Original Article

# Challenges in the management of Phenylketonuria in Malta

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**Abstract**

Phenylketonuria (PKU) is a rare metabolic disorder comprising a number of different enzyme deficiencies. In Malta, dihydropteridine reductase (DHPR) deficiency appears to be more common than phenylalanine hydroxylase deficiency (classical PKU), and is associated with greater and long term neurodisability. The absence of newborn screening for PKU in Malta results in a later diagnosis and, to-date, all affected patients require medical support for one or several problems including developmental delay, behavioural issues, cognitive impairment, epilepsy and neurodisability. These are compounded by problems in providing and adhering to strict low-phenylalanine diets and, in those with DHPR, the regular provision of neurotransmitter and cofactor supplementation. As a result, although a small cohort, these patients create a disproportionate demand on health services and, in most cases, will continue to require long term support at all levels since most will be unable to lead an independent existence. A radical and comprehensive overhaul of the local care provided to children with rare metabolic diseases is required at all levels, starting with the introduction of newborn screening, followed by effective dietary and pharmaceutical provision throughout childhood and through to later life.

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## Introduction

In Malta, during the period 1996-2015, five paediatric cases from three families with the same form of tetrahydrobiopterin ($BH_4$) disorder, namely dihydropteridine reductase (DHPR) deficiency and just one child with classical PKU due to phenylalanine hydroxylase (PAH) deficiency have been diagnosed. Out of a childhood population of about 90,000[1], the prevalence of PKU is therefore approximately $5.5 \times 10^5$. The carrier rate of DHPR deficiency in the Maltese population reported by Farrugia *et al* (2002) is high at 3.3%.[2] In comparison, the carrier rate of PAH deficiency is 2% in northern Europe, 3.8% in Turkey and 3% in Ireland, but is unknown in Malta.[2]

## Case Summaries

### Case 1: PAH deficiency (Classical PKU)

A 3 year 8 month old girl was born prematurely at 34 weeks gestation with respiratory distress and birth weight on the 50$^{th}$ centile. She was lost to neonatal follow-up and presented at 23 months of age with feeding difficulties, developmental delay and failure to thrive in the context of gross neglect and social problems. She was taken into care and fostered. As well as failure to thrive, she was noted to have microcephaly, fair hair and blue eyes. A phenylalanine (Phe) level was documented at 120umol/L with a tyrosine level (Tyr) of 38umol/L (normal Phe values: 6 – 50umol/L <1 year and 10 – 30umol/L >1 year. Table 1).

The DHPR gene was normal and sepiapterin reductase was negative. She was started on a low phenylalanine diet with Anamix Child at 23 months of age with a marked improvement in terms of developmental progress and brisk darkening of her

hair. Nevertheless, mild hypotonia persisted and an MR of the brain showed leukomalacia. CSF neurotransmitters were not tested. To-date, she has no signs of epilepsy but remains developmentally delayed and attends school with the help of a learning school assistant (LSA) on a 1:1 basis (Table 2).

***Table 1:*** *Normal Phenylalanine and Tyrosine levels at 0 – 31 days of life on protein containing feeds*

| | |
|---|---|
| Phenylalanine | 40 – 120 umol/L normal<br><br>120 – 600 umol/L hyperphenylalaninaemia<br><br>600 – 1200 umol/L mild PKU<br><br>>1200 umol/L classical PKU |
| Tyrosine | 55 – 147 umol/L normal |
| Phe : Tyr ratio | >3 is abnormal |

***Table 2:*** *Summary of patient details*

| Case | Age at diagnosis | Disorder | Phe level diagnosis | PKU phenotype | Microcephaly | Motor disorder | Develop delay | Behavioural problems | Seizures |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 23mo | PAH | 1693 | yes | yes | + | + | + | - |
| 4 | 8mo | DHPR | 906 | yes | yes | ++ | +++ | ++ | +++ |
| 2 | 5mo | DHPR | 700 | no | yes | ++ | ++ | ++ | + |
| 3 | 5mo | DHPR | 550 | yes | no | + | ++ | ++ | - |
| 5* | newborn | DHPR | - | no | no | + | + | + | - |
| 6* | newborn | DHPR | - | no | no | - | + | _ | - |

