Management of Phenylketonuria and Hyperphenylalaninemia

Helène Ogier de Baulny, Véronique Abadie, François Feillet, and Loïc de Parscau

Abstract

Hyperphenylalaninemia (HPA) is the most frequently inherited disorder of amino acid metabolism (prevalence 1:10,000). In France, a nationwide neonatal screening was organized in 1978 to control its efficacy and patient follow-up. Phenylketonuria (PKU) was diagnosed in 81.6% of screened patients, the remaining affected with either non-PKU HPA (17.2%) or with cofactor deficiency (1.1%). French guidelines were established to specify the minimal diagnosis procedures and optimal treatment of patients. A low-phenylalanine diet must be started within the first days of life for all newborns whose blood phenylalanine levels are above 10 mg/dL (600 μmol/L). The dietary control must keep the phenylalanine levels between 2 and 5 mg/dL (120 and 300 μmol/L) until 10 y of age. Thereafter, a progressive and controlled relaxation of the diet is allowed, keeping levels below 15 mg/dL until the end of adolescence and below 20 mg/dL (1200 μmol/L) in adulthood. A lifelong follow-up is recommended for PKU women to prevent for maternal PKU.

Primary hyperphenylalaninemia (HPA) are a group of inherited diseases due to defective phenylalanine hydroxylase (PAH) activity resulting in accumulation of phenylalanine in blood and other tissues. In most cases (98% of subjects), HPA results from mutations in the phenylalanine hydroxylase gene. The associated phenotypes range in severity from classic phenylketonuria to mild HPA. The remaining cases arise due to a block in the metabolism of the cofactor tetrahydrobiopterin (BH4). BH4 is also the cofactor required for conversion of tyrosine and tryptophan into catecholamine and serotonin. Thus, disorders related to defective metabolism of BH4 could be considered as neurotransmitter diseases.

HPA appears as a highly heterogeneous trait with a broad continuum of phenotypes. The term PKU is reserved to the most severe form of the disease. The classical presentation is a progressive encephalopathy in children who have appeared to be normal for the first few months of life. Other symptoms include abnormal electrencephalography with seizures, abnormal behavior with hyperactivity, autistic or schizophrenic signs, eczema and lightly pigmented skin, and a musty odor. A lesser degree of biochemical disturbance is associated with a lower risk of mental handicap. Neurological impairment can be prevented by introduction of a phenylalanine-restricted diet shortly after birth.

Approximately 1 in 10,000 neonates born with PKU or milder forms of HPA are identified in the neonatal period through population-screening programs that have been implemented in various countries to treat affected children as early as possible.

Metabolic derangement

Phenylalanine is an essential amino acid provided by the various proteins contained in the diet. Normally, a small amount is used for protein synthesis. The remainder is hydroxylated to tyrosine, which is used for synthesis of protein and several compounds or is degraded to produce energy. The hydroxylation of phenylalanine to tyrosine requires 2 enzymes, phenylalanine hydroxylase and dihydropteridine reductase, and 2 cofactors, BH4 and NADH. BH4 is synthesized de novo from guanosine triphosphate in a series of steps. BH4 is regenerated from quinonoid dihydrobipterin by the dihydropteridine reductase.

Based on plasma phenylalanine levels and residual phenylalanine hydroxylase activity in liver, 3 different inherited phenotypes of HPA due to phenylalanine hydroxylase deficiency have been described: classical or typical PKU, atypical PKU, and permanent mild HPA (Fig. 1).
When the conversion of phenylalanine to tyrosine is blocked, phenylalanine that is not used for protein synthesis accumulates in body fluids or is converted to other metabolites. Although these pathways exist in unaffected individuals, high levels of these by-products are not normally produced. The exact mechanism of mental retardation in untreated PKU is unknown, but phenylalanine probably is the initiator of harm. The fact that PKU is most often accompanied by mental retardation, whereas permanent mild HPA is not, suggests that there is a threshold level of phenylalanine in extracellular fluids above which persistent postnatal or fetal HPA causes irreversible brain damage (2).

