A CASE REPORT ON PHENYLKETONURIA: EARLY INTERVENTION AND TREATMENT.

Abstract:

Phenylketonuria (PKU) is an autosomal recessive inborn error of phenylalanine metabolism, most commonly caused by deficiency of phenylalanine hydroxylase (PAH), the hepatic enzyme that converts phenylalanine (Phe) to tyrosine. Untreated or inadequately treated PAH deficiency results in persistent elevation of blood and brain Phe and can cause neurocognitive impairment, developmental delay, seizures, behavioural abnormalities and psychiatric manifestations. [1-4]

We report an 8-year-old male child, second-born to non-consanguineous parents, who presented with hyperactivity, speech delay and behavioural problems. The child had an abnormal urine odour and dysmorphic features including triangular facies, blond hair, low-set ears, long pointed nose, hypopigmented eyes and prominent columella. Developmental assessment demonstrated significant global developmental delay. Psychological assessment showed features of combined-type attention-deficit/hyperactivity disorder (ADHD), with oppositional defiant and conduct features. In view of the behavioural phenotype, developmental delay, hypopigmentation and abnormal urine odour, a metabolic disorder was suspected. Serum amino-acid analysis demonstrated markedly elevated phenylalanine, and whole-exome sequencing identified a pathogenic PAH variant consistent with autosomal-recessive PAH deficiency. MRI brain demonstrated abnormalities involving the periventricular white matter, posterior fossa, pons and putamina, with thinning of the corpus callosum.

The child was managed through a multidisciplinary approach involving a pediatrician, metabolic/dietetic team, speech therapist, occupational therapist, special educator, ophthalmologist and geneticist. Treatment included lifelong phenylalanine-restricted dietary therapy, rehabilitation and behavioural interventions. During follow-up, serum phenylalanine decreased from the reported baseline value of 3300 to 1780 µmol/L, with improvement in developmental and behavioural measures. Developmental quotient improved from 40% to 45%, and intellectual quotient assessed by Seguin Form Board Test improved from 40% to 57%. Oppositional defiant and conduct features resolved, while hyperactivity and inattention decreased.

This case highlights the importance of considering PKU in children presenting late with unexplained developmental delay, behavioural abnormalities, hypopigmentation and an abnormal body or urine odour. Although newborn screening is the preferred strategy for early detection, late diagnosis can still permit meaningful clinical improvement following metabolic treatment and comprehensive rehabilitation.

Keywords

Phenylketonuria; phenylalanine hydroxylase deficiency; hyperphenylalaninemia; phenylalanine-restricted diet; developmental delay; ADHD; behavioural disorder; newborn screening; PAH gene; metabolic disorder.

1. Introduction

Phenylketonuria is an autosomal-recessive inborn error of amino-acid metabolism caused predominantly by pathogenic variants in the PAH gene, resulting in deficient phenylalanine hydroxylase activity. PAH normally converts phenylalanine to tyrosine in the presence of tetrahydrobiopterin (BH4) as a cofactor. When PAH activity is substantially reduced, phenylalanine accumulates in blood and tissues, including the brain. [1-4]

The neurological phenotype of untreated PKU is primarily related to chronic exposure to elevated Phe and disturbances in cerebral amino-acid transport, neurotransmitter synthesis, myelination and other cellular processes. Elevated Phe competes with other large neutral amino acids for transport across the blood-brain barrier and can consequently reduce cerebral availability of tyrosine and tryptophan. This may contribute to impaired dopamine and serotonin synthesis and to cognitive, executive and behavioural abnormalities. [5-7]

The clinical phenotype may include intellectual disability, developmental delay, seizures, microcephaly, hypopigmentation, eczema, hyperactivity, behavioural and psychiatric abnormalities and a characteristic musty or mousy odour due to phenylketones. Early diagnosis and sustained metabolic control can prevent or markedly reduce the severe neurological consequences of classical PKU. [1-4]