*Siblings of case 4 diagnosed on newborn testing

**Case 2: DHPR deficiency (atypical PKU)**

A 17 year old young man was born at 40 weeks gestation after a normal pregnancy. His birth weight was 2.7 kg (3rd percentile) and head circumference 33cms (5th percentile). Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Apart from some light meconium staining of the liquor, there were no other concerns until two months of age when he presented with seizures. These were initially not controlled with sodium valproate, and he required additional anticonvulsants with good effect. He did not have the typical 'fair hair, blue eyes' PKU phenotype, but developed hypotonia, global developmental delay and microcephaly. Amino acid analysis was carried at 5 months of age as part of the investigation for developmental delay, and confirmed a Phe level in excess of 700umol/L.

The DHPR level was low and genetics subsequently confirmed the mutation consistent with DHPR deficiency. He was started on a low phenylalanine PKU diet at 5 months of age with 8 daily exchanges, low protein diet and 4 daily PKU coolers. There was a slow response in terms of seizure control, and his developmental delay persisted with significant behavioural difficulties.
CSF neurotransmitter levels were checked regularly: homovanillic acid (HVA) and 5-hydroxyindole-acetic acid (5HIAA) levels were low, initially with reversed ratios. He required high doses of neurotransmitter precursors including L-3,4-dihydroxyphenylalanine (L-DOPA), 5-hydroxytryptophan (5HT) and folinic acid. Periodic episodes when his medication was not available or out of stock, rapidly resulted in increased symptomatology particularly with increased dystonic movements, behavioural changes and aggression generally over the subsequent 24-36 hours from not receiving medication.

This patient walked at 21 months, continued to progress and ran clumsily with feet apart. He uttered a few short sentences at 5 – 6 years of age and was able to fasten a few buttons at 8 years of age. Oculogyric crises were seen early on, with hand tremors lasting a few seconds and transient dystonia. The latter responded to clonazepam, whilst seizures responded partially to sodium valproate. No clear pyramidal or extrapyramidal motor signs were found. At 5 years of age, he was functioning at around the 3½ year level, with additional hyperactive and aggressive tendencies (Table 2). Brain imaging showed no specific abnormality.

He has been very sensitive to treatment changes. Phe levels have remained moderately high, averaging 210 – 390umol/L, with peaks up to 472 (2005) and between 500 – 600umol/L (2007) during periods of poor health and/or poor compliance. He has required a 1:1 LSA support at all times at school. He is currently employed under a 'protected' work placement attaching labels to products on a part-time basis. He is able to prepare simple meals and catch the bus home, but requires help with more complex tasks and will have difficulty leading a fully independent existence.

**Case 3: DHPR deficiency (atypical PKU)**

A 15 year old was born after a normal pregnancy and vaginal delivery at 40 weeks gestation. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Birth weight was 3.55 kg (50th percentile) and head circumference 35cms (45th percentile). He was well until 5 months of age when he presented with motor delay, hypertonia and typical PKU phenotype with fair hair and blue eyes. The first Phe level at 5 months of age confirmed a Phe level of 550umol/L with a tyrosine level of 75umol/L.

The DHPR level was low and genetics subsequently confirmed DHPR deficiency. Initial CSF neurotransmitters including homovanillic acid (HVA), 5-hydroxyindole-acetic acid (5HIAA) and methyltetrahydrofolate (MTHF) were normal. He was started on a PKU diet with significantly reduced phenylalanine content at 5 months of age, initially via highly modified milk (Lofenalac), plus Aminogram, Aminex rusks, Duocal, PKU gel, permitted but controlled Phe-containing protein exchanges and PKU coolers. There was an improvement in terms of hypertonia, and moderate developmental progress was seen. He developed a transient dermatitis as a result of being on Lofenalac without any natural protein, and subsequently low Phe levels. This responded well to alterations in the Phe exchanges and his skin pigmentation improved.

