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The Phenyl Ketonuria (PKU) and Teratogenic Risks (Congenital Defects)



**Raghavendra Rao M.V*¹, Jithendra Kumar Naik S⁶,
Balaramiah, G³, Jayalakshmi⁴, SP Pallavi⁵, Reddi Rani⁷,
Kumar Ponnusamy², Abrar A Khan⁸**

1. *Scientist-Emeritus, Director central research laboratory, Department of Laboratory Medicine, Apollo Institute of Medical Sciences, Hyderabad, T S, India*
2. *Professor and Head, Department of Biochemistry, Avalon University School of Medicine, Curacao, Central America*
3. *Professor of Pathology, Department of Diseases Immunity and therapeutics, Avalon University School of Medicine, Curacao, Central America*
4. *Assistant Professor, Department of Biochemistry, Dr Patnam Mahender Reddy Institute of Medical Sciences, Chevella, Ranga Reddy District, T S., India*
5. *Assistant Professor, Department of Sport Medicine, College of Physiotherapy, Apollo Institute of Medical Sciences, Hyderabad, T S, India*
6. *Professor of Zoology, Department of Zoology, University college of sciences, Osmania University, T S, Hyderabad, India*
7. *Vice Principal, Apollo Nursing College, Jubilee hills, Hyderabad, TS, India*
8. *Dean of Basic Sciences, American University School of Medicine Aruba, USA*

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ABSTRACT

Phenylketonuria (PKU)/ Folling disease is inborn error of metabolism resulting from a deficiency of phenylalanine hydroxylase (PAH), an enzyme that catalyses the hydroxylation of phenylalanine to tyrosine, the rate limiting step in phenylalanine catabolism. Untreated, PKU can lead to intellectual disability, seizures, behavioural problems and mental disorders. 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. Phenylketonuria is a genetic disorder inherited from a person's parents. Metabolic alterations such as oxidative stress, mitochondrial dysfunction, and impaired protein and neurotransmitters synthesis have been described both in animal models and patients. Women with PKU can have healthy children as long as they are aware of and maintain strict adherence to their low phenylalanine diet throughout their pregnancy. It is well known that women with poorly controlled PKU during a pregnancy put their baby at risk for delayed development, mental retardation, poor head growth (microcephaly), poor overall growth, heart defects, and other structural birth defects. These complications are due to the ability of high levels of phenylalanine and its metabolites to directly cause birth defects and not because the baby has PKU. Also, phenylalanine competitively inhibits tyrosine hydroxylase, which is essential for melanin production, affected individuals have, hair, eye, and skin hypopigmentation.



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INTRODUCTION

Background Untreated Phenylketonuria (PKU), one of the most common human genetic disorders, usually results in mental retardation. Although a protein-restricted artificial diet can prevent retardation, dietary compliance in adults is often poor. In pregnant PKU women, noncompliance can result in maternal PKU syndrome, where high phenylalanine (Phe) levels cause severe fetal complications. (1)

The most critical time period of fetal development is during the first three months of pregnancy when the organs systems form. It is believed that during this time period high phenylalanine and its metabolites in the mothers' blood plasma can cross the placenta and directly effect the developing embryo by inducing birth defects. However, in the latter months, the fetal brain continues to mature and abnormally high levels of phenylalanine can also influence brain development at that time. (2)

Elevated maternal phenylalanine concentrations during pregnancy are teratogenic and may result in growth retardation, microcephaly, significant developmental delays, and birth defects in the offspring of women with poorly controlled phenylketonuria during pregnancy. Women of childbearing age with all forms of phenylketonuria, including mild variants such as mild hyperphenylalaninemia, should receive counseling concerning their risks for adverse fetal effects, optimally before conceiving. (3)

During pregnancy, Phe crosses the placenta by active transport, resulting in 70% to 80% increased fetal concentration of Phe compared with maternal concentration. An elevated Phe concentration is toxic and teratogenic to a developing fetus. (4)

The developing fetus in mothers with poorly controlled PKU can be affected by intrauterine exposure to elevated Phe levels. The Maternal Phenylketonuria Collaborative Study established that elevated maternal blood Phe levels are teratogenic. (5)

