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REVIEW ARTICLE

Systematic review: hereditary thrombophilia associated to pediatric strokes and cerebral palsy☆

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KEYWORDS
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Cerebral palsy

Abstract
Objectives: This review aimed to organize and consolidate the latest knowledge about mutations and genetic polymorphisms related to hereditary thrombophilia and their potential association with pediatric stroke and cerebral palsy (CP).
Sources: Scientific articles published from 1993 to 2013, written in Portuguese, English, French, and Spanish, were selected and reviewed. The publications were searched in electronic databases, and also in the collections of local libraries. The terms ''hereditary thrombophilia'', ''polymorphisms'', ''mutation'', ''pediatric strokes'', and ''cerebral palsy'' were used for the research.
Summary of the findings: The search in databases and in the bibliographic references retrieved 75 articles for inclusion in this review. Studies that investigated hereditary thrombophilias and their associations to CP and arterial and venous pediatric stroke presented contradictory results. The meta-analysis and case-control studies that showed positive results for this association described only slightly increased relative risks and sometimes had questionable conclusions. The association of two or more hereditary thrombophilias, or the association between thrombophilia and other specific clinical risk factors, suggest a higher risk of CP and pediatric stroke than isolated hereditary thrombophilia.
Conclusions: Larger, multicenter studies should be developed in order to elucidate the role of mutations leading to hereditary thrombophilia and the development of CP and pediatric stroke. The complex and multifactorial etiology of CP and stroke makes this an arduous and difficult task; however, the benefits generated by these studies are immeasurable.

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PALAVRAS-CHAVE
Mutação;
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Acidentes vasculares cerebrais pediátricos;
Paralisia cerebral

Revisão sistemática: trombofilias hereditárias associadas aos acidentes vasculares cerebrais pediátricos e a paralisia cerebral

Resumo

Objetivo: Sistematizar e integrar os últimos conhecimentos sobre mutações e polimorfismos genéticos relacionados às trombofilias hereditárias e suas potenciais associações com acidentes vasculares cerebrais pediátricos (AVC) e paralisia cerebral (PC).

Fontes de Dados: Artigos científicos publicados de 1993 a 2013, escritos em português, inglês, francês e espanhol foram selecionados e revisados. As publicações foram pesquisadas nas bases de dados eletrônicas, como também nos acervos das bibliotecas locais. Os termos mutação, polimorfismos, trombofilias hereditárias, acidentes vasculares cerebrais pediátricos e paralisia cerebral foram utilizados para a pesquisa.

Síntese dos Dados: A pesquisa nas bases de dados e nas referências bibliográficas identificou 75 artigos para inclusão nesta revisão. Os estudos que investigaram as trombofilias hereditárias e suas associações à PC e aos AVC pediátricos arteriais e venosos apresentaram resultados contraditórios. As metanálises e os estudos caso-controle que demonstraram resultados positivos para esta associação, descreveram riscos relativos discretamente aumentados e, algumas vezes, questionáveis. A associação de duas ou mais trombofilias hereditárias, ou a junção de trombofilias específicas com demais fatores de riscos clínicos, sugerem maior risco no aparecimento da PC e do AVC pediátrico do que as trombofilias hereditárias isoladas.

Conclusões: Estudos multicêntricos de grande porte devem ser conduzidos para elucidar o papel real das mutações que levam às trombofilias hereditárias e ao aparecimento da PC e AVC pediátricos. A etiologia multifatorial e complexa da PC e dos AVC torna esta tarefa árdua e difícil, porém, os benefícios gerados por estes estudos são incalculáveis.

Introduction

Mutations in genes associated with the coagulation cascade trigger hypercoagulable states (hereditary thrombophilia) that, in theory, increase the risk of stroke and cerebral palsy (CP). In children, the incidence of different types of stroke varies from 0.67 to 23 per 100,000 live births and the evolution of these lesions to CP is quite significant (Table 1).[1–7] CP is the most common motor manifestation of childhood and its prevalence in Brazil is estimated at about 30,000 to 40,000 new cases per year.[8,9]

The main mutations associated with prothrombotic states are described in factor V Leiden, prothrombin G20210A in methylenetetrahydrofolate reductase (MTHFR; C677 T and A1298 C), in protein C, in protein S, in antithrombin and lipoprotein-A.[10] The presumed physiopathology for these mutations is described in Table 2.[10–12]

The aim of this study was to systematically review and consolidate the studies that evaluated the mutations and polymorphisms in genes associated with hereditary thrombophilias and their possible associations with pediatric stroke and cerebral palsy.

Methods

The study consisted of a systematic review of the main publications that described mutations related to hereditary thrombophilias and their potential associations with pediatric stroke and cerebral palsy.

Publication dates were 1993-2013 and languages accepted for reading were Portuguese, English, French, and Spanish. Research on the subject was conducted in electronic databases (Medline, PubMed, SciELO, OVID, Web of Science, Elsevier ScienceDirect, and CAPES Journals) and in the collections of the libraries of the Pontifícia Universidade Católica de Goiás and Universidade Federal de Goiás. The terms hereditary thrombophilia, mutations, polymorphisms, pediatric stroke, and cerebral palsy were used for the research. The methodology used was described by Green.[13]

Publications such as meta-analyses, case-control studies, case series, and descriptions of clinical cases were included. The research in the databases identified 1,731 potential articles for inclusion in the review. After reading the abstracts 67 articles were selected for full reading, of which seven were excluded for not meeting the criteria for the diagnosis of CP or due to duplicity. The search of the references from the studies that were read in full resulted in the inclusion of 15 new articles.

Pediatric stroke can be divided into arterial, ischemic and hemorrhagic, and venous stroke. These are also classified into perinatal, when they occur during pregnancy up to 28 days of life, and childhood stroke.[1,2,14] According to the 2006 International Workshop on Definition and Classification of Cerebral Palsy of Maryland, the term cerebral palsy (CP) describes a group of permanent disorders in the development of movement and posture, causing activity limitation, attributed to nonprogressive disorders that occurred in the developing fetal or infant brain. The