. Small blood samples are collected on filter paper, which are then sent to a laboratory for analysis. These tests are convenient, as they can be done at home, and are widely used in screening programs.
- High-Performance Liquid Chromatography (HPLC): A precise laboratory technique that measures phenylalanine levels by separating it from other blood components. HPLC is frequently used in specialized PKU clinics and research settings where precise measurements are crucial.
- Mass Spectrometry: An advanced technique sometimes used in conjunction with HPLC. Mass spectrometry provides highly accurate measurements of phenylalanine and other metabolites, making it particularly useful in research and detailed diagnostic settings.

Developmental and Cognitive Assessment

Regular assessments of cognitive development and mental health, especially in children, are important for early detection of developmental delays. These assessments should be conducted every 6-12 months, depending on the patient's age and symptoms.

Regular Follow-Up Visits

Patients with PKU should regularly visit specialists, such as geneticists, metabolic specialists, and neurologists, to monitor treatment progress and adjust the management strategy. These visits usually occur every 6-12 months but can be tailored to the individual needs of the patient [28].

Phenylalanine-restricted diet

The basis and most important element of treatment for people diagnosed with phenylketonuria is an adequate diet. Such a diet should be implemented immediately after diagnosis, preferably within the 10th day from birth, because its impact on health is most significant in newborns and children. The basis of management in patients diagnosed with phenylketonuria is preventing the accumulation of phenylalanine in the blood to decrease the risk of adverse effects.

To achieve this goal, the following recommendations are used:

- The first element of the treatment is natural protein restriction (up to 25% or less).
- The second is phenylalanine-free protein supplements or supplements very low in phenylalanine (synthetic protein or amino acid mixture). This is to maintain an appropriately low level of phenylalanine in the blood while avoiding protein deficiency and metabolic imbalance.
- The last step is supplementation of vitamins and minerals and ensure that the diet contains a balanced amount of all essential nutrients and energy [6,29].

Products rich in protein, including phenylalanine, which are usually excluded or restricted from the diet of patients with PKU include:

- meat (including beef, pork, poultry, fish)
- eggs
- cheese derived from animal milk (cow, goat, sheep), dairy products)
- nuts, seeds, quinoa, wheat, oats, rye, barley.
- Soy products (soybeans, tofu, tempeh and milk)
- pulses (Beans, peas, lentils)
- gelatin and plant algae (e.g. spirulina)
- aspartame-sweetener (contained in e.g. diet sodas, chewing gums, sweets, desserts, jelly).
- flour-based foods (especially whole grain)
- some vegetables (e.g. potatoes) [6,19,29].

A balanced diet for a person with PKU should consist of the following:

- Taking the prescribed protein substitute dose in at least three equal portions throughout the day. The protein substitute is typically fortified with all necessary vitamins, minerals, and long-chain fatty acids to meet nutritional needs. If the protein supplement does not provide these vitamins, minerals, and long-chain fatty acids, then additional supplementation should be administered. If adherence to the protein substitute is poor, additional vitamins and minerals may be needed, and the biochemical nutritional status should be closely monitored.
- Encourage the consumption of fruits and vegetables containing ≤75 mg of phenylalanine per 100 g. Aim for five portions per day, with at least one portion at each meal. A portion is defined as a handful, using the patient's hand size as a guide.
- Promote the inclusion of special low-protein foods, such as bread and pasta, at most meals to provide calories, improve satiety, and add variety.
- Phenylalanine intake should be spread out over the day.
- Encourage additional water intake with the protein substitute [6,29].

Goals of dietary treatment

After diagnosing phenylketonuria in a newborn, a Phe-free medical formula is introduced instead of breast milk or standard infant formula as soon as possible to achieve plasma Phe concentrations of 120-360 μmol/L (2-6 mg/dL). (5) After the age of 12 years, patients with PKU should aim for blood Phe levels of 120–600 μmol/L (2-10 mg/dL).

In previously untreated people, a diet should undoubtedly be used if blood Phe concentrations are >600 μmol/L (10 mg/dL), but this is not necessary if the Phe concentration is <360 (6 mg/dL). In people with concentrations between 360 and 600, there are no clear results as to whether treatment should be initiated, but it is likely that a Phe level closer to 360 is safer [6,30].

Quality of life

Among the factors relevant to the quality of life of patients with phenylketonuria, age, metabolic control, and adherence to medical advice appear to be the most significant. Some studies have shown that there is no statistically notable difference between the quality of life of healthy individuals and patients with phenylketonuria. Other studies, however, indicate that children with phenylketonuria experience more difficulties at school and have more emotional problems. Studies have shown that metabolic control in patients with phenylketonuria is negatively correlated with the experience of pain, anger, sexuality, and sleep quality in adults. Current levels of phenylalanine in the blood also showed a negative correlation with sexual health. Furthermore, metabolic control was associated with patients' mood, and poor metabolic control positively correlated with behavioral problems. Good metabolic control has a positive effect on both physical and mental well-being. Studies on the pediatric population have shown that children with phenylketonuria exhibit fewer positive emotions compared to their healthy peers. Patients up to the age of 12 years tend to function better physically than teenagers, which is probably related to the rebelliousness and non-compliance with diet and treatment often observed in adolescents. It has been observed that patients who strictly adhere to the diet have a higher quality of life but report less enjoyment of food. It seems that tetrahydrobiopterin supplementation may positively impact metabolic control in both children and adults. It is likely a therapeutic option that could significantly improve patients' quality of life.

The most common quality of life issues among students with phenylketonuria include slow thinking and reduced concentration, which negatively affect academic performance. Younger patients tend to have a higher quality of life than older adults, likely due to better social and psychological support, as well as participation in educational programs for children and their parents. The poorer quality of life among older adults may be due to comorbidities and feelings of loneliness. Common difficulties for adult patients include exhaustion, anxiety about phenylalanine levels, and feelings of guilt due to non-compliance with the diet.

It was also found that women with phenylketonuria have a lower quality of life than men. One explanation is greater vulnerability of women to the emotional and social effects of phenylketonuria due to societal expectations and gender roles. Pregnant women with phenylketonuria have also lower scores in social support and quality of life compared to healthy women.

A poorer quality of life is also experienced by individuals with less education and lower occupational status [31].

Conclusions

The development of science and technology allows for quick detection and easy control of the treatment of phenylketonuria. However, this disease still requires primarily dietary treatment and great commitment and self-discipline of patients or parental care to maintain the appropriate level of phenylalanine in the blood. Detecting the disease in the first days of life and immediately implementing a diet and maintaining the appropriate level of phenylalanine in the blood are undoubtedly crucial for the patient's health. Apart from the neonatal and childhood periods, pregnancy is a period of particular emphasis on following a diet due to the consequences for the fetus. Both the damage to the body and the consequences of high levels of phenylalanine in the body, as well as the diet itself and check-ups can significantly reduce the quality of life of patients and this should be remembered. There is a need for further research to accurately describe the complex interactions between the various factors that influence the quality of life of patients with phenylketonuria. This research could help identify areas for improvement in treatment.

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