Newborn screening using dried blood spots and tandem mass spectrometry has transformed PKU care. Current guidance emphasizes lifelong maintenance of Phe within the recommended target range and individualized use of dietary and pharmacological therapies. The 2025 American College of Medical Genetics and Genomics (ACMG) guideline strongly recommends lifelong treatment for PAH deficiency when untreated Phe concentrations exceed 360 μmol/L, with a target of ≤360 μmol/L. [2] The 2025 first revision of the European guidelines similarly updates earlier recommendations. [3]

2. Case Report

2.1 Patient information

An 8-year-old male child was brought by his parents with complaints of hyperactivity, speech delay and aggressive/behavioural problems. He was the second child of non-consanguineous parents. The history included an abnormal urine odour from the neonatal and postnatal period. Natal and postnatal history was otherwise uneventful, and there was no history of previous hospitalization.

2.2 Developmental and psychological assessment

Developmental assessment showed significant global developmental delay, with a developmental quotient initially reported as approximately 32 months relative to the child's chronological age. The documented screening assessments were:

Assessment	Initial result
Developmental Screening Test (DST)	DQ 40%
Vineland Social Maturity Scale (VSMS)	SQ 45%
Seguin Form Board Test (SFBT)	IQ 40%
Vanderbilt scale	Combined-type ADHD with oppositional defiant and conduct features

The behavioural phenotype prompted clinical psychological assessment. The combination of hyperactivity, inattention and behavioural dysregulation was clinically consistent with ADHD, with additional oppositional and conduct features on the reported Vanderbilt assessment.

2.3 General and systemic examination

On examination, the child was alert and afebrile. Dysmorphic/hypopigmentary features included triangular facies, blond hair, low-set ears, a long pointed nose, hypopigmented eyes and a prominent columella. Systemic examination was otherwise normal.

The combination of developmental delay, behavioural abnormalities, hypopigmentation and abnormal urine odour raised the possibility of an inherited metabolic disorder and prompted metabolic evaluation.

2.4 Biochemical and molecular evaluation

Serum amino-acid analysis showed a markedly elevated phenylalanine concentration, reported in the supplied case as 3300 µmol/L. Whole-exome sequencing identified a pathogenic variant involving the PAH gene, reported as an intronic variant with autosomal-recessive inheritance. These findings supported a diagnosis of phenylalanine hydroxylase deficiency/phenylketonuria.

The supplied case reports the phenylalanine reference interval as 38–36 µmol/L; this appears internally inconsistent and should be verified against the laboratory report before journal submission. Likewise, the precise PAH nucleotide variant and zygosity should be inserted from the original genetic report rather than inferred from the summary.

2.5 Neuroimaging

MRI brain demonstrated diffuse signal/restriction abnormalities involving the periventricular white matter, posterior fossa, pons and both putamina. Thinning of the corpus callosum, paucity of periventricular white matter and periventricular hyperintensities were also reported. These findings were considered in the context of the child's long-standing neurodevelopmental phenotype and severe biochemical hyperphenylalaninemia.

3. Diagnosis

The final clinical diagnosis was phenylketonuria due to PAH deficiency presenting late with global developmental delay, speech delay, ADHD-like behavioural manifestations, dysmorphic/hypopigmentary features and severe hyperphenylalaninemia.

The diagnosis was supported by the characteristic clinical phenotype, markedly elevated serum Phe and identification of a pathogenic PAH variant. In a contemporary diagnostic pathway, plasma amino-acid analysis and molecular confirmation are central components of establishing PAH deficiency and distinguishing it from other causes of hyperphenylalaninemia, including disorders of BH4 metabolism. [2,3]

4. Management

4.1 Phenylalanine-restricted dietary therapy

The child was started on a phenylalanine-restricted diet under dietetic/metabolic supervision. Dietary treatment is the cornerstone of PKU management and is generally lifelong. The therapeutic objective is to reduce blood Phe while providing adequate protein, energy, tyrosine, essential amino acids, essential fatty acids, vitamins and minerals through specialized protein substitutes and low-protein foods. [2-4,8]

