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REVIEW

Adult issues in phenylketonuria

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ABSTRACT

Phenylketonuria (PKU) is a classical example of an inherited metabolic disease, in which mental retardation can be prevented successfully by using a diet. However, in adult PKU new problems occur, such as vitamin deficiencies, osteoporosis and the maternal PKU syndrome. The aim of this review article is to provide guidelines for the clinician to understand and manage PKU in adults.

KEYWORDS

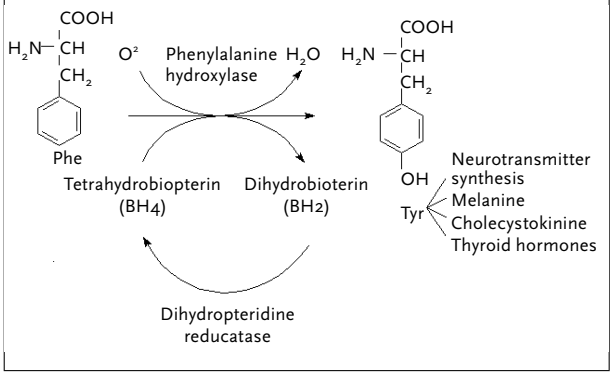
Adults, complications, phenylketonuria

INTRODUCTION

Phenylketonuria (PKU) is a hereditary metabolic disease, which is seen in approximately 1:18,000 newborns in the Netherlands.[1] In most cases it results from a deficiency of phenylalanine hydroxylase (PAH), an enzyme necessary for the conversion of phenylalanine (Phe) into tyrosine. Hyperphenylalaninaemia is the biochemical hallmark of PKU. Defects in the recycling of the cofactor required for PAH activity, tetrahydrobiopterin (BH4), can result in hyperphenylalaninaemia as well (*figure 1*). BH4 deficiency accounts for approximately 2% of the patients with elevated Phe levels.[2] Since 1974 all newborns in the Netherlands are tested for PKU within eight days after birth.[1]

The mode of inheritance of PKU is autosomal recessive. Nearly all cases are caused by mutations in the gene encoding PAH, which has been mapped to human chromosome 12q24.1.[3] Clinical and molecular studies have indicated that PAH deficiency is a highly heterogeneous disease.[4] To date, more than 400 different mutations have been characterised in the PAH gene in various ethnic groups. Genotype at the mutant PAH locus influences the biochemical phenotype in heterozygotes.[5]

Figure 1. *The metabolism of phenylalanine*



If untreated, PKU leads to the development of mental retardation and neurological disturbances.[6] Hyperactivity may occur as well as hypopigmentation and eczematous rash. The exact mechanism by which the elevated concentration of Phe causes mental retardation is unknown. Several hypotheses have been described. High Phe values can have a direct deleterious effect on the myelinisation *in cerebro*.[7] Another mechanism can be the high affinity of Phe for the transport across the blood brain barrier. This transporter is also used by e.g. tyrosine and tryptophan, which are precursors of dopamine and serotonin. Therefore, high Phe concentrations can lead to disturbances in dopaminergic and serotonergic neurotransmission.[8,9]

DIAGNOSIS

The diagnosis of PKU is based upon the finding of an elevated serum concentration of Phe (reference value 35 to 76 µmol/l). Classical PKU or just PKU is historically defined as a blood Phe level >1200 µmol/l, which indicates a complete deficiency of PAH. At that level phenylketones appear in the urine. In mild/atypical PKU levels of 600 to 1200 µmol/l are seen and hyperphenylalaninaemia (HPA) is classified

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as blood Phe levels between 240 and 600 µmol/l.[10] In the Netherlands a successive BH4 loading test is performed to detect a possible BH4 deficiency.[11] The most useful laboratory method for newborn screening is tandem mass spectrometry.[12] Other methods include the Guthrie bacterial assay, fluorometric and chromatographic analysis.

PRINCIPLES OF TREATMENT

The principle of treatment in PAH deficiency is to reduce the blood Phe concentration sufficiently to prevent brain damage. The cornerstone of PKU treatment is dietary protein restriction, supplemented with all amino acids except Phe. It should be initiated as soon as possible after diagnosis.

