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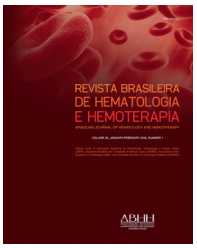

Review article

Mortality by sickle cell disease in Brazil

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ABSTRACT

This work aimed to characterize mortality by sickle cell disease in Brazil. The MEDLINE electronic database was searched using the terms 'mortality' and 'sickle cell disease' and 'Brazil' for articles published in the last five years aiming to provide a current analysis of the subject in question. Eight studies on mortality by sickle cell disease were carried out in the Brazilian states of Maranhão, Bahia, Minas Gerais, Rio de Janeiro and Mato Grosso do Sul. The majority of the deaths occurred in patients with sickle cell anemia, which is the most common genotype and causes the most severe clinical manifestation of the disease. In summary, there are few published studies on mortality related to sickle cell disease in Brazil, and most are from the state of Minas Gerais. This study emphasizes the importance of developing more studies on sickle cell disease mortality, so that it may be possible to profile gene carriers and give health professionals more data to strategize the delivery of more effective assistance to these individuals. Despite the early diagnosis of sickle cell disease by the Neonatal Screening Program and the use of preventive and therapeutic measures (penicillin, immunization and hydroxyurea), mortality by sickle cell disease on the world stage is still significant.

Introduction

Sickle cell disease (SCD) is a generic term used to define a group of genetic changes characterized by the dominance of hemoglobin S (Hb S). These changes include sickle cell anemia (Hb SS) and double heterozygosis, that is, associations of Hb S with other hemoglobin variants, such as Hb D and Hb C, and interactions with thalassemia (Hb S/α thalassemia, Hb S/β^+ thalassemia, and Hb S/β^0 thalassemia). Hb S is characterized by a missense mutation in position 6 of the β chain, in which the amino acid glutamic acid is replaced by valine ($\beta^{6\ GLU \rightarrow VAL}$).[1] It was introduced in Brazil by the slave trade of Negroes during the colonial period, mainly for sugarcane plantations in the Northeast and, later, to extract precious metals in the state of Minas Gerais.[2,3]

SCD predominantly occurs in Afro-descendants; however, it is not exclusive to this population due to evident racial admixture in Brazil. About 34% of the investigated

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individuals with SCD reported being victims of prejudice due to the disease and 48.3% reported a connection between the disease and their skin color.[4] Predominance of Black ethnicity, low education levels and income was observed in studies that characterized the sociodemographic profile of patients with SCD in Brazil.[5,6] In Brazil, the incidence of SCD is approximately 1–3/1000 live births and in states such as Bahia, where African ancestry predominates, this rate reaches 1/650 newborns.[7]

Signs and symptoms of SCD include hand–foot syndrome, chronic hemolytic anemia, vaso-occlusive crises, infections, acute chest syndrome (ACS), acute splenic sequestration (ASS), stroke, priapism and leg ulcers.[1,8] It is a chronic genetic pathology, which negatively affects the quality of life of individuals and their families.[6,9,10] It exhibits autosomal recessive inheritance and, therefore, affected individuals are homozygous for Hb S (Hb SS). Heterozygous individuals (Hb AS) have the sickle cell trait (SCT), that is, they are mutant allele carriers, which can be transmitted to their descendants.[1] For couples in whom both individuals have the SCT, identification of the condition and genetic counseling are important before starting a family.[11] Difficulty in distinguishing between the terms carrier and affected individuals was reported in two recent researches.[12,13] One showed that only 17 (14.3%) of the 119 mothers whose children presented an abnormal result in the screening test for hemoglobinopathies could acknowledge the difference between the trait and the disease.[13] The other, with 136 educators (94.9% teachers) of public schools in Montes Claros, Minas Gerais, revealed that 64.7% stated there was no difference between SCD and SCT, highlighting that this doubt exists even in people with higher levels of education.[12] Another unexpected finding was that 39% thought that SCD was a consequence of a lack of nutrients.[12]