Despite normal CSF neurotransmitter levels, this child also required regular L-Dopa with 5-hydroxytryptophan (5-HT) and folinic acid supplementation on a 4-times and daily basis, respectively. During periods when his medication was not available, he rapidly developed increased dystonic movements and behavioural changes over

the subsequent 24hrs from not receiving medication. Unfortunately, these episodes have been a relatively frequent event, especially since his medication is highly specialised, only procured for a very small number of patients locally and not readily available from many sources. Numerous attempts to guarantee continuous supply and availability of all medications and specialized dietary products for PKU with the local pharmacy service have met with varying degrees of success and, despite strenuous and repeated efforts, intermittent non-availability remains an ongoing problem for all patients with PKU.

Developmentally, he walked at 21 months of age, and ran soon afterwards. There have been significant behavioural difficulties, mainly in the form of aggression, attention deficit hyperactivity disorder and mood disturbance. He had several oculogyric crises. His head circumference remained normal, but he developed a mild motor disorder with mild hypertonia and brisk tendon reflexes. More recently, he has also developed dystonic movements and equinus gait disturbance. Neuro-imaging showed no specific abnormality. He has required a 1:1 LSA support at all times at school and now attends a special school for children/adolescents with significant neurodevelopmental problems (Table 2). He will require a sheltered and protected work placement and will be unable to lead an independent existence without significant, long term support.

**Cases 4, 5 and 6: Siblings with DHPR deficiency (atypical PKU)**

**Case 4:** An 18 year old young man was born at 38 weeks gestation by precipitate vaginal delivery. His birth weight was 2.9 kg ($5^{th}$ percentile) and head circumference 34cm ($15^{th}$ centile). His Apgar scores were 6 and 7 at 1 and 5 minutes, respectively and, apart from mild respiratory distress and hyperbilirubinaemia, was well till around 6 months of age when concerns arose relating to motor delay, reduced head growth from $50^{th}$ centile to the $10^{th}$ percentile and central hypotonia. He had a classical PKU phenotype and was subsequently diagnosed with DHPR deficiency at 9 months of age. An initial Phe level was 906umol/L, Tyr was 51umol/L, DHPR activity was low and biopterin level was high. The first CSF neurotransmitter levels showed an HVA of 85 (154 – 867umol/L); HIAA 43 (89 – 367umol/L), and folate 16.4nmol/L (normative values at ages 0-5 years: 13 nmol/L and >6 years: 10 nmol/L).

He was started on a low Phe diet at 7 months of age with Lofenalac with added aminogram, protein exchanges, aminoacid supplements, Serevit vitamins and mineral supplements. His response to diet in terms of decreasing Phe levels was very slow, and Phe levels persisted around 200umol/L. This was thought to be related to a lack of compliance with his diet. He was started on L-Dopa, 5- tryptophan and folinic acid.

At 4years 8months he was functioning at the 2.5 - 3 year level, and at 6 years he could count up to 50 and carry out simple addition and subtractions. He developed a significant dystonic four limb motor disorder with spasticity and facial tics, and frequent adjustments of medication were carried out. Neuro-imaging showed white matter changes in both occipital and temporal lobes extending to the periventricular, parietal and posterior frontal white matter. At 5 years of age, he developed absence seizures with bilateral continuous occipital discharges that were resistant to treatment. This evolved and included drop attacks that occurred several times a day, and required various combinations of anti-epileptic medications including lamotrigine, topiramate, clobazam and levetiracetam. Due to the dietary restrictions imposed by the PKU diet itself, a ketogenic diet was not possible at the time. A trial of steroids was also very difficult and not tolerated. He was referred for further assessment of his refractory epilepsy to Guy's Hospital in London where a vagal nerve stimulator (VNS) was implanted. This reduced his seizure frequency by approximately 50% but required frequent adjustments and, in one year alone, he travelled to London 11 times for treatment. The family struggled with this child's medical condition and other practical medical problems, and emigrated to the UK.

This patient has remained with significant learning difficulties and neurodevelopmental delay (Table 2). He will require a sheltered and protected work placement and will be unable to lead an independent existence without significant, long term support.

