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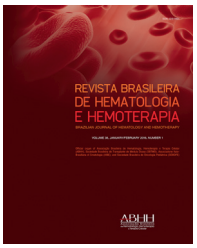

Review article

Genetic, laboratory and clinical risk factors in the development of overt ischemic stroke in children with sickle cell disease

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ABSTRACT

Cerebrovascular disease, particularly stroke, is one of the most severe clinical complications associated with sickle cell disease and is a significant cause of morbidity in both children and adults. Over the past two decades, considerable advances have been made in the understanding of its natural history and enabled early identification and treatment of children at the highest risk. Transcranial Doppler screening and regular blood transfusions have markedly reduced the risk of stroke in children. However, transcranial Doppler has a limited positive predictive value and the pathophysiology of cerebrovascular disease is not completely understood. In this review, we will focus on the current state of knowledge about risk factors associated with ischemic stroke in patients with sickle cell disease. A search of PubMed was performed to identify studies. Full texts of the included articles were reviewed and data were summarized in a table. The coinheritance of alpha-thalassemia plays a protective role against ischemic stroke. The influence of other genetic risk factors is controversial, still preliminary, and requires confirmatory studies. Recent advances have established the reticulocyte count as the most important laboratory risk factor. Clinical features associated with acute hypoxemia as well as silent infarcts seem to influence the development of strokes in children. However, transcranial Doppler remains the only available clinical prognostic tool to have been validated. If our understanding of the many risk factors associated with stroke advances further, it may be possible to develop useful tools to detect patients at the highest risk early, improving the selection of children requiring intensification therapy.

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Introduction

Sickle cell disease (SCD) is a group of autosomal recessive genetic disorders characterized by the presence of at least one β^S allele (HBB:c.20A→T) of the *HBB* gene that encodes the beta chain of hemoglobin (Hb).[1,2] The translation of a β^S allele generates Hb S which results from the substitution of a normal hydrophilic amino acid (glutamic acid) by a hydrophobic amino acid (valine) at position six in the variant beta globin chain. As the valine residue interacts with adjacent complementary sites of globin chains, the resulting protein is prone to polymerization.[3,4]

In certain situations such as hypoxia, acidosis, and dehydration, Hb S molecules form elongated polymers that modify the cytoskeleton of red blood cells (RBCs), originating the characteristic 'sickle' shape (sickling). Polymerization of Hb S causes several physical and chemical changes in RBCs, and is the primary event essential for the pathogenesis of SCD.[4,5] When a critical concentration of the Hb S polymer is reached in RBCs, cell damage occurs and, consequently, the phenotypic manifestations of SCD, characterized by chronic severe hemolytic anemia and vaso-occlusion, arise.[6]

Cerebrovascular disease (CVD) is one of the most severe complications of SCD, affecting about 50% of individuals by 14 years of age.[7] Without early therapeutic intervention, overt ischemic stroke (hereafter, stroke), the most severe type of CVD, occurs in about 11% of individuals before 20 years of age.[8] The natural history of stroke in SCD is well described[9,10]; however, its pathophysiology is not fully understood.[11] Few risk factors are established[8] except for the increased cerebral blood flow in the arteries of the Willis circle detected by transcranial Doppler ultrasonography (TCD).[12]

Although TCD is recognized as a sensitive predictor of stroke risk, the specificity of the technique is relatively low, and the positive predictive value is low. About 60% of individuals at high-risk of stroke detected by TCD will not have a stroke[13] and it is unnecessary to subject them to prophylactic blood transfusions[12] or hydroxyurea therapy.[14]

There is no available method to predict which children with high-risk TCD will not have a stroke and thus would not benefit from prophylactic blood transfusions or hydroxyurea therapy. Recent data from Nigeria showed that none out of 17 children who had high-risk TCD and whose parents or guardians had refused a prophylactic blood transfusion program developed a stroke in a mean follow-up of 27.3 ± 11.1 months.[15] Only about 10% of individuals who had high-risk TCD will suffer from stroke within one year after the confirmatory test.[16] Furthermore, it is estimated that to prevent the occurrence of an episode of stroke, it would be necessary to put seven children into the prophylactic blood transfusion program.[17]

Stroke still occurs in children with normal TCD.[13,16] There is a relatively large variability in blood flow velocities in the same children examined at regular intervals.[18] Furthermore, access to TCD screening and to prophylactic blood transfusion programs is often absent or limited,[19,20] especially in developing countries.[20,21] Additionally, TCD screening programs have poor adherence all over the world,[19,21–25] and, in some services, a TCD screening program is not available at all.

Prophylactic blood transfusion programs have several side effects, such as transfusion-transmitted infections, alloimmunization, and iron overload, among others. We emphasize the high prevalence of alloimmunization. Recently, data from Philadelphia showed that 57.7% of individuals with SCD in prophylactic blood transfusion programs become alloimmunized despite transfusion from Rh-matched minority donors.[26] The risk of iron overload and the high cost of chelation therapy also deserve a mention when evaluating the disadvantages of a prophylactic blood transfusion program.[27] There are no data about the effect of prophylactic blood transfusion and iron overload on mortality in individuals with SCD.[28] Some families and hematologists refuse long-term transfusion therapy. The reasons for refusing a prophylactic blood transfusion program are diverse, and include the high cost of treatment, unavailability of blood, and the unlimited duration of the program.[15]

Due to the phenotypic heterogeneity of SCD, there is interest in predicting which individuals would be most severely affected. However, physicians are still unable to certainly predict which children will have clinically more severe disease during childhood.[29] As mentioned before, early identification of children at the highest risk of developing a stroke would allow early interventions such as a prophylactic blood transfusion program,[12] hydroxyurea therapy,[14] or bone marrow transplantation,[30] before the development of motor and/or neurocognitive sequelae. Conversely, more accurate risk prediction would avoid the indication of risky and potentially toxic therapies in individuals with low risk. Moreover, it would be possible to avoid the considerable increase in the costs of treatment and management of individuals with stroke. The cost of prophylactic blood transfusion programs has been estimated at US$40,000 per year with deferoxamin,[31] and €45,000 per year with deferasirox.[7] Additionally, a stroke event requires additional rehabilitation costs of US$40,000 per year.[32] Also, it would be possible to reduce the incidence, morbidity, and mortality derived from stroke and, consequently, to improve the life expectancy and quality of life in children with SCD.

Several studies have been conducted to identify risk factors associated with CVD in individuals with SCD. In this review, we identify and compile data about genetic, laboratory and clinical risk factors associated with the development of stroke in individuals with SCD.

Methods

Articles indexed with the following search terms and combinations of them were retrieved from PubMed: 'sickle cell disease', 'sickle cell anemia', 'stroke', 'cerebrovascular disease', 'risk factors' and 'polymorphism'. There were no restrictions on date or language of publication. The titles and abstracts of the articles were evaluated. Articles considered outside the scope of this review were excluded. The full texts of all potential articles were read in detail. If deemed relevant by the authors, the data were extracted from the articles and were compiled in Table 1. We also included relevant articles that had been listed in the references of the articles found using the strategy described above. Review articles were cited

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