

# Phenylketonuria in an adult with normal diet

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**Phenylketonuria (PKU) is a rare inborn error of metabolism. It is caused by the deficiency of phenylalanine hydroxylase, an enzyme which converts phenylalanine to tyrosine and can cause severe learning disability in children if untreated. Drs Balaji *et al.* describe a case of an adult female with phenylketonuria and schizophrenia who was non-compliant with the PKU diet. The case raises questions about the management of this condition in adults.**



**A** 47-year-old woman with a diagnosis of phenylketonuria, mild learning disability and schizophrenia,

is known to learning disability (LD) services since she was 21 years old.

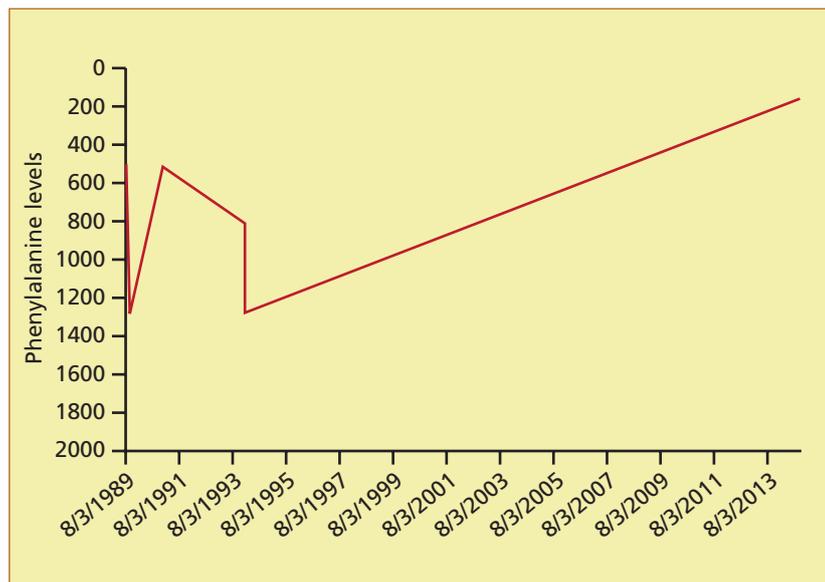
She is one of three children. There were no complications during her birth. She had a positive Guthrie test and was followed up by a paediatrician and had been on a phenylketonuria diet. Her milestones were slightly delayed. It appears that her learning disability might be due to phenylketonuria. She maintained her phenylalanine-free diet until the age of 15 years.

Her parents divorced when she was four years old and she stayed with her mother. She attended a special needs school and then a youth training scheme. She worked at a local market garden and was briefly in a relationship.

## Psychiatric history

At the age of 21 years, the patient presented with hostility, destroying property, threatening and talking inappropriately. She was also withdrawn and sullen at times.

She had several further admissions and was treated with antipsychotics and a phenylalanine-free



**Figure 1.** Phenylalanine levels in a patient with schizophrenia

diet. She was non-compliant with her diet and medication and was commenced on haloperidol depot and her mental health improved. She was stable for nearly 10 years with haloperidol 100mg intramuscularly, fortnightly.

She was discharged from outpatient clinic, as she was stable on haloperidol depot and procyclidine. She was re-referred in 2012 for a medication review. Haloperidol was gradually reduced and stopped, as she did not wish to continue with the depot. She was stable for a year but needed to be admitted to the inpatient unit in June 2014 due to deterioration in her mental health.

## Presenting symptoms

During her latest admission, the patient presented with poor sleep pattern, poor personal hygiene and disinhibited behaviour. She was walking around the streets inappropriately dressed, walking into neighbours' houses without permission and making phone calls to relatives at odd hours. She was paranoid that there was a conspiracy against her.

## Progress

She refused to eat or comply with physical examination and blood tests. She would not wash or change her clothes. She appeared to be watching the doors at all times. When she did finally go to

her room it became difficult to persuade her to come out again. She was trialled on risperidone, but did not make much improvement. So she was commenced on haloperidol and her mental state improved dramatically.

The dietitian was involved but the patient refused to comply with a phenylalanine-free diet. She was aware of her high phenylalanine levels but found it hard to adhere to her diet.

Her compliance with depot and diet improved and her mental health significantly improved. She started doing voluntary work. She went to live with her mother and helped with household chores. She is hoping to live independently in the future.

### Investigations

Her EEG showed alpha rhythm, which was slow for her age, reflecting bilateral cortical dysfunction, possibly due to damage by PKU. Her phenylalanine levels were 1500  $\mu\text{mol/L}$  on 03/08/89, 725  $\mu\text{mol/L}$  on 17/08/89, 1480  $\mu\text{mol/L}$  on 11/12/90, 1200  $\mu\text{mol/L}$  on 13/01/94, 720  $\mu\text{mol/L}$  on 17/1/94 and on 16/09/09, it was 1585  $\mu\text{mol/L}$ . As she was discharged from secondary mental health services with stable mental health, her levels were not monitored until she was admitted recently. When it was checked in October 2014, her levels were 1840  $\mu\text{mol/L}$ . (Normal phenylalanine level 60–200  $\mu\text{mol/L}$ . See Figure 1.)

