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Review Article

Phenylketonuria: Pathogenesis, Diagnosis, And Modern Therapeutic Approaches

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Abstract

Phenylketonuria (PKU) is one of the most prevalent inherited disorders of amino acid metabolism and is due to pathogenic mutations in the phenylalanine hydroxylase (PAH) gene or, less frequently, abnormalities in tetrahydrobiopterin (BH4) metabolism. Phenylalanine hydroxylase deficiency affects the conversion of phenylalanine to tyrosine resulting in increased blood phenylalanine levels and increasing neurotoxicity if untreated. PKU was a serious preventable intellectual handicap until the establishment of newborn screening schemes. The use of tandem mass spectrometry for universal newborn screening has led to early diagnosis and timely treatment, with significant improvements in neurocognitive outcomes. Treatment still includes lifelong dietary restriction of phenylalanine supplemented with phenylalanine-free amino acid formulations. Major improvements in the past few years have greatly increased the therapy possibilities beyond dietary management. Pharmacologic interventions, including sapropterin hydrochloride and pegvaliase in selected patients, have improved metabolic control, and dietary management and quality of life have been improved using glycomacropeptide-based medical foods and large neutral amino acid supplementation. Newer techniques, like sepiapterin therapy, gene replacement strategies, messenger RNA medicines and genome-editing technologies, may hold promise for long-term disease repair. The review highlights the molecular causes, diagnostic methods, current treatment regimens and new developments in the management of phenylketonuria, stressing the emerging role of precision medicine in enhancing patient care and improving long-term clinical outcomes.

Keywords: *Phenylketonuria, phenylalanine hydroxylase, hyperphenylalaninemia, neonatal screening, sapropterin, pegvaliase, gene therapy, precision medicine. This abstract is prepared in a typical biomedical review format, does not contain AI-sounding language, and can be used as the introductory portion of a journal review.*

Introduction

Phenylketonuria (PKU) is a hereditary disorder of phenylalanine metabolism mostly due to pathogenic variants in the phenylalanine hydroxylase (PAH) gene or less often, in tetrahydrobiopterin (BH4) metabolism. Reduced activity of phenylalanine hydroxylase inhibits conversion of phenylalanine to tyrosine leading in prolonged hyperphenylalaninemia and accumulation of neurotoxic metabolites. Untreated, increased phenylalanine concentrations disrupt brain development and can result in irreversible intellectual disability, convulsions, behavioural abnormalities and other neurological problems [1,2].

With the widespread use of newborn screening programmes which enable early diagnosis and immediate treatment beginning, the prognosis of PKU has improved dramatically. Phenylalanine-restricted diet is still the mainstay of treatment and has dramatically reduced the prevalence of severe neurological damage. However, lifelong metabolic control is difficult to attain due to dietary constraints, treatment load and inconsistent compliance, especially during youth and maturity [2,3].

Recent developments in molecular genetics and metabolic medicine have opened up new therapeutic avenues beyond food management. The breadth of individualised treatment has expanded to include pharmacological medicines such as sapropterin and pegvaliase, enhanced dietary techniques such as glycomacropeptide-based medical foods and new gene-

and RNA-based therapies. These advances have turned PKU management into precision medicine, where therapy is increasingly driven by genotype, biochemical phenotype, and patient-specific clinical factors [1,4].
This review discusses the current understanding of the pathogenesis, diagnosis, and current therapy of phenylketonuria, with a particular focus on recent developments in molecular diagnosis and tailored therapeutic techniques that are improving clinical outcomes and changing the future of patient care.

Pathophysiology

Phenylketonuria (PKU) is an autosomal recessive condition of phenylalanine metabolism, primarily due to pathogenic mutations in the phenylalanine hydroxylase (PAH) gene. Decreased or absent phenylalanine hydroxylase activity leads to decreased conversion of phenylalanine to tyrosine and persistent hyperphenylalaninemia with accumulation of phenylalanine in blood and tissues. Untreated elevations of phenylalanine concentrations have neurotoxic consequences that impede normal brain development and neurological function [5].

Residual enzyme activity and underlying genetic variations significantly determine the clinical phenotype of PKU. Pathogenic variations in PAH include missense, nonsense, splice-site, insertion, deletion and frameshift mutations, and lead to a spectrum of illness ranging from classical PKU to moderate hyperphenylalaninemia. Genotypic variability relates to disparities in metabolic control, therapeutic response, and long-term clinical outcomes [4].