Children born with maternal PKU syndrome suffer from microcephaly, craniofacial dysmorphism, low birth weight, congenital heart disease, developmental delays, and mental retardation. (6) (8)

Fetal outcomes in pregnant women with PKU were substantially improved by strict adherence to Phe-restricted diets. In one report, women who achieved blood Phe

concentrations of 120–360 μM by week 8 of gestation had normal outcomes. Optimum outcomes were achieved when women initiated a Phe-restricted diet before conception, however, in cases of unplanned pregnancy, the mother may be unaware of her pregnancy for 4–5 weeks and thus there is no change in dietary Phe intake. (7)

For pregnant women with phenylketonuria (PKU), maintaining blood phenylalanine (Phe) $< 360 \mu\text{mol/L}$ is critical due to the toxicity of elevated Phe to the fetus. Sapropterin dihydrochloride (sapropterin) lowers blood Phe in tetrahydrobiopterin (BH4) responsive patients with PKU, in conjunction with a Phe-restricted diet, but clinical evidence supporting its use during pregnancy is limited. (9)

Homozygotes have diminished or absent enzyme activity. This leads to abnormality of high level of phenylalanine, resulting progressive intellectual impairment, autism, seizures, motor deficits, and neuropsychological abnormalities. (10)

Approximately 3000 reproductive aged women in the USA have PKU. The carrier frequency approximately 1 in 60. PKU is one of the few metabolic disorders for which there is treatment. (11)

It has been previously postulated that high phenylalanine Phe might disturb intracerebral dopamine production, which is the main regulator of prolactin secretion in the pituitary gland. Previously, various associations between Phe and hyperprolactinemia were revealed in studies performed in phenylketonuria (PKU) children and adolescents. (12)

Phenylketonuria (PKU) was the first disorder in which severe neurocognitive dysfunction could be prevented by dietary treatment. However, despite this effect, neuropsychological outcome in PKU still remains suboptimal and the phenylalanine-restricted diet is very demanding. To improve neuropsychological outcome and relieve the dietary restrictions for PKU patients, supplementation of large neutral amino acids (LNAA) is suggested as alternative treatment strategy that might correct all brain biochemical disturbances caused by high blood phenylalanine, and thereby improve neurocognitive functioning. (13)

Women of childbearing age with all forms of phenylketonuria, including mild variants such as mild hyperphenylalaninemia, should receive counseling concerning their risks for adverse fetal effects, optimally before conceiving. The best outcomes occur when strict control of

maternal phenylalanine concentration is achieved before conception and continued throughout pregnancy. (14)

If undiagnosed and untreated, phenylketonuria can result in impaired postnatal cognitive development resulting from a neurotoxic effect of hyperphenylalaninemia.

Features other than mental retardation in untreated patients include a 'mousy' odor, light pigmentation, peculiarities of gait, stance, sitting posture, eczema and epilepsy. (15)

The developing fetus in mothers with poorly controlled PKU can be affected by intrauterine exposure to elevated Phe levels. The Maternal Phenylketonuria Collaborative Study established that elevated maternal blood Phe levels are teratogenic. (16)

Phenylketonuria (PKU) is due to a defective hepatic enzyme, phenylalanine (Phe) hydroxylase. Transport of the precursor amino acids from blood into the brain for serotonin and dopamine synthesis is reported to be inhibited by high blood Phe concentrations. Deficiencies of serotonin and dopamine are involved in neurocognitive dysfunction in PKU. (17)

The main findings presented by phenylketonuric patients are severe neurological damage, including corpus callosum, striatum, and cortical alterations and hypomyelination, that result in intellectual deficit and neurodegeneration.(18)

During the pregnancy, the baby is monitored by detailed (targeted) ultrasound to assess growth and to look for birth defects. This is usually done by a specialist who has extra training in detailed ultrasound and is aware of the birth defects and growth problems that babies of PKU mothers can have. (19)

The maternal PKU collaborative study, which included 572 pregnancies followed more than 18 years, reported that maintenance of serum phenylalanine levels between 166 and 360 $\mu\text{mol/l}$. significantly reduced the fetal abnormal risks. (20)