The practical dietary strategy consists of restriction of natural protein/Phe intake according to the child's tolerance, use of Phe-free or low-Phe protein substitutes, adequate tyrosine provision and specialized low-protein foods. Diet should be individualized and monitored by a metabolic dietitian because excessive protein restriction can cause nutritional deficiency, while inadequate Phe restriction can result in poor metabolic control. [3,8]

4.2 Multidisciplinary rehabilitation

Because the child presented after neurodevelopmental impairment had already developed, management was multidisciplinary. The team included a pediatrician, speech therapist, occupational therapist, dietician, ophthalmologist and geneticist.

- Occupational therapy with sensory integration and fine-motor training.
- Speech and language therapy for speech delay.
- Special education and individualized developmental support.
- Behavioural modification therapy and cognitive strategy training.
- Regular biochemical monitoring of blood phenylalanine.
- Genetic counselling and family education.

Vitamin B12 supplementation was also documented in the supplied management plan. The indication and dose should be confirmed from the patient's original prescription and laboratory assessment before publication.

4.3 Pharmacological and emerging treatment options

Some individuals with PAH deficiency respond to sapropterin, a synthetic form of BH4 that acts as a pharmacological chaperone/cofactor and can increase residual PAH activity in responsive patients. A therapeutic trial may be considered according to genotype, biochemical phenotype and local guidelines. [2-4,9]

Large neutral amino acids (LNAAs) have also been investigated, particularly as a strategy to reduce cerebral Phe transport by competing for the LAT1 transporter at the blood-brain barrier. Their use is generally considered within specialist metabolic practice and is not a replacement for standard dietary therapy in children. [6,10]

Pegvaliase, a PEGylated phenylalanine ammonia lyase, enzymatically degrades phenylalanine and has been developed as enzyme substitution therapy. Its role is primarily in adults with inadequate metabolic control despite conventional management, and availability/age indications vary by jurisdiction. [2,9]

Gene therapy and gene-editing strategies are active areas of research. Viral-vector and gene-editing approaches have shown promise in preclinical models, but these approaches should not currently be presented as established routine clinical therapy for children with PKU. [11]

5. Follow-up and Outcome

Serial serum phenylalanine concentrations were monitored. The reported serum Phe concentration decreased from 3300 µmol/L at diagnosis to 1780 µmol/L during follow-up, demonstrating a downward biochemical trend, although the latter remains substantially above the recommended target range for children.

At follow-up, developmental and behavioural measures showed improvement:

Parameter	Initial	Follow-up
Serum phenylalanine	3300 µmol/L	1780 µmol/L
Developmental quotient	40%	45%
SFBT intellectual quotient	40%	57%
Oppositional/conduct features	Present	Resolved
ADHD hyperactivity/inattention	Marked	Reduced

The child showed clinical improvement in speech and behavioural problems over the reported one-year follow-up. Although biochemical control improved, the reported Phe level remained above the recommended therapeutic range; continued intensive metabolic management is therefore important. Current ACMG guidance recommends lifelong Phe maintenance at ≤360 µmol/L for optimal intellectual outcomes. [2]

6. Discussion

6.1 Phenylketonuria and PAH deficiency

PKU is an autosomal-recessive disorder caused most commonly by deficient PAH activity. The enzyme catalyzes conversion of phenylalanine to tyrosine using BH4 as a cofactor. Deficient activity causes accumulation of Phe and reduction in downstream tyrosine availability. [1-4]

The phenotype is highly dependent on residual PAH activity and metabolic control. Untreated classical disease can cause severe intellectual disability, epilepsy, microcephaly and behavioural abnormalities, whereas early-treated individuals generally have far better developmental outcomes. Nevertheless, subtle executive, attentional and psychosocial difficulties may persist even among individuals treated from early infancy, emphasizing the importance of lifelong metabolic monitoring. [3,8,12]

