FOCUS ON PKU: PAEDIATRIC

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Phenylketonuria (PKU) is a genetically inherited condition of amino acid metabolism, with a prevalence of approximately one in 10,000 in the UK.[1] This means that each year 60-70 babies are born with PKU in the UK.

PKU is caused by a mutation in the gene for the enzyme phenylalanine hydroxylase (PAH). PAH is responsible for breaking down the essential amino acid phenylalanine, to tyrosine. A deficiency of PAH results in raised serum (and brain) phenylalanine levels and decreased tyrosine levels.

NEWBORN SCREENING

In the UK, a nationwide newborn screening programme for PKU began in 1969.[2] Currently, every baby born in the UK is offered the screening test for PKU at approximately day five of life. This is commonly known as the 'heel prick test', which is a blood test performed by midwives. Prior to the 'heel prick test' there was a urine test or 'nappy test' that was carried out in certain areas of the UK.

The screening test today also includes the following inherited metabolic conditions:

- Medium-chain-acyl-CoA dehydrogenase deficiency (MCADD)
- Glutaric aciduria type 1 (GA1)
- Maple syrup urine disease (MSUD)
- Homocystinuria (HCU)
- Isovaleric acidaemia (IVA)

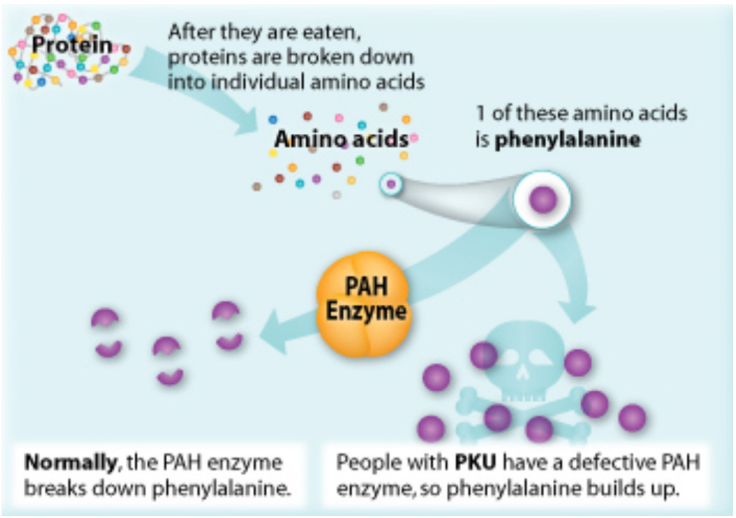
As well as these disorders:

- Cystic Fibrosis
- Congenital hypothyroidism
- Sickle cell disease

CLINICAL SEVERITIES

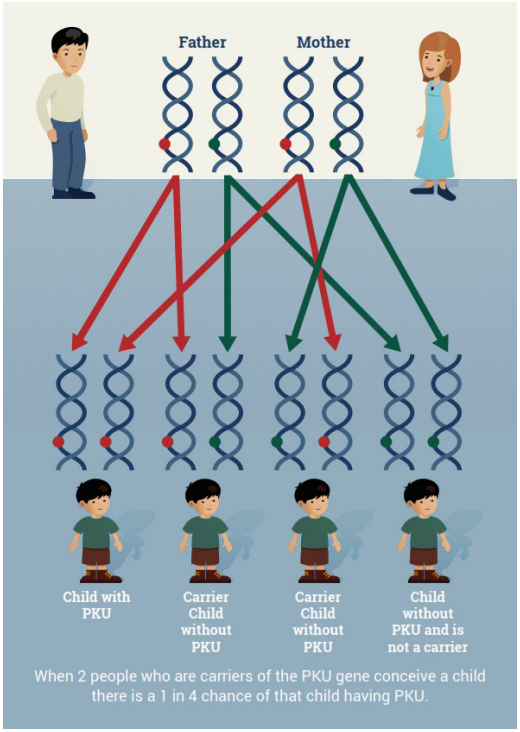
PKU exhibits a wide range of clinical severities, depending on the level of residual enzyme activity.[1] In patients with PKU, the PAH enzyme is not functioning properly or is absent and, therefore, it cannot convert phenylalanine into tyrosine. This leads to a build-up of phenylalanine in the blood and brain, as well as a deficiency

Figure 1:
The PKU pathway



Source: University of Utah, Health Sciences, Learn Genetics: http://learn.genetics.utah.edu/content/disorders/singlegene/pku/

Figure 2: Inheritance of PKU



Source: Vitaflo *Introduction to PKU* booklet

of tyrosine. Tyrosine is normally used to make other proteins as well as the pigment melanin and the neurotransmitter dopamine. Dopamine has important functions in the brain and melanin is a brown pigment, which affects the colour of the skin, hair and eyes. This is why late-treated or untreated people with PKU have pale coloured hair and skin, as well as brain damage and severe behavioural problems.[3]

PKU is the most common inborn error of protein metabolism[1] and is inherited as an autosomal recessive condition, which means that two copies of the mutated PAH gene is required to result in a child with PKU. The carrier rate for PKU in the UK is one in 50. For two people who are both carriers, there is a one in four chance for each pregnancy, of the baby having PKU and a two in four chance of the baby being a carrier. This is illustrated in the diagram below.