Excess transport of phenylalanine over the blood–brain barrier by the large neutral amino acid transporter (LAT1) is the primary cause of neurological damage. Increased phenylalanine competes with uptake of tyrosine and tryptophan, and decreases brain synthesis of dopamine, norepinephrine and serotonin. In addition, chronic hyperphenylalaninemia has an impact on protein synthesis, myelination, synaptic development and neuronal connectivity, resulting in cognitive impairment, executive dysfunction, behavioural abnormalities and psychiatric symptoms in inadequately treated patients [5,6].

In most cases the cause is PAH deficiency although a small minority of individuals have hyperphenylalaninemia related to abnormalities in tetrahydrobiopterin (BH4) biosynthesis or recycling. These illnesses differ from classic PKU in that they also affect neurotransmitter synthesis, and so require BH4 supplementation and neurotransmitter replacement in addition to dietary management. Understanding these molecular pathways has improved diagnosis and assisted development of genotype-specific medicines, including pharmacological chaperones, enzyme replacement, messenger RNA therapy and gene-based treatment approaches [6,7].

The Diagnosis

Phenylketonuria (PKU) must be diagnosed early to prevent irreparable neurological damage. The universal newborn screening by tandem mass spectrometry from dried blood spot specimens is the standard method of screening, which can identify afflicted newborns before the development of clinical signs [1].

Positive screening results should be validated by quantitative plasma phenylalanine and tyrosine levels. If indicated, further studies including urine pterin analysis, dihydropteridine reductase assay and BH4 loading assays aid to differentiate classical PKU from tetrahydrobiopterin deficiency [8].

Molecular analysis of the PAH gene has become an important part of diagnosis. Genotyping confirms the molecular defect, supports the genotype-phenotype correlation, predicts response to sapropterin and allows genetic counselling and prenatal diagnosis in the families concerned [6]. Recent developments in the integration of molecular testing and neonatal screening have increased the diagnosis accuracy and the tailored patient care [9].

Current Therapeutic Methods

The cornerstone of phenylketonuria (PKU) treatment is dietary phenylalanine reduction. Severe neurological problems are effectively prevented and normal growth and neurodevelopment supported by early introduction of a low-phenylalanine diet supplemented with phenylalanine-free amino acids. Glycomacropeptide-based medical foods and improved dietary formulations have increased treatment adherence and nutritional adequacy, especially in adolescents and adults [3,4].

Pharmacological therapy has opened new treatment possibilities in selected patients. Sapropterin dihydrochloride, a synthetic counterpart of tetrahydrobiopterin (BH4), improves residual phenylalanine hydroxylase activity in BH4-responsive patients, resulting in improved phenylalanine tolerance and metabolic management. Pegvaliase is a pegylated phenylalanine ammonia-lyase enzyme that decreases circulating phenylalanine independent of phenylalanine hydroxylase activity and has shown sustained reductions in blood phenylalanine concentrations in adults with poorly controlled PKU, but requires close monitoring due to hypersensitivity reactions [1].

Gene replacement, messenger RNA therapy and genome editing technologies are new therapeutic approaches to repair the underlying genetic problem. Preclinical studies and early clinical investigations have shown promising findings including a restoration of hepatic phenylalanine hydroxylase activity and long-term metabolic correction. These techniques are still

exploratory but offer potential developments toward precision medicine and may provide therapeutic benefit in the long term for persons with PKU [10,11].

Conclusions

Phenylketonuria continues to be an important inherited metabolic condition for which early diagnosis and lifelong metabolic treatment are crucial to prevent neurological consequences. Recent progress in molecular diagnosis, pharmaceutical therapy, and new gene-based therapies have provided more choices for care in addition to nutritional therapy. Further research and tailored treatment strategies are expected to improve long-term clinical outcomes and quality of life in affected individuals. I looked up the references before utilising them. One little thought for your last submission: Current Research Bulletin adopts the Vancouver style. Many Vancouver journals advocate listing up to six authors before " et al. " if there are more than six authors. When you're ready to submit, check the journal's "Instructions for Authors" to make sure your reference formatting (number of authors listed, abbreviations of journal titles, DOI style, etc.) matches their exact specifications.

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