Recently, it has also been demonstrated that these patients are more susceptible to neurological symptoms caused by cerebral dopamine deficiency, such as. The decrease of these neurotransmitters levels could be related to the effect of high Phe concentration on amino acids transport through the blood-brain barrier (BBB) (such as Tyr and tryptophan – Trp) or on enzymes involved in neurotransmitters synthesis. (21)

First small steps of History --Research on PKU

Before the causes of PKU were understood, PKU caused severe disability in most people who inherited the relevant mutations. Nobel and Pulitzer Prize winning author Pearl S. Buck had a daughter named Carol who lived with PKU before treatment was available, and wrote a moving account of its effects in a book called *The Child Who Never Grew*. (22)

Many untreated PKU patients born before widespread newborn screening are still alive, largely in dependent living homes/institutions. (23)

Phenylketonuria was discovered by the Norwegian physician Ivar Asbjørn Følling in 1934 when he noticed hyperphenylalaninemia (HPA) was associated with intellectual disability. (24)

In Norway, this disorder is known as Følling's disease, named after its discoverer. Følling was one of the first physicians to apply detailed chemical analysis to the study of disease. (25)

In 1934 at Rikshospitalet, Følling saw a young woman named Borgny Egeland. She had two children, Liv and Dag, who had been normal at birth but subsequently developed intellectual disability. When Dag was about a year old, the mother noticed a strong smell to his urine. Følling obtained urine samples from the children and, after many tests, he found that the substance causing the odor in the urine was phenyl pyruvic acid. The children, he concluded, had excess phenyl pyruvic acid in the urine, the condition which came to be called phenylketonuria (PKU). (26)

His careful analysis of the urine of the two affected siblings led him to request many physicians near Oslo to test the urine of other affected patients. This led to the discovery of the same substance he had found in eight other patients. He conducted tests and found reactions that gave rise to benzaldehyde and benzoic acid, which led him to conclude that the compound contained a benzene ring. Further testing showed the melting point to be the same as phenyl pyruvic acid, which indicated that the substance was in the urine.

In 1954, Horst Bickel, Evelyn Hickmans and John Gerrard published a paper that described how they created a diet that was low in phenylalanine and the patient recovered. Bickel, Gerrard and Hickmans were awarded the John Scott Medal in 1962 for their discovery.

PKU was the first disorder to be routinely diagnosed through widespread newborn screening. Robert Guthrie introduced the newborn screening test for PKU in the early 1960s. (27)

With the knowledge that PKU could be detected before symptoms were evident and treatment initiated, screening was quickly adopted around the world. Ireland was the first country to introduce a national screening program in February 1966 (28), Austria also started screening in 1966 and England in 1968. (29)

In 2017 the European Guidelines were published. (30)

They were called for by the patient organizations such as the European Society for Phenylketonuria and Allied Disorders Treated as Phenylketonuria. (31)

They have received some critical reception. (32)

Where the research go next?

Phenylalanine and tyrosine are structurally related to aromatic amino acids. Phenylalanine is essential amino acid, whereas tyrosine is non-essential amino acid. Besides its incorporation into protein. The only function of phenylalanine is its conversion to tyrosine. For this reason, ingestion of tyrosine can reduce the dietary requirement of phenylalanine. This phenomenon is referred as "Sparing action of tyrosine and phenylalanine. About 300-400 grams of protein/day is constantly degraded and synthesized in the human body. The amino acids are mainly synthesized for protein biosynthesis, production of specialized products (Creatin, porphyrin, purines and pyrimidines) and generation of energy. the collection center for the amino-groups in the biological system, while glutamine is the storehouse of NH_3 . Free NH_3 can be liberated predominantly from glutamate.

The hyperphenylalaninemia result from impaired conversion of phenylalanine to tyrosine. The increased concentration of phenylalanine and its byproducts in body fluids causes severe intellectual disability if untreated in infancy. It results from reduced activity of phenylalanine hydroxylase. The accumulation of phenylalanine inhibits the transport of other amino acids required for proteins or neurotransmitter synthesis, it reduces synthesis and increases degradation of myelin and leads to inadequate formation of norepinephrine and serotonin.