THE PKU DIET

PKU is treated with a diet that is very low in phenylalanine and must be initiated by 20 days of age.[4] All naturally occurring proteins contain phenylalanine, so the diet for PKU can only contain very small amounts of natural protein. However, as phenylalanine is an essential amino acid, it must be provided in small quantities in the diet to allow for growth of the child with PKU. Additional 'safe' protein is provided as a protein substitute containing tyrosine and all other essential and non-essential amino acids, except phenylalanine.

The amount of natural protein tolerated by each child will vary and depends on the residual enzyme activity present. There is a spectrum of severities of PKU from very mild PKU (children may tolerate 20g natural protein or more per day) to very severe PKU (children tolerate only 3.0-5.0g natural protein per day).

Initially, this means a phenylalanine-free formula is given to a baby with PKU until phenylalanine levels have fallen to within a safe range. Subsequently, the phenylalanine-free formula is given in conjunction with breastfeeding, or a measured quantity of standard infant formula. A breastfeeding mum requires considerable support to continue expressing her breast milk in the initial stages of treatment.

The PKU diet consists of four main parts:

1 *Restriction of all sources of natural protein*

No meat, fish, chicken, cheese, pulses, eggs or nuts are allowed, as they are too high in protein and phenylalanine. Other foods such as bread, pasta and pastries, biscuits or cakes also contain significant amounts of protein for most people with PKU and are usually replaced by special low protein foods available on prescription.

2 *Phenylalanine exchanges*

These are measured quantities of foods containing some protein, such as potatoes, sweetcorn, peas, rice, baked beans, cereals and milk. 1.0g protein = 50mg phenylalanine. These foods need to be carefully weighed out at each meal. Families are taught how to read nutritional information on food labels and work out the amount of food that contains 1.0g protein or one exchange.

3 *Protein substitute*

This is the 'medicine' in the PKU diet as it is essential and makes the PKU diet nutritionally

Table 1: Guidelines for total protein requirements for amino acid disorders (protein equivalent from protein substitute and natural protein)[5]

Age (years)	Total protein (g/kg/day)
0-2	3.0
3-10	2.0
11-14	1.5
>14	1.0 (maximum 80g/day)

Table 2: Protein substitutes for PKU (available in the UK)[5]

Product	Age suitability	Manufacturer	Energy (kcal)	Protein equivalent (g)
PKU Anamix Infant (Per 100ml)	From birth	Nutricia	69	2.0
PKU Anamix First Spoon (Per 12.5g)	6 months - 5 years	Nutricia	41	5
PKU Squeezie (Per 85g)	6 months - 10 years	Vitaflo	135	10
PKU Gel unflavoured (Per 24g)	6 months - 10 years	Vitaflo	81	10
PKU Anamix Junior (Per 36g sachet)	1 - 10 years	Nutricia	135	10
PKU Anamix Junior LQ (Per 125ml)	1 - 10 years	Nutricia	118	10
XPhe Jump 10/20	3 years +	MetaX	56	10 / 20
PKU Cooler 10/15/20 (87ml/130ml/174ml)	3 years +	Vitaflo	62/92/124	10/15/20
PKU Lophlex LQ 10/20 (62.5ml/125ml)	3 years +	Nutricia	58/116	10/20
XP Maxamaid (Per 20g)	1 - 8 years	Nutricia	62	5
PKU Air 15/20 (130ml/174ml)	3 years +	Vitaflo	75/100	15/20
PKU Express 15/20 (Per 25g/34g sachets)	3 years +	Vitaflo	74/101	15/20
XP Maxamum (Per 50g sachet)	8 years +	Nutricia	149	20
PKU Lophlex Powder (Per 27.8g sachet)	8 years +	Nutricia	86	20
Phlexy-10 drink mix* (Per 20g sachet)	8 years +	Nutricia	69	8.3 (10g amino acids)
Phlexy-10 tablets* (Per 10 tablets)	8 years +	Nutricia	38	8.3 (10g amino acids)
Add-Ins (Per 18.2g)	4 years +	Nutricia	86	10
Easiphen (Per 250ml)	8 years +	Nutricia	263	16.8
PK Aid 4* (Per 5g)	Infants, children and adults	Nutricia	17	3.95

*These protein substitutes do not contain any vitamins, minerals or trace elements - they require micronutrient supplementation.

safe and adequate. The protein substitute contains all essential and non-essential amino acids, except phenylalanine, with added vitamins, minerals and trace elements.