Due to its prevalence and clinical importance, SCD is considered a public health problem in Brazil, and therefore public policies were implemented, including the Sickle Cell Disease Program[14] and National Policy for Comprehensive Care of Persons with Sickle Cell Disease and Other Hemoglobinopathies,[15] aimed at providing better assistance to affected individuals. Another advance was the early diagnosis of SCD and other hemoglobinopathies by the Guthrie test, established by Government Decree of the Ministry of Health n° 822, dated June, 6, 2001, which instituted the National Neonatal Screening Service.[16] Historic evolution of the creation process of neonatal screening around the world, in particular in Brazil, was reviewed by Rodrigues et al.[2] Inclusion of SCD in the National Neonatal Screening Service was of utmost importance because affected individuals do not present clinical signs at birth, making early diagnosis essential.

Therapeutic options available for SCD include bone marrow transplantation, chronic transfusions and hydroxyurea (HU).

Studies with patients using HU showed significant reductions in vaso-occlusive crises, ACS, infections, hospitalizations and the number of transfusions.[17,18]

This work aimed to characterize mortality by sickle cell disease in Brazil in respect to the frequency, death rate or mortality coefficient, age and causes.

Methods

The MEDLINE electronic database was searched using the terms 'mortality' and 'sickle cell disease' and 'Brazil' over the last five years aiming to provide a current analysis of the subject in question. Fifteen papers were identified, of which only seven were selected based on the title and abstract. Case reports were excluded and only those that were published as full-length articles in English were considered. Other databases, such as SciELO and BIREME, were also searched, but the same articles were found. The reference lists of the articles were systematically searched in order to identify any potential additional studies that could be included. Eight studies were included in this systematic review.

Results

Eight studies on mortality by SCD were carried out in the Brazilian states of Maranhão,[19] Bahia,[20] Minas Gerais,[21–23] Rio de Janeiro[24,25] and Mato Grosso do Sul.[26]

The study carried out in Maranhão assessed the impact of the implementation of neonatal screening on hospitalization and death rates due to SCD. The mortality rate increased from 0.115 to 0.216, that is 1.88 times higher, but this was not statistically significant (p-value = 0.586) and the median age at death increased from 10 years to 14 years (p-value = 0.665).[19]

A recent research carried out in Bahia, the Brazilian state with the largest black population and highest prevalence of SCD, described the epidemiological profile of the deaths by SCD and reported 74 deaths in 2011 corresponding to a mortality coefficient of 0.54 per 100,000 individuals.[20] Yet, the causes of death were not specified. About 42% of the deaths occurred in adults (age range: 20–39 years). The majority of the deaths (n = 64; 86.4%) occurred in hospital with Salvador being the city with the highest number (14 deaths; 18.9%).[20]

The mortality and survival of children with SCD were investigated in Minas Gerais.[21,22] Between 1998 and 2012, 2591 children were diagnosed with SCD (1:1.400). There were 193 deaths (7.4%): 153 (79.3%) children had Hb S/β^0 thalassemia, 34 (17.6%) had Hb SC and six (3.1%) had Hb S/β^+ thalassemia. Of the deaths, 56.5% occurred in children under the age of two and 76.7% in under five-year olds. The main causes of death were infection (45%), indeterminate (28%) and ASS (14%).[21] The term 'sickle cell' was not cited in 46% of death certificates. The mortality rate between 1998 and 2005 was 5.43% vs. 5.12% between 2005 and 2012.[21] Another study showed that the 5-year estimated mortality was lower, albeit not significantly, for children born between 2009 and 2011 (n = 509) than for those born between 1999 and 2001 (n = 624) [mean (standard deviation): 5.8% (1.1) vs. 6.2% (1.0), respectively].[22]

Of the 912 newborns with SCD (639 with Hb SS, 201 with Hb SC, 26 with Hb SD and 46 with Hb S/β^+-thal) in Rio de Janeiro referred for treatment in the Fundação Hemorio in the period from 2000 to 2010, 34 children (3.7%) died due to ACS (n = 14; 36.8%), sepsis (n = 12; 31.6%) or ASS (n = 8; 21.1%).[24]

Two studies analyzed the effect of HU therapy in patients with SCD.[25,26] A total of 267 children were treated with hydroxycarbamide therapy for two years with a total of 38 deaths.

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