One of the most controversial issues is whether to stop or continue dietary treatment throughout adulthood. Before 1970, clinicians believed that dietary treatment was only necessary until the end of childhood.[13,14] The rationale for this approach was that the brain is only vulnerable to the toxic effects of elevated Phe in the period of its maximal myelinisation throughout childhood.[15] Later on, concerns were raised about the safety of discontinuing the diet. Several studies suggested that elevated Phe concentrations in adults adversely affect cognitive function, neuropsychological and psychiatric outcome.[12] Apart from in France, this led to the recommendation of 'diet for life' in most treatment centres, although recommendations about blood Phe levels do vary. The actual recommendation of 'diet for life' is based on lack of sufficient evidence to support the relaxation of diet in adults. Channon *et al*. found that after discontinuing the diet, only subtle changes in cognitive performance occurred compared with adolescents who remained on a diet.[16]

According to the Dutch guidelines of management of adult PKU, the target blood Phe level is 120 to 600 µmol/l. In Germany the target level is 40 to 1200 µmol/l, in the UK 120 to 700 µmol/l and in the USA 120 to 900 µmol/l. In our centre we encourage those on diet to monitor regularly (one to three monthly) and take their nutritional supplements with the aim to keep the Phe level <600 µmol/l. There is a very real risk of vitamin B12 and other micronutrient deficiencies in those patients restricting their protein intake, but not taking vitamin supplements. Therefore, for those who choose to be off diet, we recommend that they eat a completely normal diet with full protein and vitamin intake. Side effects of dietary treatment such as vitamin deficiencies and osteoporosis, possibly due to long-standing dietary deficiency of protein, calcium, vitamin D, vitamin B12 or trace elements, can be prevented by this approach. The role of essential fatty acid supplementation in the diet of PKU patients remains to be explored.

The poor palatability of protein substitutes leads to a decrease in compliance with the diet, especially in adolescents. Furthermore time constraints, social pressure and dissatisfaction with restrictions challenge dietary compliance.[17] Consequently, the need for an alternative treatment is growing.

Many new approaches have been discovered in the last ten years. The most ultimate and definitive therapy for PKU patients would be a liver transplantation, because it would correct the molecular disorder. But it is too complicated and hazardous to be justifiable as an appropriate substitute for the diet.[18] However, the availability of the classic effective treatment militates against a therapy requiring immune suppressive therapy, with its attendant complications.

In 1999, it was discovered that some PKU patients can benefit from administration of the cofactor BH4. Many studies confirmed the decrease on the blood Phe levels.[19-21] In a large study, 38% of the PKU patients (not BH4 deficient) responded to BH4 administration with a decrease of ≥30% in Phe. The prevalence of responsiveness was unfortunately highest in patients with mild forms of PKU. Only 7 to 10% of the patients with classical PKU responded to BH4 therapy.[21] BH4 therapy may be used as an adjunct to dietary restriction. However, BH4 is not registered in the Netherlands and may have uncertain long-term availability; also there is minimal clinical experience and the potential costs may be high.

Another treatment that may be promising is the use of oral large neutral amino acids (LNAA). LNAA (e.g. phenylalanine, tyrosine, tryptophan, leucine, isoleucine) compete with each other at the blood brain barrier. High blood levels of LNAA can result in carrier saturation and competitive inhibition of Phe, resulting in a decrease in Phe.[22] LNAA cross the intestinal mucosa by carrier proteins similar to those of the blood brain barrier. The affinity of the LNAA at the blood brain barrier is much higher than in the intestinal mucosa, so high concentrations must be present in the intestines in order to influence brain Phe levels.

A double-blind, randomised, controlled trial with LNAA therapy showed a significant decrease in blood Phe levels with a mean of 39% from the baseline (from 932 µmol/l to 568 µmol/l).[22] An advantage compared with BH4 therapy is the lowering of Phe levels in all PKU patients, not only in milder forms. LNAA therapy is not available in the Netherlands at present.

Brain Phe is deducted from the blood Phe levels, but a linear relation may not be present. New techniques to noninvasively assess brain Phe would be most welcome.

At a more basic level, new modalities in PKU treatment are being studied, for example: somatic gene therapy and enzyme therapy.[23-27] However, these efforts have not led to an effective treatment so far. Although all of the new approaches may be useful in the future, the dietary treatment of PKU remains the most important clinical tool in PKU.

COMPLICATIONS IN ADULTHOOD

The adult complications in PKU consist of two components. On the one hand complications of high Phe levels can be seen, such as neurological and (neuro)psychological problems. On the other hand, complications occur as a cause of dietary protein restriction, for example vitamin deficiencies and osteoporosis.