The protein substitute must be given every day, spread out evenly over the course of the day, usually three to four times per day In patients with amino acid disorders such as PKU, who require severe restriction of natural protein intake, the provision of a suitable protein substitute is essential for two reasons:

i) To prevent protein deficiency
ii) To optimise metabolic control[5]

There are guidelines on the amount of total protein equivalent (from the protein substitute and from natural protein) that children with PKU should be having, according to their age, weight and severity of PKU (see Table 1).

There are many PKU protein substitutes available in the UK for children with PKU (see Table 2).

The protein substitutes are presented in different forms, such as powders, liquids, purees and tablets (for older children and adults). They are also available in numerous different flavours and tastes, as well as unflavoured versions.

4 *'Free' foods* - These are low protein prescribable foods, as well as foods that are naturally low in phenylalanine such as some vegetables and all fruits (except passion fruit). They are called 'free' foods as they contain very little phenylalanine and do not need to be measured/weighed to be incorporated into the PKU diet.

WEANING

Babies with PKU can be weaned at a similar age as other children, but may benefit from weaning before six months of age.[6]

Weaning is commenced at around six months of age and not before four months or 17 weeks of age. In babies with PKU, there may be some advantages to starting the weaning process slightly earlier than six months.[6] This is because there are many additional components to weaning a PKU baby, such as the introduction of a more concentrated protein substitute, measuring phenylalanine exchanges and encouraging low phenylalanine 'free' foods.[6]

MONITORING

It is essential to monitor the PKU diet with regular finger prick blood tests that measure the phenylalanine and tyrosine levels.[7] This is to make sure that a child is given the appropriate amount of natural protein per day for optimum growth and phenylalanine control.

There are recommendations for target phenylalanine levels and frequencies for children and adults with PKU.[4] However, there is still some controversy as to the optimum range and frequency of phenylalanine levels for different age groups.

Table 3: Frequency of blood spot monitoring in PKU[7]

Age	Frequency
0 - School entry	weekly
School age	weekly to fortnightly
Adolescents/Adults	fortnightly to monthly

More frequent blood samples may be analysed from older children if the parents wish or if the phenylalanine concentrations are high or abnormally low.

DESIRED BLOOD PHENYLALANINE LEVELS IN TREATED PATIENTS

The current acceptable range of phenylalanine is based upon the MRC report.[1] **Please note**: Evidence-based European PKU Guidelines are under development (due to be published in 2016) and these target phenylalanine ranges may need to be amended following publication of the European PKU Guidelines:

0-5years	120-360µmol/L
Greater than 5 years	120-480µmol/L
Greater than 10 years	120-480µmol/L
Adults	120-700µmol/L

The European PKU Guidelines will be recommending the following target phenylalanine levels for PKU:

0-12 years	120-360µmol/L
>12 years and adults	120-600µmol/L

Table 4: Sample menu for an eight-month-old infant with classical PKU
Diagnosed on routine neonatal screening
Number of exchanges = six per day (6.0g natural protein/day)
Breastfeeding
Weight = 8.0kg (50th centile)
Length = 69cm (50th centile)

Meal	Food/drinks	PKU exchanges
On waking	Breastfeed + 100ml PKU Anamix Infant	Approx one
Breakfast	10g Weetabix Low protein milk Fruit, e.g. raspberries or a small banana Low protein toast with butter	one
Snack	Low protein biscuit or cracker	
Lunch	25g peas, cooked soft Carrots, cooked soft Low protein pasta White sauce made with low protein milk and cornflour 20g yoghurt (check protein content of brand) **10g PE from PKU protein substitute, e.g. 1 sachet PKU Gel or 2 sachets PKU Anamix First Spoon**	one one
Snack	Satsuma/grapes	
Evening meal	20g baked beans Grated Violife cheese* Low protein toast fingers Slices cucumber, peppers and baby tomatoes **5.0g PE from PKU protein substitute, e.g. ½ sachet PKU Gel or 1 sachet PKU Anamix First Spoon**	one
Bedtime	Breastfeed + **100ml PKU Anamix Infant**	Approx one
TOTAL		**Six exchanges + 19g protein equivalent**

*Violife is a vegan cheese that is also very low in protein and suitable for a PKU diet

Important points and calculations for the case study shown in Table 4:

- At approximately six months of age, a more concentrated protein substitute (PS) needs to be introduced to an infant with PKU, in order to provide adequate protein equivalent for growth and metabolic control.
- An infant protein substitute (PKU Anamix Infant) is continued alongside breastfeeding and the more concentrated PS.
- Initially, when weaning begins, solids contain very little phenylalanine and do not need to be counted in the exchanges.
- Once weaning is established, foods containing slightly higher amounts of protein are introduced and natural protein from breast milk or infant formula is reduced.

Calculations:

- Aim for total protein equivalent (PE) = 3.0g/kg/day
  3 x 8 = 24g PE total
  24 – 6 = 18g PE from protein substitute
- This can be provided as either 1.5 sachets PKU gel (provides 15g PE) 200ml PKU Anamix Infant (4g PE), **OR** 3 sachets PKU First Spoon (5.0g PE per sachet) + 200ml PKU Anamix Infant (4.0g PE).