**Case 5:** A younger brother of case 4, now aged 13 years, was diagnosed with DHPR deficiency by genetic testing shortly after birth. Unlike his brother, he did not have a classical PKU phenotype.

Nevertheless, his first Phe level was also elevated and CSF neurotransmitters showed: HVA 222 nmol/L; HIAA223 nmol/L, and folate 19.9 nmol/L. He was started on a low Phe diet at 2 weeks of age with Minaphlex, a special formula with a linoleic:α-linolenic acid ratio of 4:1, and was used to correct fatty acid imbalance associated with a PKU diet. Like his older brother, there was a very slow response in lowering Phe levels.

Despite the early diagnosis and treatment, this boy also manifested developmental delay, albeit milder when compared to his older brother. At 4 years of age he managed 5 to 6 word sentences, developed an early motor disorder with paucity of spontaneous movements, hypertonia and lead pipe rigidity reminiscent of symptomatic Parkinsonism. Neuro-imaging showed persistent prominence of the terminal myelination zone, but there were no definite white matter abnormalities.

He was managed with L-Dopa, 5-HT and folinic acid. At 4 years of age he developed significant behavioural disturbances, frequent falls, attention deficit and frequent temper outbursts during mealtimes. He was very fussy in his choice of food, making day to day management very difficult when considering the reduced choice of food available to him. This behavioural profile was very similar to that of his brother but improved in tandem with his improved epilepsy control.

Significant learning difficulties and neurodevelopmental delay necessitated a full time LSA in mainstream school (Table 2) and, as an adult, he will require sheltered and protected work placement and will also be unable to lead an independent existence without significant, long term support.

**Case 6:** The youngest brother of cases 4 and 5 was born and diagnosed in the UK after the family emigrated and clinical details of his condition are limited. He does, however, also have DHPR deficiency and manifests moderate global delay despite immediate diagnosis and initiation of therapy and a specialized diet shortly after birth. He remains on regular medication and a restricted diet as per his siblings. He has an LSA on a 1:1 basis at school and is likely to require long term support, even into adulthood (Table 2). This patient and his brothers are currently under the care and follow up of colleagues in the UK where they are now resident.

## Discussion

### Medical impact on patients and families

#### *Dietary intervention*

The goal of PKU treatment is to maintain plasma phenylalanine (Phe) levels with a 'normal' range that supports growth, development and mental function while providing a nutritionally complete diet. Phe is an essential amino acid and required for protein synthesis, therefore very low levels are also detrimental. Individuals with hyperphenylalaninaemia require a low Phe diet that is based on two interrelated dietary modifications to achieve metabolic control of plasma Phe levels. Natural foods are severely restricted to limit protein intake while providing adequate amounts of Phe. This involves elimination of all sources of animal protein, legumes and nuts, as well as limiting amounts of bread, pasta, rice and some vegetables. Low protein bread and pasta products made from starch are used to provide energy.

Consumption of an amino-acid based, Phe-free formula milk or amino-acid medical food is required to provide adequate protein, vitamins, minerals and energy due to their restriction in natural foods. The UK Medical Research Council Working Party on PKU recommends a total protein intake of 3g/kg/day for children under 2 years of age and 2g/kg/day for children over 2 years of age. These amounts exceed recommendations for protein intake in the non-PKU population by 30%. A typical low phe diet is based on a system of exchanges. In the UK system, one 'exchange' amounts to 50mg Phe which is approximately 1g protein. Unfortunately, this assumption does not work for protein from fruit and vegetables, the content of which are calculated using special databases.[3]

#### *Medication*

In children with atypical PKU, CSF amino acids and neurotransmitter imbalance is common and need to be managed. This requires periodic lumbar punctures and daily supplementation with folinic acid, tryptophan and L-Dopa. Epilepsy and behaviour disturbance are frequent problems in this group of children and need to be managed appropriately with anticonvulsants, behavioural therapy and, if necessary, sedative medication.