Phenylketonuria Pathophysiology:

Oxidative stress is defined as the lack of balance between reactive oxygen/nitrogen species production and the antioxidant system. Such imbalance may induce oxidative damage to proteins, lipids, or DNA. In fact, oxidative stress has been associated with the pathophysiology of several neurodegenerative diseases, including Parkinson's and Alzheimer's disease, epilepsy, and demyelination. It has been demonstrated that the brain tissue is particularly vulnerable to oxidative stress due to high O₂ consumption, high tissue concentrations of iron, low level of antioxidant defenses, the presence of excitatory amino acids and dopamine metabolism, which generate hydrogen peroxide. (33)

Over the last years, oxidative damage to macromolecules has been investigated in HPA animal models and biological samples from PKU patients. It was demonstrated that high Phe levels are associated with DNA, protein, and lipid damage, as well with decreased antioxidant defenses in phenylketonuric patients. In this scenario, DNA damage was reported in peripheral blood from PKU patients in vivo and in vitro in a dose dependent manner. In addition, protein and lipid oxidative damage, measured by carbonyl formation and sulfhydryl oxidation, and thiobarbituric acid-reactive species (TBA-RS) and malondialdehyde (MDA) content, respectively, were described in plasma and erythrocytes from PKU patients. (34)

Decreased antioxidant defences, both enzymatic and non-enzymatic, were also found in these subjects. Low levels of plasma total antioxidant status and reactivity, L-carnitine, betacarotene and coenzyme Q10, and altered catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities in PKU patients samples indicate an impairment of antioxidant defense that could result in oxidative stress. (35)

PAH deficiency can be diagnosed by newborn screening based on detection of the presence of hyper phenylalanemia using a blood spot obtained from a heel prick. Normal blood phenylalanine levels are 58+ 15 micro.mol/L in adults, 60 + 18 micro.Mol/L, in teenagers 62+ 18 Micro .Mol/L in childhood. In newborn, the upper limit of normal is 120 micro.mol/L (2mg/dl). Classical PKU, blood levels as high as 2.4 mico.Mol/L can be found.

Infants with PKU are often asymptomatic before consuming food containing Phe and may not be identified by newborn screening, explaining the insidious onset of PKU, where symptoms may not appear until early infancy. In general, untreated infants and children with PKU develop a range of impairments, including behavioural, mental, neurological, and

physical symptoms. Almost all untreated PKU patients demonstrate behavioral impairments, including aggressiveness, anxiety, hyperactivity, purposeless movements, social withdrawal, and stereotypy.

The mental retardation observed in patients with PKU is also associated with neurological impairments, such as electroencephalogram abnormalities, epilepsy, gait and tic abnormalities, hyperreflexia, Parkinsonian signs, pyramidal signs, limb spasticity, and tremors. In addition, the brains of untreated PKU patients exhibit disrupted myelination, impaired synaptogenesis, and reduced dendrite arborisation. (36)

Phenylalanine compound Summary

(US National Library of Medicine) (National centre for Biotechnology information)

Phenylalanine is an essential amino acid and the precursor of the amino acid tyrosine. Like tyrosine, phenylalanine is also a precursor for catecholamines including tyramine, dopamine, epinephrine, and norepinephrine. Catecholamines are neurotransmitters that act as adrenalin-like substances. Interestingly, several psychotropic drugs (mescaline, morphine, codeine, and papaverine) also have phenylalanine as a constituent. Phenylalanine is highly concentrated in the human brain and plasma. Normal metabolism of phenylalanine requires bipterin, iron, niacin, vitamin B6, copper, and vitamin C. An average adult ingests 5 g of phenylalanine per day and may optimally need up to 8 g daily. Phenylalanine is highly concentrated in a number of high protein foods, such as meat, cottage cheese, and wheat germ. An additional dietary source of phenylalanine is artificial sweeteners containing aspartame. As a general rule, aspartame should be avoided by phenylketonurics and pregnant women. When present in sufficiently high levels, phenylalanine can act as a neurotoxin and a metabotoxin. A neurotoxin is a compound that disrupts or attacks neural cells and neural tissue. A metabotoxin is an endogenously produced metabolite that causes adverse health effects at chronically high levels. Chronically high levels of phenylalanine are associated with at least five inborn errors of metabolism, including Hartnup disorder, hyperphenylalaninemia due to guanosine triphosphate cyclohydrolase deficiency, phenylketonuria (PKU), tyrosinemia type 2 (or Richner-Hanhart syndrome), and tyrosinemia type III (TYRO3). Phenylketonurics have elevated serum plasma levels of phenylalanine up to 400 times normal. High plasma concentrations of phenylalanine influence the blood-brain barrier transport of large neutral