6.2 Neurotoxicity: how elevated phenylalanine affects the brain

The neurotoxicity of Phe is multifactorial and incompletely explained by a single mechanism. One important mechanism involves competition between Phe and other large neutral amino acids for transport across the blood-brain barrier via LAT1. Because elevated circulating Phe has a high effective availability for this transporter, increased Phe influx can reduce cerebral availability of tyrosine, tryptophan and other essential LNAAs. [5-7]

Reduced cerebral tyrosine and tryptophan availability can contribute to impaired synthesis of dopamine and serotonin. Phe can also interfere with enzymes involved in neurotransmitter synthesis. These mechanisms provide a biologically plausible link between metabolic control and the executive, attentional, behavioural and psychiatric phenotype observed in PKU. [5-7]

Other proposed mechanisms include impaired cerebral protein synthesis, altered myelin synthesis, oxidative stress, altered cerebral glucose metabolism and disturbances in neuronal development. White-matter abnormalities are therefore frequently considered in the neurological phenotype of poorly controlled PKU. [5,7]

6.3 Clinical features relevant to this case

- Developmental delay and intellectual disability.
- Speech and language impairment.
- Hyperactivity and behavioural dysregulation.
- Seizures in untreated/severely affected individuals.
- Microcephaly.
- Hypopigmentation of skin, hair and eyes compared with unaffected family members.
- Eczema in some individuals.
- Characteristic musty/mousy odour of breath, skin or urine.
- Psychiatric and social-cognitive manifestations.

The child in this case had several classic clues—hypopigmentation, abnormal urine odour, developmental delay and behavioural disturbance—which, taken together, appropriately prompted metabolic testing.

6.4 Phenotypic classification

The supplied manuscript classifies PKU according to blood Phe concentration as mild, moderate and classical. Because classification thresholds vary among sources and contemporary guidelines increasingly emphasize untreated Phe concentrations and treatment thresholds rather than rigid severity labels, the precise

classification should be stated according to the guideline used by the reporting centre. The child's reported Phe of 3300 µmol/L represents severe hyperphenylalaninemia and is clearly above contemporary treatment thresholds. [2,3]

6.5 Newborn screening

Newborn screening is the most important public-health intervention for preventing the neurological consequences of PKU. Dried blood spot testing can be performed using tandem mass spectrometry to quantify Phe and tyrosine and assess the Phe:Tyr relationship. [2-4]

Current guidance emphasizes rapid confirmation and initiation of treatment after a positive newborn screen. The purpose is to establish metabolic control before prolonged exposure of the developing brain to high Phe. Early and sustained treatment substantially improves cognitive outcomes compared with untreated disease. [2-4]

The late presentation of this child illustrates the consequences of missed or unavailable early detection and reinforces the importance of robust newborn screening systems and follow-up of abnormal screening results.

6.6 Maternal PKU and prenatal considerations

Maternal hyperphenylalaninemia is teratogenic. Women with PAH deficiency require strict metabolic control before conception and throughout pregnancy because elevated maternal Phe can adversely affect fetal neurodevelopment and is associated with congenital abnormalities, including congenital heart disease. [3,13]

Contemporary guidelines recommend achieving target Phe concentrations before conception and maintaining metabolic control throughout pregnancy. [2,3]

6.7 Dietary therapy as the cornerstone of management

Dietary therapy remains the foundation of PKU treatment. The treatment has three principal components: controlled natural protein/Phe intake, provision of a Phe-free or low-Phe protein substitute containing essential amino acids and adequate micronutrients, and use of low-protein specialized foods. Tyrosine supplementation is important because tyrosine becomes a conditionally essential amino acid when PAH activity is deficient. [3,8]

Adherence can be challenging, particularly as children become older and socially independent. Long-term management therefore requires education, regular dietetic review, psychosocial support and repeated biochemical monitoring.