### Discussion

Phenylketonuria was discovered by the Norwegian physician Ivar Asbjørn Følling in 1934<sup>1</sup> when he noticed hyperphenylalaninemia (HPA) was associated with intellectual disability. In Norway, this disorder is known as Følling's disease, named after its discoverer.<sup>2</sup>

### Cause

Phenylketonuria is an autosomal recessive disorder and is due to

absence or reduced activity of phenylalanine hydroxylase. Phenylalanine hydroxylase is important in the formation of catecholamines, neurotransmitters and melanin. The defect is due to mutation of the gene on chromosome 12. This leads to accumulation of phenylalanine and phenylketonuria. Accumulation of phenylalanine can lead to nerve cell damage.<sup>3</sup>

### Clinical features

In the absence of neonatal diagnosis, patients present mostly with progressive developmental delay associated with severe signs including stunted growth, microcephaly, seizures, tremors, eczema, vomiting, musty odour, and subsequently behavioural (hyperactivity) and motor disorders. Untreated, patients develop profound, permanent intellectual impairment and deterioration of cognitive performance and motor skills.<sup>1</sup>

Diagnosed children who cease dietary manipulation may show deterioration in their motor skills and cognitive function. Hypomyelination may be proportional to the degree of phenylketonemia.<sup>3</sup>

### Maternal phenylketonuria

The frequency of congenital abnormalities increases with increasing maternal phenylalanine levels. Roose *et al.* showed significant relationships with average phenylalanine levels at weeks 0 to 8 with congenital heart disease and with average phenylalanine at weeks 8 to 12 with brain, foetal, and postnatal growth retardation, wide nasal bridge, and anteverted nares; and average phenylalanine exposure during the entire pregnancy with neurologic signs.<sup>4</sup>

### Diagnosis

The Guthrie test is a simple screening test for phenylketonuria. All babies should be sampled within 6–14 days of birth. In the event of

a positive test arrangements need to be made for immediate follow up within 24 hours. This should include referral to a consultant paediatrician in a specialist centre and immediate access to supportive health professionals and laboratory services.<sup>5</sup>

All positive screening tests must be confirmed with a quantitative measure of phenylalanine on a repeat specimen of blood and investigations undertaken to exclude the possibility of a defect in bipterin metabolism.<sup>5</sup>

### Management

Despite recent advances in the management of phenylketonuria and hyperphenylalaninemia, there is no effective / standard treatment for the management of this disorder. Guidance exists on the need for neonatal screening and early treatment, yet there is no guidance over threshold levels of blood phenylalanine for starting treatment, target blood phenylalanine levels and the management of older patient groups. The mainstay of treatment is a phenylalanine-restricted diet, but it varies between and within countries.<sup>6</sup>

The PKU diet is mainly made up by variable amounts of vegetables and fruits, milk, low-protein foods and phenylalanine-free protein substitutes, which provide mainly essential amino acid and micronutrients, to reach the required amount of daily protein, minerals and vitamins.<sup>7</sup>

A key issue around management of adults with PKU is whether lifelong dietary treatment is essential in all patients to maintain neurological and psychological well-being. The documented complications of PKU in adulthood are neurological and neuropsychological complications, dietary deficiencies and risks to the fetus in maternal PKU.<sup>1</sup>

Sapropterin treatment, with or without dietary treatment, improves

blood phenylalanine control and increases phenylalanine tolerance. Sapropterin dihydrochloride, a synthetic tetrahydrobiopterin (BH4), works with phenylalanine hydroxylase (PAH) in phenylketonuria to facilitate and stabilise folding of PAH into its most active conformation. No standard pharmacogenetic tests exist to identify responsive genotypes.<sup>8</sup>

### Conclusion

The relapse in the patient's psychosis coincided with stopping haloperidol. She improved dramatically after commencing on the same. This clearly highlights the need for the maintenance dose of antipsychotics despite a long period of stability.

Also, the phenylalanine levels had no association with her mental health deterioration. The management of adult patients with

phenylketonuria highlights the need for more research in blood phenylalanine concentration target recommendations and consensus guidelines.<sup>9</sup>

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### Declaration of interests

No conflicts of interest were declared.

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## POEMs



### Half of adults and older teens with mild traumatic brain injury have symptoms 1 year later

#### Clinical question

What is the natural history of mild traumatic brain injury?

#### Reference

Theadom A, Parag V, Dowell T, et al, for the BIONIC Research Group. Persistent problems 1 year after mild traumatic brain injury: a longitudinal population study in New Zealand. *Br J Gen Pract* 2016;66(642):e16-e23.

#### Synopsis

Patients with mild TBI experience a loss of consciousness for less than 30 minutes and disorientation for less than 24 hours. These researchers from New Zealand wanted to know what happens to these patients over the course of the following year. The authors used multiple information sources to identify all patients with mild TBI who resided in a mixed urban and rural region of the North Island of New Zealand. Nearly 900 patients, 16 years or older, experienced mild TBI,

but nearly 500 either declined to participate or were unavailable. The researchers evaluated the remaining 341 patients within 2 weeks of the injury and then at 1, 6, and 12 months using a variety of scales. Nearly 80% of the patients had at least one comorbid condition, approximately 12% consumed alcohol heavily, and approximately 33% had more than one prior brain injury. Based on the authors' home-grown scoring system, just about half of the patients experienced 4 or more postconcussion symptoms 1 year after their TBI, such as headaches, dizziness, nausea/vomiting, noise sensitivity, fatigue, irritability, memory problems, and so forth. Additionally, approximately 1 in 10 experienced very low levels of cognitive functioning. Finally, women; non-white patients; and those who lived alone, used psychotropic medications, or had comorbid conditions or multiple brain injuries were more likely to continue to have problems.