amino acids. The high plasma phenylalanine concentrations increase phenylalanine entry into the brain and restrict the entry of other large neutral amino acids.

Phenylalanine has been found to interfere with different cerebral enzyme systems. Untreated phenylketonuria (PKU) can lead to intellectual disability, seizures, behavioural problems, and mental disorders. It may also result in a musty smell and lighter skin. Classic PKU dramatically affects myelination and white matter tracts in untreated infants; this may be one major cause of neurological disorders associated with phenylketonuria. Mild phenylketonuria can act as an unsuspected cause of hyperactivity, learning problems, and other developmental problems in children. It has been recently suggested that PKU may resemble amyloid diseases, such as Alzheimer's disease and Parkinson's disease, due to the formation of toxic amyloid-like assemblies of phenylalanine. Phenylalanine also has some potential benefits. Phenylalanine can act as an effective pain reliever. Its use in premenstrual syndrome and Parkinson's may enhance the effects of acupuncture and electric transcutaneous nerve stimulation (TENS). Phenylalanine and tyrosine, like L-DOPA, produce a catecholamine-like effect. Phenylalanine is better absorbed than tyrosine and may cause fewer headaches. Low phenylalanine diets have been prescribed for certain cancers with mixed results. For instance, some tumours use more phenylalanine than others (particularly melatonin producing tumours called melanomas).

Biochemical and molecular genetic diagnosis

PKU diagnosis is performed by detecting an elevated serum Phe concentration; this is the standard method for confirming the positive neonatal screening results. (37)

Tandem mass spectrometry is one of the most useful laboratory tools for measuring various analytes, including Phe and Tyr, in a single sample. PKU diagnosis is also supported by normal or low Tyr levels, in addition to high serum Phe concentrations.

All neonates with high serum Phe concentrations should also be evaluated for Pterin disorders by analysis of the urine or blood. Enzyme activity analysis can be performed to determine the activities of the enzymes involved in BH₄ synthesis and regeneration. However, PAH activity cannot be analyzed effectively in the urine or blood because PAH activity is typically only observed in hepatic and renal cells. (38)

PKU diagnosis should be confirmed by molecular analysis. In families with confirmed affected individuals, carriers can be identified by genetic testing. The mutation profile of the gene(s) involved in PKU is limited to certain regions, which are distributed among the structural domains. However, the position and nature of any of these mutations determine the effects of the mutations on enzyme activity, yielding patients with different clinical and biochemical phenotypes. (39)

Treatment

Treatment, which includes a low Phe diet supplemented with amino acid formulas, commences soon after diagnosis within the first weeks of life. Although dietary treatment has been successful in preventing intellectual disability in early treated PKU patients, there are major issues with dietary compliance due to palatability of the diet. Other potential issues associated with dietary therapy include nutritional deficiencies especially vitamin D and B12. Suboptimal outcomes in cognitive and executive functioning have been reported in patients who adhere poorly to dietary therapy. There have been continuous attempts at improving the quality of medical foods including their palatability. Advances in dietary therapy such as the use of large neutral amino acids (LNAA) and glycomacropeptides (GMP; found within the whey fraction of bovine milk) have been explored. Gene therapy and enzyme replacement or substitution therapy have yielded more promising data in the recent years. (40)

