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Phenylketonuria (PKU): An Inborn Metabolic Disorder

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Abstract

During process of digestion, proteins are broken down in into amino acids. Mainly the proteins contain 22 standard amino acids and several non-standard amino acids. We possess synthetic pathways for only 11 amino acids out of 22 standard amino acids. The remaining ones must be obtained from diet and hence they are referred to as essential amino acids. During day to day protein turnover most of amino acids used in protein synthesis were not from food but obtained through endogenous protein breakdown. The amino acid degradation occurs in Liver, Muscles and Kidneys. The liver being the major site of degradation while for some specific ones Muscles and Kidneys are the sites. During the amino acid degradation the nitrogen is removed from the carbon skeleton and transferred to the alpha-ketoglutarate which results into Glutamate. The carbon skeletons are converted into intermediates of mainstream carbon oxidation pathways via specific adapter pathways. Surplus nitrogen is removed from glutamate, and excreted in urea. In the degradation process, the amino acids are converted into the intermediates of the citric acid cycle to pyruvate which in turn can serve as precursors for gluconeogenesis, can be referred as *glucogenic* amino acids. Those amino acids which yield acetoacetate are termed as *ketogenic*.[1] Phenylketonuria (PKU) is a metabolic disorder occurring since birth which results into decreased metabolism of the amino acid phenylalanine.[2] It is observed that the untreated, PKU can develop intellectual disability, seizures, behavioral problems, and mental disorders.[3] It may also result in a musty smell and lighter skin. A baby born to a mother who has poorly treated PKU may have heart problems, a small head, and low birth weight.[2] Present review study will compare the prevalence of disease in the countries with special focus to India.

Keywords: Amino acids; Phenylketonuria (PKU); Metabolism; Phenylalanine.

Introduction

During process of digestion, proteins are broken down in into amino acids. Mainly the proteins contain 22 standard amino acids and several non-standard amino acids. We possess synthetic pathways for only 11 amino acids out of 22 standard amino acids. The remaining ones must be obtained from diet and hence they are referred to as essential amino acids. During day to day protein turnover most of amino acids used in protein synthesis were not from food but obtained through endogenous protein breakdown. The amino acid degradation occurs in Liver, Muscles and Kidneys. The liver being the major site of degradation while for some specific ones Muscles and Kidneys are the sites. During the amino acid degradation the nitrogen is removed from the carbon skeleton and transferred

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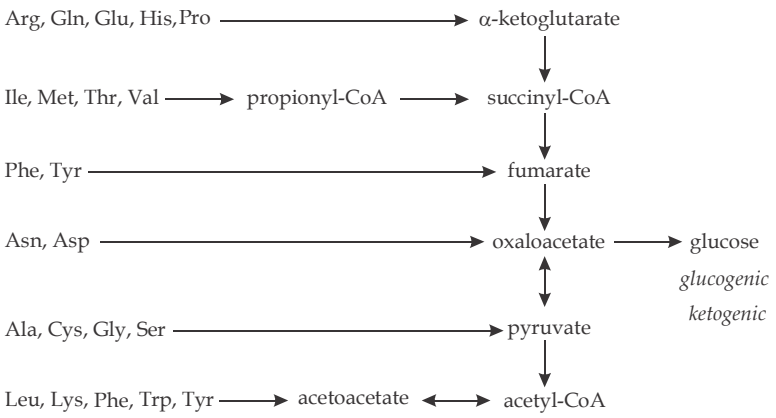

Fig. 1: Amino acid breakdown pathways join mainstream carbon utilization at different points of entry
(alanine – ala, arginine – arg, asparagine – asn, aspartic acid – asp, cysteine – cys, glutamine – gln, glutamic acid – glu, glycine - gly, histidine – his, isoleucine – ile, leucine – leu, lysine – lys, methionine – met, phenylalanine – phe, proline – pro, serine – ser, threonine – thr, tryptophan – trp, tyrosine – tyr, valine - val)

This disease is an example of non-allelic genetic heterogeneity. The PAH gene is located on chromosome 12 in the bands 12q22–q24.1. It is shown that more than 400 disease-causing mutations have been found in the PAH gene. PAH deficiency causes a spectrum of disorders, including classic phenylketonuria and hyperphenylalaninemia (a less severe accumulation of phenylalanine). As PKU is an autosomal recessive genetic disorder, both parents must have at least one mutated allele of the PAH gene. The child must inherit both mutated alleles, one from each parent.[4]