NEUROLOGY/NEUROPSYCHOLOGY

Adults with PKU who were treated from early infancy have normal intelligence, but their neuropsychological test scores are somewhat lower than those of the general population, their parents, and unaffected siblings.[28] In many functional domains, such as motor speed, speech, language and some aspects of memory, treated PKU patients perform comparably with healthy controls. However, the domains of abstract reasoning, executive functioning, and attention have been identified as areas of weakness despite adhering to the diet.[29] Even continuously treated PKU patients show decreased performance at neuropsychological tests, which improves when Phe levels are lowered by a more strict PKU diet.[30]

Furthermore, adults with PKU who were continuously treated but relaxed the diet have displayed white matter abnormalities on structural magnetic resonance imaging,[31,32] which are considered to be indicative of a reduction in myelin.[33,34] These abnormalities disappear after reintroducing a strict diet. The hypothesis suggests that elevated Phe concentrations impact on myelin production and maintenance. Using a murine model, Dyer *et al*. have shown that Phe can inhibit the activity of HMG-CoA reductase, which leads oligodendrocytes to develop into non-myelinating oligodendrocytes. A strict diet on the other hand normalises the HMG-CoA reductase activity and produces myelinating oligodendrocytes.[34] However, this theory has not yet been confirmed in humans.

Neurological investigations in early-treated adults with PKU who discontinued the diet reveal a higher incidence of minor neurological signs including tremor, brisk deep tendon reflexes or clumsy motor co-ordination.[31,35,36] In rare cases severe neurological deterioration may occur after cessation of dietary treatment. The symptoms, including spastic paresis, late-onset epilepsy, ataxia and tremor, are very similar to those of untreated PKU patients.[35,37] Poor early control seems to be a risk factor in all reported cases. Neurological deterioration has not yet been reported in early-treated PKU patients.[38] However, it cannot be excluded that further neurological deterioration could emerge later in life.[36] In all patients with late-onset neurological deterioration it is mandatory to exclude a possible vitamin B12 deficiency.[38]

PSYCHOLOGICAL PROBLEMS

Severe behaviour and psychiatric problems are seen in profoundly retarded (untreated) adults with PKU in the third and fourth decade of life.[39] With introduction of a Phe-restricted diet, these symptoms are sometimes reversible.[40] It has been reported that early-treated adults with normal intelligence whose diet has been discontinued developed psychiatric and/or psychological problems, including depression, anxiety, social withdrawal, agoraphobia, low self-esteem, neurotic behaviour, and other phobias.[41-43] Other studies have found no difference between PKU patients and sibling controls on psychological outcome.

Several studies showed reduced levels of noradrenalin and serotonin in PKU patients which has been linked to panic attacks,[44] and depression or agoraphobia,[45] respectively. High blood Phe levels lead to disturbances in dopaminergic and serotonergic neurotransmission through the same mechanism as described earlier.[44,46,47] Koch *et al*. showed a clinical improvement in depressed PKU patients, who were treated with LNAA.[48]

VITAMIN DEFICIENCIES

Vitamin B12 is only found in animal protein, the sources being meat, fish and poultry. Since the PKU diet is restricted in protein, vitamin B12 must be provided either combined with the amino acid supplement or from a separate supplement. Vitamin B12 deficiency can occur when PKU patients relax their diet in adolescence.[15] They tend to choose products that are low in animal protein and amino acid supplements are not taken properly.[49] Vitamin B6, folic acid and iron can also be deficient in a PKU diet, although it occurs less frequently than vitamin B12 deficiency. Methylmalonic acid (MMA) and homocysteine are both highly sensitive markers to assess vitamin B12 deficiency at tissue level.[50]

Vitamin B12 serves as a co-factor for two enzymes: L-methylmalonyl-coA mutase and methionine synthetase. Deficiency of vitamin B12 will lead to higher concentrations of homocysteine and MMA.[50] Vitamin B12 deficiency can cause a wide range of clinical symptoms including neuropathy, subacute combined degeneration of the cord, glossitis, anaemia, dementia and psychiatric states such as depression and psychoses.[15] The clinical manifestations of a vitamin B12 deficiency appear years after the start of an inadequate intake.[51] The large body storage, long half-life and the efficient re-absorption in the intestines are the main reasons.[52] However, low serum vitamin B12 levels correlate in only 25 to 50% with a vitamin B12 deficiency at tissue level.[53] Combined deficiencies of iron and vitamin B12 are frequently seen

in PKU patients, so haematological parameters such as haemoglobin and mean corpuscular volume are not good indicators for vitamin B12 deficiency.

OSTEOPOROSIS

Osteoporosis is an important cause of morbidity and mortality in later life. Diagnosis is usually made following a fracture but may be preceded by an asymptomatic period of osteopenia. One of the predisposing factors to fracture is thought to be failure in achieving an optimal peak bone mass in early adult life.[51] Modan-Moses *et al.* showed a decreased peak bone mass in PKU patients.[52] Many other studies have shown a decreased bone mineral density (BMD) in patients with PKU.[53-55] The exact mechanisms of osteopenia and osteoporosis in PKU and HPA patients remain unclear. Possible explanations include long-standing dietary deficiency in protein, calcium, vitamin D or trace elements, or a primary defect in bone turnover inherent to the disease itself.[52] PKU patients may be at risk for osteoporosis in later life. However, there is no evidence that a life-long dietary treatment can prevent or treat osteoporosis.