Phenylketonuria (PKU) was the first inherited metabolic disease in which dietary treatment was found to prevent the disease's clinical features. Treatment of phenylketonuria remains difficult due to progressive decrease in adherence to diet and the presence of neurocognitive defects despite therapy. This review aims to summarize the current literature on new treatment strategies. Additions to treatment include new, more palatable foods based on glycomacropeptide that contains very limited amount of aromatic amino acids, the administration of large neutral amino acids to prevent phenylalanine entry into the brain or tetrahydropterina cofactor capable of increasing residual activity of phenylalanine hydroxylase. Moreover, human trials have recently been performed with subcutaneous administration of phenylalanine ammonia-lyase, and further efforts are underway to develop an oral therapy containing phenylalanine ammonia-lyase. Gene therapy also seems to be a promising approach in the near future. (41)

Due to the severe restriction of protein intake, PKU patients must be supplemented with medical food substitutes containing the right mix of essential amino acids, vitamins, minerals and trace nutrients. Normally, about 90% of the dietary phenylalanine intake is converted into tyrosine; therefore a crucial part of the treatment is tyrosine supplementation. (42)

GMP is a protein derived from cheese whey that is naturally low in Phe and is rich in valine, isoleucine and threonine. GMP manufactured to sufficient purity and supplemented with the essential amino acids tyrosine, tryptophan, arginine, cysteine and histidine can be a useful adjunct to the Phe restricted diet. Studies suggest that PKU patients find foods containing GMP more palatable than their usual amino acid formula, preferring a diet supplemented with GMP. (43)

Phenylketonuria: a review of current and future treatments

There have been continuous attempts at improving the quality of medical foods including their palatability. Advances in dietary therapy such as the use of large neutral amino acids (LNAA) and glycomacropeptides (GMP; found within the whey fraction of bovine milk) have been explored. Gene therapy and enzyme replacement or substitution therapy have yielded more promising data in the recent years. (44)

Consanguinity

Two individuals are considered consanguineous if they have at least one recent ancestor in common. First degree relatives share half of their genes. Second degree relatives share a fourth and third degree relatives-cousins, share one eighth. Because of the potential for shared deleterious genes, consanguinity confers an increased risk to have offspring with otherwise rare autosomal recessive disease or multifactorial disorders first cousin have a twofold increased risk 4 to 6 % overall, in the absence of a family history of genetic disease.

Related to the result of clinical Research

Children with classic PKU which accounts for more 98% of cases are normal at birth and usually manifest at 2-3 months with progressive mental retardation, neurological features like irritability, seizures and hypertonica. Fair complexion with blond hair, blue eyes and occasionally eczema.

Management of PKU

Guthrie's test-- Bacterial inhibition test, Ferric chloride test, Random mass spectrography, Urine chromatography, High performance liquid chromatography, Genetic mutation studies are commonly employed in laboratory diagnosis. Phenylalanine restricted diet. Overtreatment is dangerous. Other treatments like synthetic BH₄ (Sapropterin dihydrochloride (Kuvan) Concentrate of large amino acids tyrosine/tryptophan. Large neutral amino acids reverse the competitive inhibition of phenylalanine on transporters and allow tyrosine and tryptophan to enter into brain. Neonatal screening for PKU that is widely practices in many countries, involving whole blood phenylalanine assay after 48-72 hours of birth, feeding by semiquantitative bacterial inhibition assay (Guthrie test) using a drop of capillary blood on filter paper. However quantitative plasma chromatography as transient hyper alanemia is not uncommon in newborns.

Although mutation analyses are not absolutely essential in the management of patients with PKU, they help in understanding the molecular characteristics of PAH deficiency in the individual patient and assist in treatment decisions. They are useful in the management of all patients with PKU provided that the necessary expertise to interpret the results correctly is available, and the costs of DNA studies are not prohibitive.

Women who achieved optimal phenylalanine levels before 10 weeks of gestation had children with mean IQ score in the normal range when assessed at age 6-7 years. Pre counselling is recommended with a goal of maintaining an optional phenylalanine concentration from 3 months before conception and continuing their through pregnancy. (45)

Recommendations

The recommendations of the American Academy of Pediatrics reflect the guidelines of the Maternal Phenylketonuria Collaborative Study of the National Institutes of Health.^{3,19} These recommendations are to be applied to individual patients and their particular care plan with the guidance of their primary care physician in coordination with the patient's metabolic expert physician.