Historical Perspective of PKU

The disease PKU was first described by a Norwegian physician Asbjørn Følling in 1934.[8] He observed 10 children who were excreting large amount of phenylpyruvic acid in their urine. An interesting story was there behind his findings of PKU, when a mother of two mentally retarded children came to see Følling and informed her children is not only retarded but their urine had a peculiar smell. Følling in his usual thorough way examined children's urine with all routine

methods including ferric chloride test for ketones. Normally, it is brown and turns purple in the presence of ketones. But it turned green in the case of these two children. Følling repeated the test for a few days and was convinced it is indeed not an artifact but the children are excreting something that normal people do not, and he later detected it to be phenylpyruvic acid when the compound on processing smelt like benzoic acid and he called the disease oligophrenia phenylpyruvica, which later came to be known as phenylketonuria (PKU). Jervis described the enzyme defect and the Canadian physician Robert Guthrie who had an affected son and niece devised the newborn screening test.[9]

Treatment

The treatment mainly focused on diet with no phenylalanine and other nutrients. In the United States the current recommendation this diet need to be maintained for whole life. It is observed that if patients follow strict diet can live normal life with normal mental development. However, recent research suggests that neurocognitive, psychosocial, quality of life, growth, nutrition, and bone pathology are slightly suboptimal.[4]

Detection

Most babies in developed countries are screened for PKU soon after birth. Screening for PKU is done with bacterial inhibition assay (Guthrie test), immunoassays using fluorometric or photometric detection, or amino acid measurement using tandem mass spectrometry (MS/MS). Measurements done using MS/MS determine the concentration of Phe and the ratio of Phe to tyrosine, both of which will be elevated in PKU.[4]

Guthrie test: It is a simple screening blood test for phenylketonuria (PKU). The Guthrie test was the original impetus to newborn metabolic screening. The history of development of test has interesting story that in 1958–59 Dr. Robert Guthrie (1916–95) was asked if he might to develop a simple method to monitor the blood phenylalanine (Phe) level. He developed a test in 3 days. It was a "bacterial inhibition assay."In this test a spot of blood placed on a filter paper disc on surface of agar plate which contains substance inhibiting growth of bacteria. The inhibition can overcome by the presence of high phenylalanine concentration. After incubating the agar plate overnight, the diameter of the growth zone around the test disc is compared to that of a control disc of blood serum to which a known quantity of phenylalanine (Phe) has been added. This permits one to estimate the amount of phenylalanine (Phe) in the test disc.

Bob Guthrie used a common, standardized strain of soil bacterium, *Bacillus subtilis*. The inhibitor was -2-thienylalanine, which inhibits the growth of *B. subtilis*, an effect that was relieved by phenylalanine (Phe). Guthrie's original agar dish was a Pyrex baking pan. Guthrie went on to develop bacterial inhibition assays for other inherited disorders of metabolism, including maple syrup urine, galactosemia, maple syrup urine disease and homocystinuria. These assays are simple, inexpensive, and suited to screening large numbers of individual specimens. The three main laboratory methods now used in the US are the Guthrie bacterial inhibition assay (BIA), fluorometric analysis, and tandem mass spectrometry. Each of these methods can reliably detect PKU.[5]

Prevalence of Phenylketonuria in the World special focused to India:

In India the prevalence of the Phenylketonuria is less as compared to rest of countries. Appaji Rao during screening of 172,369 newborns in Bangalore, detected six cases of PKU (1 in 28728 screened).[6] Kaur et al.[7] while screening for PKU, 4451 cases for inborn errors of metabolism in Delhi and detected PKU in 4 (0.08%) cases.

Conclusion

The various countries like Saudi Arabia, United States of America, United Kingdom are more affected from occurrences of PKU. In India there are few studies for screening of this disease. These studies show less occurrences of this disease in India. Still there is need for the in-depth study epidemiologically in whole country to understand the quantum of the problem. Public and Government need to have equal participation for the screening studies for detection of PKU. There is chance of more better and healthy life of PKU patients if disease diagnosed early.

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