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Clinical Aspect of Phenylkeatnuria-Comprehensive Review

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Abstract

This paper describes the history and clinical manifestation of the Phenylketanuria(PKU).The PKU is caused by a specific PAH gene mutation and is a recessive autosomal genetic disease that is mainly inheritedwithin families.Because of the absence of the action of enzyme Phenylalanine hydroxylase it result in this genetic disorder, it causes serious brain damage.

Keywords: *Phenylketanuria(PKU),recessive autosomal genetic disease, inherited, families, genetic disorder, brain damage.*

INTRODUCTION

Phenylketonuria (PKU) is an autosomal recessive genetic disorder and clinical manifestation that aggrandizes the levels of a the amino acid;phenylalanine in the blood. The body can't metabolize phenylalanine. Phenylalanine is in almost all the foods. If the phenylalanine level gets too high, it can damage the brain and assisted neuroglia and cause severe intellectual disability. All new born babies must now have a keen screening test for PKU. This makes it easier to diagnose and treat the problem much early.

History of PKU

PKU was first delineated by AsbjørnFølling, one of the first Norwegian physicians to apply chemical methods to the study of medicine. In 1934, the mother of the two intellectually impaired children approached researcher Følling to ascertain whether the strange musty odour of her children's urine might be rakished to their intellectual impairment.3 The urine samples were tested for a number of substances encompassing ketones(MacDonald et al.,2006). When ketones are present, the urine usually develops a red-brown colour upon the addition of ferric

chloride, but in this instance the urine yielded a much dark-green colour. After confirming that the unusual result was not due to any of the medications and repeating the test every other day for two months, Følling proceeded with the more detailed chemical analysis involving organicextraction and purification of the responsible compound, and the determination of its melting point. The basic elements were mainly quantitated by combustion, and an empiric formula of C9H8O3derived (Sweeney et al., 2012).The Mild oxidation of the purified substance produceda compound which mainly smelled of benzoic acid, leading Føllingto postulate that the compound was phenylpyruvicacid. There was no change in the melting points upon mixing of the unknown compounds with phenylpyruvic acid thus confirming the mystery compound was indeed phenylpyruvic acid.

Clinical Manifestation

In individuals with the PKU, a secondary pathway of phenylalanine metabolism comes into play. In this pathway phenylalanine undergoes the transamination with pyruvate to yield phenylpyruvate(Rohde et al.,2015). Phenylalanine and the phenylpyruvate accumulate in the blood and tissues and are excreted in the urine— hence the name "phenylketonuria.The Phenylpyruvate can be catabolized into phenylacetate and phenyllactate. Phenylacetate imparts quiet a characteristic odor to the urine, which nurses have traditionally availed to detect PKU in infants. Diet of PKU individuals: diet must supply only enough phenylalanine and the tyrosine to meet the needs for protein synthesis. The Consumption of protein-rich foods must be curtailed. Artificial sweetener aspartame is a dipeptide of the aspartate and the methyl ester of phenylalanine. Therefore, it should be avoided by thePKU individuals. Phenylketonuria can also be caused by a defect in the enzyme that biocatalyzes the regeneration of cofactor tetrahydrobiopterin. The treatment in this case is much more complex than restricting the intake of phenylalanine and the tyrosine. Tetrahydrobiopterin is also required for the formation of the L-3,4-dihydroxyphenylalanine (L-dopa) and 5-hydroxytryptophan—precursors of the neurotransmitters norepinephrine and the serotonin, respectively—and in phenylketonuria of this type, these starting material must be supplied in the diet. Supplementing the diet with the tetrahydrobiopterin itself is ineffective because it is unstable and does not cross the bloodbrain barrier(Ahring et al.,2011)

GENETIC CAUSE

23 pairs of chromosomes make up the human system, 22 of which are auto somes and one of which is a pair ofthe sex chromosomes. The long arms of chromosome 12 (12q22–12q24.1) contain the PAH gene. The PKU is caused by a PAH gene mutation and is a recessive autosomal genetic disease that is mainly inherited within families. A kid will only get the condition if all of the PAH genes from both the parents are mutated, since each chromosome is passed down to the child in two copies, one from the mother and one from the father. A child has 100% PKU if both the parents have it and has a 50% chance if one parent has it and the other is a recessive gene carrier. In the third case, child has a 25% chance of developing the condition if both the parents are carriers(Rhode et al.,2014) .