All girls and women of childbearing age with elevated Phe concentrations, including those with PKU and milder forms of hyperphenylalaninemia, should be counselled concerning their risks of having an adverse fetal outcome if they have uncontrolled blood Phe concentrations

during pregnancy. Education regarding the risks of maternal PKU should begin when an infant is diagnosed with PKU in the newborn period. We recommend that the paediatrician include this information again in anticipatory guidance counselling during preadolescence and adolescence for girls with PKU. All individuals, particularly women and girls of childbearing age, should be referred to an experienced PKU treatment centre for genetic and nutritional evaluation and counselling throughout their lifetime.

Women with hyperphenylalaninemia who are unable or unwilling to maintain blood Phe concentrations in the range for optimum pregnancy outcome should be counseled before conception regarding the risk of microcephaly, mental retardation, and fetal anomalies in their offspring. Emphasis should also be placed on the education that structural defects, such as congenital heart disease, are associated with poor control early in pregnancy. Dietary therapy should be in place before conception to ensure optimal outcome for the foetus. It is important that these women receive assistance to obtain adequate means for access to reproductive services.

Genetic counselling should be offered for all women with PKU before and after conception. Pregnant women with hyper phenylalaninemia should be counselled concerning the risks to the foetus and offered detailed ultra-sonographic examinations and foetal echocardiography to detect foetal abnormalities (eg, growth retardation, congenital heart defects). Consideration should be given to maternal Phe concentrations during critical time periods of organogenesis. It is equally important that these women obtain assistance in locating centres with skilled clinicians who are able to provide medical care for pregnant women with PKU.

Mothers who give birth to children with features suggestive of maternal PKU, such as congenital heart disease, microcephaly, and suggestive facial dysmorphic features without a known cause, should undergo blood testing for hyperphenylalaninemia. The Phe level of a newborn of a mother with PKU is usually.

An opinion arrived at through a process of reasoning

Phenylketonuria is the most prevalent disorder caused by an inborn error in amino acid metabolism. It results from mutations in the phenylalanine hydroxylase gene. Phenotypes can vary from a very mild increase in blood phenylalanine concentrations to a severe classic phenotype with pronounced hyperphenylalaninaemia, which, if untreated, results in profound and irreversible mental disability. Neonatal screening programmes identify individuals with

phenylketonuria. The initiation of a phenylalanine-restricted diet very soon after birth prevents most of the neuropsychological complications. However, the diet is difficult to maintain and compliance is often poor, especially in adolescents, young adults, and pregnant women. Tetrahydrobiopterin stimulates phenylalanine hydroxylase activity in about 20% of patients, and in those patients serves as a useful adjunct to the phenylalanine-restricted diet because it increases phenylalanine tolerance and allows some dietary freedom. Possible future treatments include enzyme substitution with phenylalanine ammonia lyase, which degrades phenylalanine, and gene therapy to restore phenylalanine hydroxylase activity. (46)

Future research should also focus on measuring the Disability-Adjusted Life Year (DALY) to demonstrate overall burden of this disease as well as other genetic diseases. Estimating DALY is another successful measure to estimate years of life lost due to premature mortality (YLL) and years of life lived with disability (YLD). Providing such data will definitely give true estimates of this problem and allow for effective intervention programs to reduce disease burden.(47)

Shortened version of large work

Newborn screening helps in the early establishment of a Phe-restrictive diet and the possibility of avoiding brain damage resulting from HPA in patients with PKU. However, the difficulties of maintaining a strict life-long diet and the occurrence of other complications (despite treatment) make the investigation of new therapeutic strategies of great importance. Moreover, information regarding PKU pathogenesis has increased over the past decade, enabling the development of various novel therapeutic strategies. New treatments, therefore, will eventually become available for addressing the observed HPA in patients with PKU, enabling personalized therapy based on individual genotypes and other specific conditions. Molecular diagnosis by high-throughput sequencing techniques also helps confirm neonatal laboratory-screening results and facilitates the discovery of novel mutations associated with PKU. However, many concerns regarding existing therapeutic strategies need to be addressed and much effort has to be exerted before many of these new therapies can become available for patients. (48)

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