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Phenylketonuria: Biochemical findings of a case

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Case Description

A 17-month-old boy, born preterm without perinatal complications and showing no metabolic abnormalities, exhibited developmental delays, poor eye contact, and delayed motor milestones. Subsequently, he developed language delays and behavioural concerns.

Physical examination revealed normal growth without dysmorphic features, with an occasional body musty odour.

Questions to consider

1. How does elevated phenylalanine cause neurotoxicity in PKU?
2. Why is the Phe/Tyr ratio an important biochemical marker in diagnosis?
3. What is the chromosomal location and function of the PAH gene?
4. What are the current treatment options beyond dietary restriction?
5. Why is newborn screening essential in the management of PKU?

Biochemical investigations

Initial urine screening with the Ferric Chloride ($FeCl_3$) test produced a characteristic green colour, suggestive of Phenylpyruvic acid. Paper chromatography confirmed the presence of excess Phenylalanine. Serial metabolic evaluations showed persistently elevated plasma phenylalanine concentrations. Tandem Mass Spectrometry (TMS) between 1.5-3 years demonstrated phenylalanine levels of 580-991 µmol/L (reference range: <120 µmol/L), with Phe/Tyr ratios ranging 3.5-23.05 (reference range: <2).

Ultra-High-Performance Liquid Chromatography (UHPLC) performed at age 7 years revealed the following plasma amino acid profile. The phenylalanine concentration was markedly elevated at 762 µmol/L, with a Phe/Tyr ratio of 19.54 (reference <2.0).

Genetic testing

Whole exome sequencing (2019) identified a homozygous *PAH* splice-site mutation (c.169-2A>G, intron 2), previously reported as pathogenic and consistent with classic PKU. A secondary homozygous variant in *GRIN1* (c.1256C>T, p.Thr419Ile) was also detected, classified as a variant of uncertain significance.

Diagnosis

The child was diagnosed with classic Phenylketonuria (PAH deficiency) based on clinical presentation, persistent hyperphenylalaninemia, elevated Phe/Tyr ratio, and confirmed genetic findings.

Discussion

Phenylketonuria (PKU) is a prototypical inborn error of metabolism that was first described by Asbjørn Følling in 1934. It is caused by biallelic pathogenic variants in the *Phenylalanine Hydroxylase* (*PAH*) gene located on chromosome 12q23.2. The *PAH* enzyme normally catalyses the hydroxylation of phenylalanine to tyrosine in the presence of Tetrahydrobiopterin (BH_4). A deficiency in *PAH* activity leads to the accumulation of phenylalanine and its transamination products, such as phenylpyruvate, phenyl lactate, and phenylacetate, which are neurotoxic.

Defects in specific enzymatic steps lead to distinct metabolic disorders, such as phenylalanine hydroxylase deficiency and phenylketonuria. The prevalence of PKU varies globally, primarily because of differences in newborn screening programs. In the United States, the incidence is approximately 1 in 10,000-15,000 live births, whereas the reported incidence in India varies regionally and is estimated between 1:10,000 and 1:25,000 live births in screened populations.

The present case involves a child born to consanguineous parents in Maharashtra, India. Family history revealed that both parents were second-degree relatives and heterozygous carriers of a *PAH* splice-site mutation (c.169-2A>G). No other family members have been reported to have any metabolic disorders. The patient is currently undergoing clinical and biochemical evaluations.

Beyond *PAH*, other genetic contributors to neurodevelopmental impairment in metabolic encephalopathies have been increasingly recognized. The *GRIN* gene family, which encodes subunits of the N-methyl-D-aspartate receptor (NMDAR), is critical for synaptic transmission, plasticity, and neuronal survival. Pathogenic variants of *GRIN1*, *GRIN2A*, *GRIN2B*, and *GRIN2D* have been linked to epileptic encephalopathies, intellectual disabilities, and movement disorders. These variants can alter receptor function, either enhancing (gain-of-function) or reducing (loss-of-function) neuronal excitability.

Identifying *GRIN* mutations alongside classical metabolic gene defects may help explain phenotypic variability and open avenues for precision therapeutics, such as memantine for hyperactive N-Methyl-D-aspartate Receptor (NMDAR) variants or L-serine supplementation for loss-of-function variants.

Conclusion

- PKU is an autosomal recessive disorder caused by mutations in the PAH gene on chromosome 12q23.2.
- Persistent hyperphenylalaninemia disrupts neurotransmitter synthesis and myelination, leading to intellectual disability.
- Elevated Phe/Tyr ratio is a key biochemical marker for diagnosis.
- Dietary phenylalanine restriction remains the cornerstone of therapy; BH4 supplementation and enzyme therapy are adjuncts.
- Lack of newborn screening in resource-limited settings leads to delayed diagnosis and poor neurodevelopmental outcomes.

Abbreviations: PKU: Phenylketonuria; PAH: Phenylalanine Hydroxylase; Phe: Phenylalanine; Tyr: Tyrosine; BH4: Tetrahydrobiopterin.

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