**Psycho-social and educational impact**

A study by Di Ciommo et al [4] focused on the lived experience of patients with PKU. This was a phenomenological study of 20 patients using a validated semi-structured interview in an Italian tertiary level metabolic centre. They looked at the personal experiences of these patients through (a) their knowledge and conceptualization of PKU, (b) their perception of being different and (c) their adherence to diet. It was shown that children and young adults with early treated PKU had a fair knowledge of their condition but did not feel that they were truly ill.[4] Although they perceived no direct, immediate, adverse effects of their disease, they adhered to their diet. They reported a difference between themselves and their peers. The fear of stigmatization tended to prevent them from participating in social occasions during which food was shared. One coping strategy reported by these individuals to overcome isolation was to disclose their condition to their peers.

From the cognitive point of view, early diagnosis and treatment of PKU can prevent the severe neurocognitive consequences of this disorder. However, even early- and well-treated patients experience hidden disabilities, including subtle deficits in executive functioning, mild reductions in mental processing speed, social difficulties, and emotional problems that may remain unnoticed for years.

PKU has been shown to be associated with poor executive function that may impact treatment adherence and may lead to psychosocial deficits including difficulty in forming interpersonal relationships, achieving autonomy, attaining educational goals, and having healthy emotional development. A degree of depressive and anxiety symptoms may also be present. The combination of cognitive and psychiatric disturbances acts as a hidden disability.[5] Patients with atypical and $BH_4$ disorders are more likely to be adversely affected with a greater incidence and degree of neurodisability.[6] From the parental point of view, mothers of children with biochemical genetic disorders report greater stress and worry, less satisfaction with social support, greater difficulty meeting their child's extra care needs, and more impact on multiple aspects of their personal lives.[7]

**Financial impact**

A review of the cost of special dietary needs in 10 PKU specialist centres, reported that the mean annual cost of protein substitutes across 4 age groups (2, 8, 15 years and adults) ranged from €4,273 to €21,590 per patient. The cost of low-protein products also differed; the mean cost of low-protein bread varied from €0.04 to €1.60 per 100kcal. All protein substitutes were either fully reimbursed or covered by health insurance. However, reimbursement for low-protein products varied and state benefits differed between centres.[8]

In a cross-sectional study about time consumption and cost of PKU in the Netherlands, it was shown that the median out-of-pocket cost per patient was shown to be €604 annually (in all age groups)[9]. These costs were mainly due to expenditure on low-protein food products and for a small part on costs related to PKU testing equipment, postage of Phe blood tests, taking extra luggage on holiday to accommodate PKU equipment and attending PKU events. This study assessed whether these additional PKU-related costs are offset by the potentially cheaper natural diet imposed upon PKU patients that contains very little or no regular bread, dairy products or meat. In comparison to the general population, a Dutch adult on a normal diet will spend a mean amount of €1,200 annually on meat, cheese, milk, yoghurt and bread. For patients with PKU this expenditure is replaced by the costs of the low protein products. It may be expected that costs between protein containing and low protein food products will balance out in patients depending on disease severity and the need for low protein food products. Taking this into account, the authors concluded that it is unlikely that there will be a large burden of extra out-of-pocket cost for families of patients with PKU.[9]

It must be stressed, however, that the costs of the Phe free protein supplements in a mixture with vitamins and minerals, which are an essential part of the diet of patients with PKU, vary per country but may be as high as €30,000 annually. In most European countries these costs are reimbursed by the government, or as is the case in the Netherlands, by health insurance. To guarantee proper dietary treatment and compliance of patients with PKU and to avoid a disproportionate financial burden for patients and families, it is essential that costs of the

Phe free protein supplements are reimbursed in all countries.[9]

**Impact on Health services**

According to the National Institutes of Health Consensus Development Conference Statement about the management of phenylketonuria, health systems need to respond effectively in order to ensure metabolic control across the lifespan of individuals with PKU. Comprehensive, multidisciplinary, and integrated systems are needed to deliver this type of care to individuals with PKU. Consistent and coordinated screening, treatment, data collection, and patient support programs are necessary. Moreover, there should be equal access to culturally sensitive, age-appropriate treatment programs. They also state that uniform policies must be established to remove financial barriers to the acquisition of medical foods and modified low-protein foods and to provide access to support services needed to maintain metabolic control in individuals with PKU.[10] In practical terms, the above requirements are best met by a coordinated, expert team.[11]

