Phenylketonuria

Maureen Anne Cleary

Abstract

Phenylketonuria remains one of the most common inborn errors in the United Kingdom. It is detected on the newborn heel-prick screening sample allowing early treatment with a strict low phenylalanine diet supplemented with artificial amino acids, and appropriate vitamin and minerals. Although the long-term prognosis is good, there is an increasing body of evidence highlighting subtle problems in neuropsychological function with slower reaction times and poorer executive function than peers. White matter changes clearly seen on brain magnetic resonance imaging may have some relationship to these neuropsychological difficulties but their significance is not clearly understood. The diet, although successful, is difficult to follow lifelong and with its attendant risks of nutritional deficiencies needs careful specialist management. In view of these challenges new treatments such as sapropterin (a tetrahydrobiopterin analogue) and large neutral amino acids are currently being used in phenylketonuria and a human trial has started using ammonia lyase as enzyme replacement therapy. Maternal phenylketonuria syndrome remains a risk for those who conceive whilst blood phenylalanine is elevated and females must be counselled early in childhood to avoid this risk.

Keywords hyperphenylalaninaemia; phenylketonuria; PKU; sapropterin therapy

Phenylketonuria (PKU) can claim at least three 'firsts': the first metabolic disorder to have a successful treatment; the first to be controlled by diet; and the first to be detected by newborn screening. This review describes the current management and outcome of PKU and summarizes developments of new therapies.

Terminology

PKU was first described in 1934 by Folling as 'imbecillitas phenylpyruvica' following the finding of phenylpyruvic acid (a phenylketone) in the urine of two siblings with mental retardation. The term phenylketonuria was later used by Penrose and has remained the most widely used name for hyperphenylalaninaemia (HPA) due to phenylalanine hydroxylase deficiency. It is now generally applied to the more severe end of the spectrum in which phenylalanine is greater than 1200 μmol/l whilst consuming a normal protein intake and this type is also referred to as *classical* PKU. HPA is a frequently used term to describe those with phenylalanine (phe) levels 600—1200 μmol/l on a normal protein intake. Individuals with levels between 120 and 600 μmol/l on a normal protein diet are usually said to have *mild* HPA. All variants arise due to defects in the enzyme phenylalanine hydroxylase (PAH); the severity relates to the nature of the underlying genetic mutation. In less than 2% of cases a raised phe level is caused by a defect in the production or recycling of tetrahydrobiopterin (BH4). PKU is still the most commonly used term in the United Kingdom (UK) and is used in the remainder of this article.

Natural history

PKU causes severe intellectual impairment. In classical PKU developmental delay is apparent within the first year of life and progresses to severe mental retardation (IQ < 50). Examination shows limb spasticity, tremor and microcephaly. A seizure disorder is frequently present and EEG abnormalities are common. Other findings may include hypopigmentation of the hair, skin and iris due to reduced melanin synthesis. Parkinsonian features and gait abnormalities are also often observed in the untreated individual. Abnormalities of behaviour are very common including hyperactivity, aggression, anxiety and social withdrawal. The natural phenotype is rarely seen now due to widespread newborn screening for this condition. However, PKU should be considered as a possible diagnosis particularly in an individual born in a country where newborn screening may not be available.

Detection

In most first-world countries the diagnosis of PKU is made through newborn screening. PKU can be readily detected by a raised phenylalanine on the newborn heel-prick blood test. Blood phe and tyrosine (tyr) are measured. In PKU the ratio between these two metabolites is greater than three. The cut-off value for a presumed positive screen varies between countries depending on the infant's age at screening. The UK practice is to sample between days 5—8, using a cut-off phe of 240 μmol/l. Other causes of elevated phe, aside from PKU, include a disorder of biopterin production or recycling, liver dysfunction or premature babies receiving amino acid containing parenteral feeds.

Disorders of biopterin production or recycling can cause raised phe since tetrahydrobiopterin (BH4) is the co-factor for the phenylalanine hydroxylase enzyme (see Figure 1). These disorders, previously called 'malignant PKU', are best named by their respective enzyme deficiency. In all positive screening cases a disorder of biopterin is excluded by measuring total biopterins and DHPR enzyme activity on blood spots. BH4 disorders result in neurotransmitter deficiencies and individuals need replacement of dopamine and 5-hydroxytrypophan in addition to BH4; some still need dietary treatment to reduce phe levels.

Liver dysfunction can cause an elevation of phe but in these cases other amino acids such as tyrosine, methionine and leucine/isoleucine are also raised thus keeping the phe: tyr normal or less than three. Preterm babies may have raised phe levels whilst on a high protein intake. Again, in this situation other amino acids are also elevated making it unlikely that PKU would be missed. Preterm babies should be tested at the same time as other newborns and their gestation and feed content noted on the request form.