Classification

The normal range for Phenylalanine(Phe) in the blood is under 120 micromoles per liter (μmol/L). Based on the blood the Phe concentration, there are basically three types of PKU: mild hyperphenylalaninemia PKU (MHP),the mild PKU (mPKU), and classical PKU (cPKU). A Phe concentration between 120 and 600 μmol/L is considered as MHP, which is the lowest level above normal. A Phe concentration of about 600 to 1200 μmol/Lis defined as mild PKU (mPKU). And a Phe level greater than about 1200 μmol/L is cPKU, which is themost severe type. From the global data, the phenotypic distribution of the PKU was about 16% MHP, 22%mPKU and 62% cPKU. However, the distribution and the severity of various phenotypes of PKU varygreatly according to the different countries and regions(Abadie et al.,2005)

CLINICAL MANIFESTATIONS

If detected early and treated early, people with PKU have almost no symptoms. However, if not detected and treated in time, PKU can also damage the brain and nerves, leading to cognitive impairment. Eczema, alighter color of the skin and hair compared to other family members, a small head, and a rat odor in the breath, the skin, or urine are the common symptoms for untreated PKU patients.

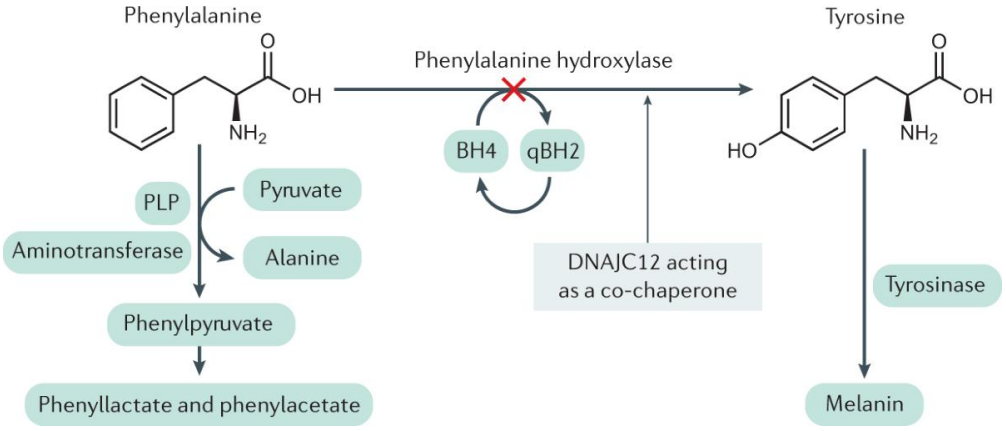

Figure no 1: (Action of Phenylalanine)

Severe symptoms encompass behavioral problems such as irritability, hyperactivity, poor self-esteem, the developmental delay, and intellectual disabilities (FIG-1). PKU patients with MHP have a much lower risk of developing intellectual disabilities in the absence of treatment. However, infants with specifically classical PKU will develop apermanent intellectual disability in a few months (McLeod et al.,2010).

DIAGNOSIS

Early diagnosis of the PKU is of great significance. At present, newborn screening is basically carried out in most areas of the world for the diagnosis of the PKU. Diagnostic techniques are also constantlyevolving, increasing diagnostic sensitivity, the specificity, and positive prediction rates (MacDonlad et al.,2011).