**Current challenges in management of PKU in Malta**

***Late diagnosis***

The absence of neonatal screening in Malta is a major drawback that mitigates against early treatment. This is further compounded by the fact that, in Malta, atypical PKU appears to be more common than classical PKU where the prognosis is perhaps more heavily dependent on careful and early treatment. Given the absence of newborn screening in Malta, over the past 18 years, 4 children with PKU were diagnosed after the age of 5 months and, in some cases, much later in childhood, as shown in Table 1. Two siblings of the index case were screened immediately and diagnosed shortly after birth.

Paediatricians need to keep the possibility of PKU always in mind in those children with unexplained developmental delay, abnormalities in tone, movement disorders, or atypical cerebral palsy. Despite current literature stating that the use of 'metabolic screens' in the investigation of children with global developmental delay tends to have a low positive yield, this may be an argument in favour of performing a metabolic screen in such situations. Furthermore, since PKU is a rare disease, medical practitioners will find it difficult to acquire enough experience to identify clinical signs suggestive of PKU early enough. This effectively strengthens the case for neonatal screening.

***Shared care***

PKU is best managed in a tertiary metabolic centre, and this type of management has been shown to be more effective in PKU when compared to management by general paediatric centres.[5] Outside of these Centres, the level of experience in dealing with PKU is very limited. This scenario applies to Malta, whereby patient care is shared with a tertiary specialist centre in London. Phe levels need to be checked as often as needed/frequently, and communicated with the specialist team. Delays in the availability of results may not allow for appropriate titration of doses and changes in diet. Furthermore, CSF neurotransmitter levels may not be assayed often enough according to recommendations because of logistical problems with sampling and non-availability of laboratory assays at a local level. Indeed, CSF amine levels are obtained in London and necessitate an annual visit overseas. Despite this, local follow-up remains an important part of long term management with families still seeking advice about common problems in PKU such as doses of L-Dopa, 5-HT, seizure control and management of movement disorders.

***Dietary supplies***

The lack of specialist dietetic support is another important local drawback. This is regularly associated with and compounded by frustrating difficulties in procuring certain special food items, ensuring adequate stocks and avoiding 'out of date' issues, making provision and compliance with a low Phe diet very difficult. It would also seem that in contrast to other conditions requiring special dietary and/ or nutritional support, families of children with PKU struggle in order to secure timely delivery of the required special dietary items. These children only consume small amounts of specific food items that change from time to time, and are not widely available, thereby discouraging local pharmaceutical agents to stock these items.

## Conclusion

### *National screening*

PKU is a chronic condition with significant morbidity for affected patients and a burden on health care costs. It fulfils all criteria for newborn screening and is sufficiently prevalent in the local population such that an official report strongly recommended it's addition to the current National Programme in 2005.[12] There is no medical reason why neonatal screening should not be introduced in Malta in line with current international recommendations.[13] Once introduced, infants who are found to have high phenylalanine levels will be recalled urgently to (a) confirm high Phe levels, and (b) depending on the level, plan further investigation, (c) liaise with tertiary centre and start a low Phe diet. It is important to keep in mind that failure to pick up PKU early on and any delay in starting effective treatment may carry medico-legal implications.

### *Central pooling of supplies*

Although there are only very few children who require low Phe food products, they should receive the required products at the right quantity and at the right time. This is an important issue that has ethical as well as potentially serious medico-legal implications.

It is therefore time to push for appropriate changes in pharmacy service that effectively respond to the nutritional requirements of these children in real time. It may be possible to introduce a system whereby these families are given access to carefully-monitored credit that can be used to order and purchase their special foodstuffs directly from their tertiary centre. At this day and age, this is technically very feasible and convenient for all. It may also be more cost-effective as it eliminates expired / unused / surplus items.

### *Shared care*

PKU, like other rare disease, needs to be managed under the direction of a specialist centre. Nonetheless, appropriate and effective joint care needs to be maintained between the local team and the tertiary team, and should incorporate dietetic input.

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