MATERNAL PHENYLKETONURIA

One situation where a phenylalanine-restricted diet is mandatory is for women with PKU and HPA who are pregnant or planning a pregnancy. Charles Dent was one of the first physicians to recognise the teratogenic effects of maternal Phe on the foetus in 1956.[56] These effects include mental retardation, facial dysmorphism, microcephaly, intrauterine growth retardation (IUGR), developmental delay and congenital heart disease (CHD).[56,57] In untreated pregnancies of women with PKU and Phe levels ≥1200 µmol/l, more than 90% of the offspring have microcephaly and mental retardation, 40% have IUGR and 12 to 15% have CHD. When the range of Phe is between 600 and 1200 µmol/l these teratogenic effects are less frequent, and when dietary treatment lowers the blood Phe level to 120 to 360 µmol/l, the offspring may be normal. This indicates a dose-response relation.[58]

During pregnancy, the placenta naturally selects for higher concentrations of amino acids, including Phe. There is an active transplacental Phe gradient during pregnancy. Phe levels are amplified (1.5 to 2.0 times) which leads to high Phe levels in the foetal circulation.[59] During the early stages of embryogenesis high Phe levels can have a deleterious effect on neural crest cell migration, thereby explaining facial dysmorphisms and cardiac anomalies. During fetogenesis Phe has deleterious effects on neuronal multiplication and myelinisation.[60] However, these hypotheses have only been tested in animal studies.

Not only the blood Phe levels are of importance. Too little maternal weight gain and low intake of either protein or calories can also interfere with foetal growth.[61]

The most important weapon for preventing embryopathy is preconceptional information, since a good metabolic state must be achieved before conception. However, it is still beneficial to the foetus to reduce levels within the first trimester in case of an unexpected pregnancy.

The Dutch guidelines recommend blood Phe levels of 120 to 240 µmol/l in pregnancy. It is advised to determine Phe levels once or twice a week. After three months, tyrosine should be supplemented. The critical period for the nervous system, cranium and heart is at five to eight weeks of pregnancy. Consequently, good metabolic control must be achieved before week 5, to prevent teratogenic effects on the developing foetus.[59] Recent data suggest that swings in blood Phe levels, even within the target ranges, have significant impact on the offspring neuropsychometric outcome.[62]

Nowadays, few teratogenic effects on newborns are seen, thanks to good metabolic control. Hanley and colleagues have shown that a small number of untreated or poorly treated PKU pregnancies result in normal offspring, while a few apparently well-treated pregnancies are not successful. The exact mechanisms remain unclear. However, teratogenesis is a multi-factorial phenomenon with protective and toxic mechanisms, so that poorly treated PKU mothers can have normal offspring, and apparently well-treated PKU pregnancies are not successful.

RECOMMENDATIONS

PKU patients should be encouraged to remain on a lifelong diet and take their nutritional supplements. Blood Phe levels should be monitored every three months. It is recommended to do a clinical review on patients every year. Not only dietary status and blood Phe level should be monitored, but all other items in *table 1* need to be considered. Full amino acid spectrum is recommended. A dedicated dietician should be part of the team caring for PKU patients. It is advised to assess bone marrow density (BMD) every two to five years. Treatment with calcium and vitamin D supplements should be given in every patient with PKU and a low BMD. Furthermore, women need to be informed about strict dietary control in (intended) pregnancy. All pregnant PKU patients should be under the control of a physician specialised in metabolic diseases, a dietician and a gynaecologist and should be offered a detailed ultrasound at 20 weeks of gestation. Pregnant PKU and HPA woman should be seen every three to four weeks and blood Phe levels must be monitored at least once a week.

Table 1. *Guidelines in the management of phenylalanine*

Laboratory values (once a year)	Additional tests
Phenylalanine (every 3 months)	Dual X-ray
Amino acid spectrum	Absorptiometry (every 2-5 years)
Vitamin B12	
Vitamin B6	
Folic acid	
Methylmalonic acid	
Iron status	
Ferritin	
Calcium	
Vitamin D	
Albumin	
Haemoglobin	
Mean corpuscular volume	
Creatinine	

CONCLUSION

PKU is a success story. Its ascertainment and treatment from early infancy has led to excellent outcomes. At the same time new problems occur with the PKU patients getting older. Knowledge of the adult issues in PKU will lead to a better understanding among clinicians and can overcome these difficulties, resulting in (almost) normal lives for PKU patients. Still many aspects of adult PKU remain unclear and need further elucidation in the near future.

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