NEWBORN SCREENING

Newborn blood screening or neonatal screening analyzingPhe concentrations is the main means of detecting the PKU, which is currently adopted by many countries. It can almost diagnose all cases of PAH deficiency. Normally, newborn or neonatal screening is done by having a few drops of blood taken from his or her heel after 24 hours but before 70- 72 hours of birth. If the blood Phe level is higher than 242 μmol/L (4mg/dL), baby should be considered to have PKU. 1% of the tested infants have positive results during the first screening, but only 11% of those with positive results have PKU. That means the false-positive rate is as high as90 percent. If the initial tesst shows a positive result, the infant's blood sample should be sent to areferral metabolic center to specifcally perform a confirmatory quantitative test. False-negatives are veryrarely seen(van Spronsen et al.,1993).

DIAGNOSTIC TECHNOLOGY

Over the past few decades, testing technology has specifically evolved to make newborn screening for PKU more and more accurate. Aspecifc test named The Guthrie test is also known as the Guthrie bacterial inhibition assay (BIA),which has been availed in initial newborn screening tests for the PKU for more than half a century in many countries(Camp et al.,2014). BIA uses bacteria, which is Bacillus subtilis, to measure the blood Phe concentrations, and if the blood Phe concentration is greater than the cut value (approx. 4mg/dL or 242 μmol/L), further examination and diagnosis should be made. BIA has a very high sensitivity of above 99% for mild and classical PKUin infants since it is much more sensitive to detect blood Phe levels between 180 and 240 μmol/L (3–4mg/dL). The identification of the MHP, however, is unclear and probably not comprehensive. According to research over 3 years during the 1990s, the specificity of the BIA was 99.9% and the positive predictive value was 12.8% for infants tested after 24 hours. BIA is much inexpensive, easy to develop, and widely used. The disadvantage factor for BIA is that the bacterial growth is easily impacted by many things; antibiotics present in the blood, for instance, can pave to an inaccurate test result(Singh et al.,2016) .

The McCaman and Robins fluorescence assay is a routine PKU screening and analysing method based on the theory that fluorescence will be released from the Phe after incubation with fluorophores. The sensitivity of the fluorometry assay is 100%, and the specificity is 51%(MacDonald et al.,2006).This test has its own demerits. This screening method may be more positive than BIA, especially if the patient's Phe level is close to the threshold. In other word, it is much more likely to detect the PKU infections near the threshold. Although this test has a high degree of precision, its accuracy is still below ideal for the fluorescence in rakished compounds is nonselective. Tandem mass spectrometry (MS/MS) is the most current cutting-edge technology, availing two or more mass spectrometers connected to each other to improve the ability of analysis. This method can be availed as a screening method for newborns younger than 24 hours. MS/MS have the pros of high sensitivity, high specificity, and high detection efficiency, with sensitivity and specificity of 100%and 98.1%, respectively . MS/MS is widely availed for newborn screening for PKU now(Goodwin, et al.,1964)

CONVENTIONAL TREATMENT

Tyrosine in PKU -Tyrosine is a nonessential amino acid as it comes from the Phe hydroxylation; however, in patients with the disorder PKU, it becomes essential because it cannot be synthesized. It is important to garner an adequate supply of Tyr, as either a Phe-free supplemented formula or Tyr supplement to maintain the blood levels in normal ranges. The Tyr deficiency can decrease dopamine, noradrenaline, and the melanin synthesis. To ensure an adequate supply, about 8% to 10% of total protein (macromolecule) calculated in the diet must come from Tyr.