6.8 Treatment targets

The 2017 European guideline recommended a target Phe concentration of 120–360 µmol/L for children aged 0–12 years and for maternal PKU. [1,3] The 2025 ACMG guideline strongly recommends lifelong maintenance of Phe ≤360 µmol/L for individuals with PAH deficiency. [2]

In the present case, the fall from 3300 to 1780 µmol/L represents biochemical improvement but does not yet constitute adequate metabolic control by contemporary targets. This distinction is important when reporting treatment response: clinical improvement may occur even while the biochemical target remains unmet, but continued efforts to reduce and stabilize Phe are necessary.

6.9 Relationship between metabolic control and executive function

Executive dysfunction, attentional difficulties and processing-speed abnormalities can persist even in treated PKU. Variability in blood Phe, rather than a single measurement, may be relevant to cognitive and social-cognitive outcomes. [12,14]

The improvement in DQ, SFBT IQ and behavioural symptoms in this child after initiation of treatment is encouraging and supports the value of metabolic intervention and rehabilitation even after late diagnosis. However, a single case cannot establish causality, and improvements may reflect combined effects of dietary treatment, maturation, speech therapy, occupational therapy, special education and behavioural interventions.

7. Strengths and Limitations of the Case

7.1 Strengths

- The diagnosis was supported by both biochemical evidence of severe hyperphenylalaninemia and molecular identification of a pathogenic PAH variant.
- The case demonstrates characteristic clinical clues that can help clinicians recognize late-presenting PKU.
- The child received multidisciplinary treatment with longitudinal biochemical and developmental follow-up.
- Objective developmental/behavioural measures were available before and after intervention.

7.2 Limitations

- The exact PAH nucleotide variant, zygosity and ACMG molecular classification were not provided in the supplied case summary.
- The reported initial Phe reference range is internally inconsistent and should be checked against the original laboratory report.
- The case does not provide detailed dietary Phe intake, protein substitute composition, caloric intake or adherence data.
- The precise duration and timing of follow-up assessments are incompletely specified.
- MRI findings are described from the summary; correlation with the original radiology report would strengthen the report.
- The improvement in developmental and behavioural measures cannot be attributed solely to dietary treatment because multiple rehabilitation interventions were administered simultaneously.

8. Conclusion

Phenylketonuria is a treatable inherited metabolic disorder in which early diagnosis and sustained metabolic control can prevent severe neurological disability. This case illustrates the importance of considering PKU in a child with developmental delay, speech impairment, hyperactivity, behavioural disturbance, hypopigmentation and an abnormal urine odour, even when the child presents well beyond the newborn period.

The diagnosis in this child was supported by severe hyperphenylalaninemia and a pathogenic PAH variant. Following initiation of phenylalanine-restricted dietary therapy and multidisciplinary rehabilitation, the child demonstrated a fall in serum Phe and improvement in developmental and behavioural parameters. However, the follow-up Phe concentration remained substantially above the recommended target, emphasizing the need for continued specialist metabolic management.

The case reinforces that PKU management is lifelong and multidisciplinary, encompassing metabolic monitoring, individualized dietary therapy, developmental rehabilitation, psychological support, genetic counselling and, where appropriate, pharmacological therapies such as sapropterin. Contemporary guidelines support maintaining Phe at or below 360 µmol/L for optimal long-term intellectual outcomes. [2,3]

9. Learning Points

- PKU should be considered in unexplained developmental delay accompanied by hypopigmentation, behavioural abnormalities or a characteristic musty/mousy odour.
- PAH deficiency is inherited in an autosomal-recessive manner and is most commonly caused by pathogenic PAH variants.
- Elevated Phe can impair brain function through several mechanisms, including competition with other LNAAs at the blood-brain barrier and disruption of neurotransmitter and myelin metabolism.
- Newborn screening allows treatment before irreversible neurological injury develops and remains the cornerstone of population-level prevention.
- Dietary therapy remains the cornerstone of PKU management and should generally continue lifelong.
- Blood Phe should be monitored regularly; contemporary guidance supports maintaining Phe ≤360 µmol/L.
- Late-diagnosed children can still benefit from metabolic treatment combined with speech, occupational, educational and behavioural interventions.

10. References – Vancouver Style

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