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ORIGINAL ARTICLE

Genetic determinants and stroke in children with sickle cell disease☆,☆☆

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KEYWORDS
Sickle cell anemia;
Stroke;
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Abstract
Objective: To verify genetic determinants associated with stroke in children with sickle cell disease (SCD).
Methods: Prospective cohort with 110 children submitted to neonatal screening by the Neonatal Screening Program, between 1998 and 2007, with SCD diagnosis, followed at a regional reference public service for hemoglobinopathies. The analyzed variables were type of hemoglobinopathy, gender, coexistence with alpha thalassemia (α-thal), haplotypes of the beta globin chain cluster, and stroke. The final analysis was conducted with 66 children with sickle cell anemia (SCA), using the chi-squared test in the program SPSS® version 14.0.
Results: Among children with SCD, 60% had SCA. The prevalence of coexistence with α-thal was 30.3% and the Bantu haplotype (CAR) was identified in 89.2%. The incidence of stroke

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☆☆ Study carried out at Fundação Hemominas and Universidade Federal de Juiz de Fora (UFJF), Juiz de Fora, MG, Brazil.
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was significantly higher in those with SCA (27.3% *vs.* 2.3%; $p = 0.001$) and males (24.1% *vs.* 9.6%; $p = 0.044$). The presence of α-thal ($p = 0.196$), the CAR haplotype ($p = 0.543$), and socioeconomic factors were not statistically significant in association with the occurrence of stroke.
Conclusion: There is a high incidence of stroke in male children and in children with SCA. Coexistence with α-thal and haplotypes of the beta globin chain cluster did not show any significant association with stroke. The heterogeneity between previously evaluated populations, the non-reproducibility between studies, and the need to identify factors associated with stroke in patients with SCA indicate the necessity of conducting further research to demonstrate the relevance of genetic factors in stroke related to SCD.
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PALAVRAS-CHAVE
Anemia falciforme;
Acidente vascular cerebral;
Marcadores genéticos;
Alfa talassemia;
Haplótipos

Determinantes genéticos e Acidente Vascular Encefálico em crianças com doença falciforme

Resumo
Objetivo: Verificar fatores genéticos associados ao acidente vascular encefálico (AVE) em crianças com Doença Falciforme (DF).
Métodos: Coorte prospectiva de 110 crianças submetidas à triagem neonatal pelo Programa de Triagem Neonatal, entre 1998-2007 com o diagnóstico de DF, atendidas em serviço público regional de referência em hemoglobinopatias. As variáveis analisadas foram: tipo de hemoglobinopatia, sexo, coexistência da alfa Talassemia (α-Tal), haplótipos do cluster da cadeia beta globina e AVE. A análise estatística final foi realizada com 66 crianças com Anemia Falciforme, por meio do teste do Qui-quadrado no programa SPSS® 14.0.
Resultados: Entre as crianças com DF, 60% eram portadoras de Anemia Falciforme. A prevalência da coexistência com a α-Tal foi de 30,3% e o haplótipo Bantu (CAR) foi identificado em 89,2%. A incidência de AVE foi significativamente maior nas crianças com AF (27,3% *versus* 2,3%; p = 0,001) e no sexo masculino (24,1% *versus* 9,6%; p = 0,044). A presença da α-Tal (p = 0,196), do haplótipo CAR (p = 0,543) e fatores socioeconômicos não foram significantemente associadas à ocorrência de AVE.
Conclusão: O AVE apresenta alta incidência em crianças com AF e em crianças do sexo masculino. Coexistência de α-Tal ou de haplótipos do cluster da beta globina não apresentaram associação significante com AVE. A heterogeneticidade entre as populações previamente avaliadas e a não reprodutibilidade entre estudos indicam a necessidade de realização de novas pesquisas para verificar o papel desses fatores genéticos no AVE em crianças com DF.
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Introduction

Sickle cell disease (SCD) is the most common monogenic hereditary disease in Brazil, occurring predominantly among those of African descent. The term SCD includes sickle cell anemia (SCA) and pathological conditions in which the hemoglobin S gene is associated with other hemoglobinopathies, such as SC, S/beta^0 and S/beta$^+$ thalassemia (S/b), and SD Punjab, among others.[1] SCA, caused by a single mutation in the β-globin gene, produces a diversity of phenotypic expressions in affected patients.[2,3] SCA is the most severe form of SCD presentation; for the disease to manifest, homozygosity of β^S alleles in the gene responsible for the synthesis of β chain of hemoglobin is required, determining the formation of hemoglobin S (HbSS).

HbSS, under conditions such as low oxygenation, metabolic acidosis, or dehydration, becomes polymerized, irreversibly changing the structure of erythrocyte, thus determining inefficient oxygenation, endothelial inflammatory reaction, and the entire complex physiopathology of the disease.[3,4] The polymerization process leads to vascular occlusion, which can trigger painful crises, stroke, acute chest syndrome, splenic sequestration, and priapism, among other manifestations.

In Brazil, studies have shown that 700–1000 children/year are born with SCD,[1,4–6] making this disease a public health problem. The state of Minas Gerais (MG) is a pioneer in Brazil in the early diagnosis of SCD, with the introduction of the Neonatal Screening Program of the State of Minas Gerais (Programa de Triagem Neonatal do Estado de Minas Gerais [PETN-MG]) in March 1998. PETN-MG is coordinated by the Center for Action and Research in Support Diagnostics (Núcleo de Ações e Pesquisa em Apoio Diagnóstico [NUPAD]) of Universidade Federal de Minas Gerais, which refers newborns diagnosed with SCD to be followed at

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