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ORIGINAL ARTICLE

BH_4 deficiency identified in a neonatal screening program for hyperphenylalaninemia☆,☆☆

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KEYWORDS
Phenylketonuria;
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Abstract
Objectives: To show the general prevalence and to characterize tetrahydrobiopterin (BH_4) deficiencies with hyperphenylalaninemia, identified by the Neonatal Screening Program of the State of Minas Gerais (NSPMG).
Methods: Descriptive study of patients with BH_4 deficiency identified by the NSPMG.
Results: The prevalence found was 2.1 for 1,000,000 live births, with a frequency of 1.71% among hyperphenylalaninemias. There were four cases (40%) with 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency, three with GTP cyclohydrolase I – autosomal recessive form (GTPCH I) deficiency, and three with dihydropteridine reductase (DHPR) deficiency (30% each). Six patients were diagnosed due to clinical suspicion and four cases due to systematic screening in neonatal screening. After the start of the treatment, patients identified by neonatal screening had rapid improvement and improved neuropsychomotor development compared to those diagnosed by the medical history.

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☆☆ Study carried out at Universidade Federal de Minas Gerais (UFMG), Hospital das Clínicas, Núcleo de Ações e Pesquisa em Apoio Diagnóstico (NUPAD), Belo Horizonte, MG, Brazil.

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Conclusions: The prevalence of BH_4 deficiencies in Minas Gerais was slightly higher than that found in the literature, but the frequency among hyperphenylalaninemias was similar. Although rare, they are severe diseases and, if left untreated, lead to developmental delays, abnormal movements, seizures, and premature death. Early treatment onset (starting before 5 months of age) showed good results in preventing intellectual disability, justifying the screening of these deficiencies in newborns with hyperphenylalaninemia identified at the neonatal screening programs for phenylketonuria.

PALAVRAS-CHAVE
Fenilcetonúria;
Triagem Neonatal;
Deficiência Intelectual;
Doenças raras

Deficiências de BH_4, identificadas em um programa de triagem neonatal para hiperfenilalaninemias

Resumo
Objetivos: Apresentar a prevalência geral e caracterizar as deficiências de tetrahidrobiopterina - BH4 - com hiperfenilalaninemia, identificadas pelo Programa de Triagem Neonatal do Estado de Minas Gerais - PTNMG.
Métodos: Estudo descritivo de pacientes com deficiência de BH4 do PTNMG.
Resultados: A prevalência encontrada foi de 2,1 para 1.000.000 recém-nascidos vivos e a frequência de 1,71%, dentre as hiperfenilalaninemias. Quatro casos (40%) com deficiência de PTPS, três com deficiência de GTPCH I e três com deficiência de DHPR (30% cada um). Seis pacientes foram diagnosticados por suspeita clínica e quatro pela pesquisa sistemática na triagem neonatal. Após o início do tratamento, os pacientes identificados pela triagem neonatal tiveram melhora rápida e melhor desenvolvimento neuropsicomotor em comparação com aqueles diagnosticados pela história clínica.
Conclusões: A prevalência das deficiências de BH4 em Minas Gerais foi um pouco maior que a encontrada na literatura, mas a frequência, entre as hiperfenilalaninemias, foi semelhante. Embora raras, são graves e, se não tratadas, levam a atraso de desenvolvimento, movimentos anormais, convulsões e morte precoce. O tratamento precoce (início antes dos 5 meses) mostrou bons resultados na prevenção de deficiência intelectual, justificando a pesquisa dessas deficiências nos recém-nascidos com hiperfenilalaninemia pelos programas de triagem neonatal para fenilcetonúria.

Introduction

Hyperphenylalaninemias are manifestations of the genetic defects most frequently involved in amino acid metabolism.[1] To date, five defects are known to lead to hyperphenylalaninemia states: defect in the phenylalanine hydroxylase enzyme, causing phenylketonuria, and in four different enzymes involved in the synthesis or regeneration of tetrahydrobiopterin (BH_4), which is an important cofactor of the enzymes involved in the synthesis of tyrosine, dopamine, serotonin, nitric oxide, and glycerol.[2]

The four BH_4 deficiencies that occur with hyperphenylalaninemia are deficiency of GTP cyclohydrolase I – autosomal recessive form (GTPCH I), 6-Pyruvoyl-tetrahydropterin synthase (PTPS) deficiency, dihydropteridine reductase (DHPR) deficiency, and pterin-4α-carbinolamine dehydratase (PCD) deficiency. They account for approximately 2% of cases of hyperphenylalaninemia, with a worldwide prevalence of 1 per 1,000,000 live births.[3]

As BH_4 is involved in the synthesis of neurotransmitters such as dopamine and serotonin, deficiencies of this cofactor can lead not only to hyperphenylalaninemia states but also neurological symptoms and signs, resulting from the deficiency of these neurotransmitters.[4]

Since these deficiencies occur with hyperphenylalaninemia, their identification is possible through the neonatal screening programs for phenylketonuria, allowing the diagnosis to be made in the first weeks of life[5,6] and prompt treatment to be initiated. The current routine of investigating BH_4 deficiencies in every newborn with hyperphenylalaninemia by analyzing pterins and DHPR enzyme activity in blood samples on filter paper, then starting early treatment, has resulted in better intellectual levels in affected patients than were obtained previously to this routine.[7]

The treatment of BH_4 deficiencies should be individualized due to the great inter-individual allelic and non-allelic heterogeneity, a characteristic of the disease.[4]

In Brazil, neonatal screening for hyperphenylalaninemias started in the 1980s. In 2001, the National Neonatal Screening Program was created and since then, neonatal screening for hyperphenylalaninemias has been expanded