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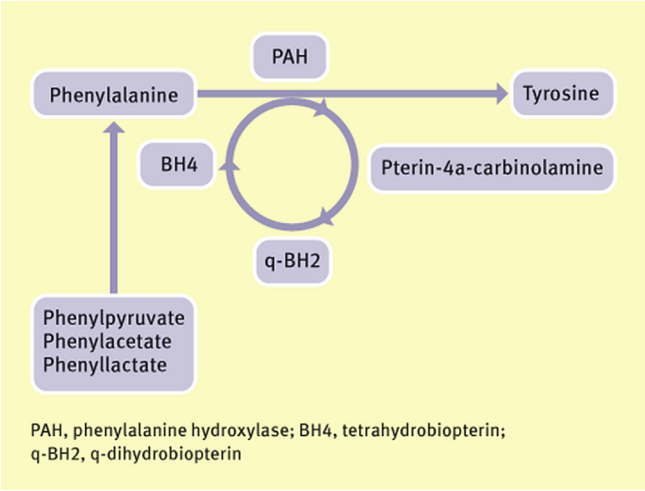

Figure 1 The phenylalanine hydroxylation system.

Epidemiology

The incidence of this condition in the UK is approximately 1 in 10 000 newborns. PKU is prevalent in Europe and the US. It is relatively common in some parts of China but is rare in African nations. The highest incidence is observed in Turkey where the incidence is 1 in 2600.

Biochemistry and genetics of PKU

Phenylalanine is an essential amino acid which is metabolized in the liver by the enzyme phenylalanine hydroxylase (PAH). The first step of catabolism of phenylalanine is irreversible conversion to tyrosine. The PAH enzyme requires tetrahydrobiopterin as its co-factor. PKU develops due to deficiency in, or absent activity, of the PAH enzyme and results in elevated phe and reduced levels of tyrosine. When the pathway to tyrosine is blocked, excess phe is transaminated to phenylpyruvic acid and excreted in urine. The enzyme is coded by the PAH gene located on the long arm of chromosome 12. More than 400 pathological mutations are recognized and most affected subjects are compound heterozygotes in that they carry two different mutations. There is a good correlation between pre-treatment phe levels, phe tolerance and genotype. However, outcome is affected by many factors and genotype knowledge is of limited value in predicting clinical management. But mutation analysis has some value in predicting BH4 responsiveness (see below).

PKU is inherited as an autosomal recessive condition. Prenatal diagnosis, although rarely requested, is possible by mutation analysis if the mutations are already identified in the index case.

Treatment

The aim of PKU treatment is the reduction of blood phe to a level allowing normal brain development. An individual's blood phe depends upon dietary intake of phe and the residual activity of phe hydroxylase. Although in some cases it is possible to augment phe hydroxylase activity (see *new treatments*), in most cases treatment relies upon reducing phe intake by a restriction of natural protein. In most cases meat, cheese, bread, fish and milk must be avoided. A semi-synthetic diet is used which comprises:

- foods of low phe content in unlimited amounts such as many fruits and vegetables;
- weighed amounts of foods containing medium amounts of phe (e.g. broccoli, potato). The amount of phe ingested is often calculated using an exchange system. In the UK system 1 'exchange' = 50 mg phe which is approximately 1 g protein;
- phe-free amino acid mixtures to provide normal or supra-normal total protein intake;
- vitamins, minerals and trace elements.

The diet should be strictly followed with these food groups evenly distributed throughout the day. Aspartame should be avoided as it contains large amounts of phe. Infant formulae feeds which are phe-free are available; many contain added essential fatty acids. These are used in conjunction with a small amount of standard infant formulae. It is possible to continue breast feeding even in severe PKU by giving a measured amount of phe-free formula prior to a breast feed. All PKU diets should be administered with the advice of a specialist dietician.

Monitoring of treatment

It is vital to monitor phenylalanine levels, usually through frequent blood spot analysis. Guidelines vary between countries regarding frequency and acceptable phe levels. In the UK, infants and young children should have weekly samples aiming at levels 120–360 μmol/l; school-age children fortnightly samples with a range of 120–480 μmol/l; and in adolescents and adults monthly samples with an upper limit of 700 μmol/l. These guidelines were reviewed in 2010 but despite intense debate on 'safe' levels of phe particularly at the milder end of the spectrum, the guidelines were unchanged. Details of these discussions are available through the UK newborn bloodspot screening programme website (see below).

Treatment target debate outside UK

The US PKU guidelines have recently been updated. They recommend lifelong dietary treatment aiming for the therapeutic target used in young children in UK i.e. 120–360 μmol/l rather than allowing any relaxation with age. Recent evidence supports a lowering of the target range for a longer period of time, that is, at least through adolescence. The brain is still undergoing important organization during adolescence and relaxing diet at this age may result in subtle deficits in neuropsychological function as an adult. A new European Guideline is currently underway and is due to be published in 2015. There is an appetite to develop a uniform treatment policy throughout Europe.

In addition to monitoring phe levels, other nutritional indices such as vitamin B12, folate, iron, calcium, phosphate and essential fatty acids should be measured in those with poor dietary adherence. Growth parameters are also monitored. Some clinics advocate regular neuropsychological testing whereas others only refer for such assessment where difficulties are suspected. It is likely that the new European guideline will be more offer more specific recommendations on such