PKU and HPA are inherited in an autosomal recessive manner. The active PAH is a tetramer of the protein encoded by the PHA gene. About 500 mutations are known and most PKU patients are compound heterozygotes. This genetic heterogeneity may explain in part the large phenotypic variability encountered in the patient population (3,4).

**PKU screening: general organization in France**

In France, PKU screening was started by the end of the 1960s and 10 years later, a national organization based on the federation of 23 regional associations was established. Each of the regional associations has a dedicated medical and laboratory team responsible for neonatal screening and management of the screened patients. The national association and the health ministry manage the financial agreement to provide the costs of the screening program and of the special dietary products required for treatment. They also collect the results of the regional screening program and the yearly follow-up of each treated case. About 80 children with HPA are identified each year, among which ~98% have phenylalanine hydroxylase deficiency and two-thirds have PKU requiring a dietary treatment (5).

**Medical approach of the neonates screened with HPA**

The objective is to specify the diagnosis and to apply the adequate treatment as early as possible after birth (5,6).

The plasma level at screening indicates the degree of severity. Those infants with blood phenylalanine levels between 150 and 300 μmol/L are retested; those with levels between 300 and 600 μmol/L are controlled, investigated, and then monitored at the outpatient clinic. The neonates with blood phenylalanine levels >600 μmol/L are hospitalized for further investigations, treatment, and parental information and education.

Most of the screened newborns have primary HPA. However, secondary HPA due to various liver diseases should be excluded. Premature or small-for-gestation-age babies may have transient HPA, especially when they are fed a parenteral nutrition containing amino acids.

Disorders of BH4 metabolism are systematically excluded by analysis of the pterin profile in urine and measurement of dihydropteridine reductase activity in erythrocytes. In a few clinics, an oral BH4 loading test (20 mg/kg) is used to rapidly screen for BH4 synthesis defects and eventually to test BH4 responsiveness in some atypical PKU patients.

The phenotypes of the phenylalanine hydroxylase defect are determined by measuring blood phenylalanine and tyrosine levels while the infants are fed a normal diet containing at least 500 mg/d of phenylalanine for 5 consecutive days. The patients with the classical or typical form of PKU have phenylalanine levels above 1200 μmol/L due to hepatic phenylalanine hydroxylase residual activity <1%. Atypical PKU patients have levels between 600 and 1200 μmol/L and 1–5% residual activity. Permanent mild HPA patients have levels <600 μmol/L and >5% residual activity.

Patients affected with both the classical and atypical PKU require a (lifelong) dietary phenylalanine restriction, whereas patients affected with mild permanent HPA will develop normally without treatment. Moreover, treating such children with a phenylalanine-restricted diet can lead to undesirable nutritional problems. Recently, some BH4 responsiveness has been described in patients affected with atypical PKU and BH4 supplementation may offer them an alternative to a burdensome diet (7).

From a practical point of view, all the measurements required to define the disorder can be performed within 24 h for those patients whose blood phenylalanine levels are above 600 μmol/L. Those patients with blood phenylalanine levels between 300 and 600 μmol/L may require a phenylalanine load for 5 consecutive days if they do not receive a sufficient amount of phenylalanine in their usual diet. This phenylalanine load could be followed by a BH4 loading test. The general protocols used in our unit are summarized in Figure 2.

Between 1989 and 2002, this BH4 loading test has been applied to 51 HPA patients. Five were affected with BH4 disorders. Among the 46 remaining patients, 19 had some degree of responsiveness, but only 2 atypical PKU patients and 4 mild HPA patients displayed complete responsiveness with blood phenylalanine levels that were decreased by 30% within the 24 h following the BH4 load.

**FIGURE 1** Phenylalanine metabolism and causes of HPA. 1, Phenylalanine hydroxylase; 2, BH4 synthesis; 3, BH4 recycling; 4, tyrosine and tryptophan hydroxylase. TBH, BH4; qDHB, quinoid dihydrobiopterin.