There are also age-specific Tyr recommendations, and it is suggested to assess and calculate the contribution from medical Phe-free formula plus the contribution of food availed as Phe source and most importantly to have the Tyr blood concentrations frequently monitored(Bloxam et al.,1960). It is pertinent to take into account that the water solubility of this amino acid is poor, so it could precipitate and form a waste residue at the bottom of the container in which medical formula was prepared(observations), so parents and patients must shake well the mixture to ensure the calculated Tyr intake. The Protein Recommendations in PKU There are recommended daily intakes (RDIs) for the total protein in patients with PKU ; however, the optimal dosage depends on individual needs. Achieving optimal protein intake to maintain the adequate levels of lean body mass is possible only with close biochemical and nutritional monitoring. The main biosource of protein and nitrogen in patients with PKU must be the Phe-free formula, and it is suggested that the formula should represent between 70% and 85% of the total protein requirements in patients with a severe form of the disease; hence, their use is indispensable and is much essential for an adequate control, growth, and development. Few researchers studied 2 groups of patients with PKU with different amounts of Phe-free protein substitute, with and 1.2 g/kg/d, respectively. The higher dosage of the protein was allied with lower blood Phe concentrations; however, variations were observed depending on its carbohydrate contents(Smith,1960). The Phe-free formula must be carefully selected because variations are wide in terms of the macromolecules- carbohydrates, protein, fats, and Tyr contents. Formula distribution throughout the day is quiet important and a minimum intake of 3 servings is recommended; when it is given as a single dose, the urinary nitrogen excretion, the protein catabolism, and amino acids oxidation could increase with a concomitant protein synthesis decline. Regarding the natural protein consumption, this one accounts for about 15% to 30% of the total protein recommendation and must come from

different food groups to garner variety; titration to give the maximum amount is needed because it is rakished to benefits such as better muscle mass, vitamin, and mineral status, among others(Berry et al.,1958). Lipids and the PKU ,Several studies have reported lower levels of the total cholesterol in untreated patients with PKU, and there are different hypotheses for this; the first one is a low intake through the diet because it is devoid of animal foods, which are the primary biosources of cholesterol. Another explanation is that high levels of Phe are allied with impairment of cholesterol synthesis due to down regulated expression of the 3-hydroxy-3-methylglutarylCoA reductase and inhibition of mevalonate 5-pyrophosphate decarboxylase, besides the high consumption of the acetyl CoA to synthesize phenylacetylglutamine. Recent research and further data support that high Phe levels rather than an effect of a low protein diet pave tohypocholesterolemia in patients with PKU. Low plasma total concentrations of the linolenic acid, arachidonic acid (AA), and significantly reduced docosahexaenoic acid (DHA) an theeicosapentaenoic acid (EPA) have been demonstrated in patients with the PKU. Phenylketonuria diet is deficient in essential fatty acids; AA, DHA, and the EPA supplementation and observance are necessary since these fatty acids play an important role in the brain and also in retina(Mabry et al.,1962). Researchers conducted a study supplementing 36 children with the PKU with fish oil, providing a daily dose of 15 mg DHA/kg/d, founding a significantly much faster visualevoked potential latencies and an improvement in the motor function and coordination.35 Increased DHA and the AA concentrations have been reported after administration of 200 mg of AA and 100 mg of DHA in a powdered blend to patients with the PKUdisease. Cerain researchers found high levels of linolenic acid and low DHA in PKU adults. A systematic review of literature showed that the supplementation with DHA may be an effective way to increase the omega-3 long chain polyunsaturated fatty acid levels. Even though the number of commercial Phe-free formulas supplemented with the fatty acids has increased, currently some of them contain linoleic and the linolenic acid but they do not have DHA, so it is important that health-care personnel treating PKU be aware of this situation to specifically consider an optimal supplementation dosage (Woolf et al.,1961).Genomic analysis along with biotechnological innovations has accelerated the scientific innovation(Dr. S. Sreeremya,2024). New age genetic techniques like usage of CRISPR tools also has stimulated the inventions in the scientific field(Dr. S. Sreeremya,2025). To treat genetic diseases like PTC(Dr.S.Sreeremya,2020),Cornelia De Lange Syndrome, CF, Glucose-6-Phosphate deficiency and other genetic disease these innovations can be used(S. Sreeremya,2018a).

Genetic councsellng it is another efficient step in the treatment of genetic diseases(S. Sreeremya,2018b).

CONCLUSION

Phenylkeatnuria is the genetic disorder which has many clinical implications, it mainltdamges the brain.Low plasma total amount of the linolenic acid, arachidonic acid (AA), and significantly reduced docosahexaenoic acid (DHA) an the eicosapentaenoic acid (EPA) have been demonstrated in patients with the PKU.This paper discusses the clinical manifestations of PKU and several case studies

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