**FIGURE 2** Evaluation of the neonates screened with HPA. A 5-d phenylalanine load (500 mg/d) can discriminate atypical PKU and mild HPA. Oral BH4-loading test (20 mg/kg) screens either for defective metabolism of biotinidase or for BH4-responsive atypical PKU. AAC, Amino acids chromatography; DHPR, dihydropteridine reductase activity measured on dried blood spots sampled on Guthrie’s cards.
**Principles of phenylalanine-restricted diet**

Phenylalanine, an essential nutrient, is not only required for protein synthesis but also serves as a precursor for tyrosine and its derivatives. In the absence of phenylalanine hydroxylase, tyrosine becomes an essential amino acid.

Therefore, the technical challenge of the dietary treatment is to devise a phenylalanine-controlled diet that allows the reduction of systemic phenylalanine concentration, satisfactory tyrosine provision, and optimal growth and development.

Natural foods provide a measured amount of the offending phenylalanine in a quantity sufficient to meet the normal metabolic requirement but not so great that toxic levels accumulate in the blood. This amount of phenylalanine intake, usually called tolerance, is individually determined and varies from 1 patient to another depending on PAH residual activity, anabolism, and rate of growth.

Reducing the phenylalanine solely by restricting dietary protein from natural food would cause protein malnutrition and nutrient deficiency. Thus, such diets necessitate the use of phenylalanine-free amino acid formula containing adequate amounts of nitrogen, vitamins, minerals, and micronutrients. These dietary products have progressively been refined but remain unpalatable and are a frequent source of difficulty with the diet.

At the start of treatment in infants, a period of phenylalanine-free milk brings blood levels down. As levels approach the therapeutic range, phenylalanine is added using measured amounts of normal milk and then adjusted until serial blood controls have stabilized. This period of treatment is quite easy to manage but is the most important time for parents’ education.

Once the addition of solids begins, the diet is progressively adapted with the following main principles explained to the parents and later to the patients: High-protein foods (meat, fish, eggs, dairy, and wheat products) are excluded. Foods with low-protein content (milk, vegetables, and fruits) are used to meet the required amount of phenylalanine. To allow calculation and diversification of the diet, serving lists were established in which 1 weighed portion is equivalent to a previously determined amount of phenylalanine (usually 15–20 mg). Low-phenylalanine foods either natural (fat and carbohydrates) or manufactured (special bread, biscuits, pasta, and flour) are free and useful in meeting the energy requirement and to satisfy the appetite of these growing children.

**Assessment for treatment**

Serial monitoring of blood phenylalanine levels (weekly for the first 2 or 3 y of life declining to monthly by the age of 7–8 y) is an essential element of treatment. The choice of therapeutic ranges for blood levels and the duration of diet are still a matter of debate. However, in children <10 y of age, it is universally admitted that the blood phenylalanine levels should be kept between 2 and 5 mg/dL (120–300 μmol/L). Life-long dietary treatment is quite universally recommended but because of the practical difficulties involved in sustaining a strict diet, many clinics allow a relaxation at some point between adolescence and adulthood. In France, it is recommended to keep the blood phenylalanine levels between 2 and 15 mg/dL (120–600 μmol/L) until the age of 15–18 y and below 20 mg/dL (1200 μmol/L) thereafter.

Such a restrictive diet poses nutritional risks and psychological burden that must be monitored by experienced teams that would regularly evaluate the clinical and biological status of patients and offer educational and psychological support. Whatever the decision regarding the diet discontinuation, sustained follow-up is essential for the affected females who are at risk for maternal PKU.

**Maternal PKU**

This term defines the embryopathy that affects the infants born to untreated PKU mothers despite the fact that usually the children do not themselves have PKU. The syndrome is characterized by low birthweight, microcephaly, dysmorphism, congenital defects, and developmental retardation. There is evidence that an increased risk is directly correlated to maternal phenylalanine levels during pregnancy. There is now good evidence that a strict low-phenylalanine diet along with provision of adequate energy and nutrients can prevent these devastating effects (8).

**Literature Cited**