



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.

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### 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/ $\alpha$  thalassemia, Hb S/ $\beta^+$  thalassemia, and Hb S/ $\beta^0$  thalassemia). Hb S is characterized

by a missense mutation in position 6 of the  $\beta$  chain, in which the amino acid glutamic acid is replaced by valine ( $\beta^6$  GLU  $\rightarrow$  VAL).<sup>1</sup> 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.<sup>2,3</sup>

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.<sup>4</sup> Predominance of Black ethnicity, low education levels and income was observed in studies that characterized the sociodemographic profile of patients with SCD in Brazil.<sup>5,6</sup> 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.<sup>7</sup>

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.<sup>1,8</sup> It is a chronic genetic pathology, which negatively affects the quality of life of individuals and their families.<sup>6,9,10</sup> 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.<sup>1</sup> For couples in whom both individuals have the SCT, identification of the condition and genetic counseling are important before starting a family.<sup>11</sup> Difficulty in distinguishing between the terms carrier and affected individuals was reported in two recent researches.<sup>12,13</sup> 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.<sup>13</sup> 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.<sup>12</sup> Another unexpected finding was that 39% thought that SCD was a consequence of a lack of nutrients.<sup>12</sup>

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<sup>14</sup> and National Policy for Comprehensive Care of Persons with Sickle Cell Disease and Other Hemoglobinopathies,<sup>15</sup> 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.<sup>16</sup> Historic evolution of the creation process of neonatal screening around the world, in particular in Brazil, was reviewed by Rodrigues et al.<sup>2</sup> 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.<sup>17,18</sup>

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,<sup>19</sup> Bahia,<sup>20</sup> Minas Gerais,<sup>21–23</sup> Rio de Janeiro<sup>24,25</sup> and Mato Grosso do Sul.<sup>26</sup>

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).<sup>19</sup>

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.<sup>20</sup> 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%).<sup>20</sup>

The mortality and survival of children with SCD were investigated in Minas Gerais.<sup>21,22</sup> 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/ $\beta^0$  thalassemia, 34 (17.6%) had Hb SC and six (3.1%) had Hb S/ $\beta^+$  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%).<sup>21</sup> 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.<sup>21</sup> 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].<sup>22</sup>

Of the 912 newborns with SCD (639 with Hb SS, 201 with Hb SC, 26 with Hb SD and 46 with Hb S/ $\beta^+$ -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%).<sup>24</sup>

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

The causes of death were ACS ( $n=17$ ; 45%), infection/sepsis ( $n=13$ ; 34%), stroke ( $n=4$ ; 10%), death during painful episodes ( $n=3$ ; 8%) and one death was unrelated to SCD (3%). There were 36 deaths among non-hydroxycarbamide users and only one among hydroxycarbamide users ( $\chi^2=4.57$ ;  $p$ -value = 0.03). Survival among hydroxycarbamide-treated children was significantly greater than that among untreated patients (99.5% vs. 94.5%;  $p$ -value = 0.01).<sup>25</sup> A study carried out in Mato Grosso do Sul assessed mortality and cause of death in 63 patients with SCD (55 had Hb SS and 8 had Hb SC), taking ( $n=39$ ) and not taking HU ( $n=24$ ).<sup>26</sup> Ten (15.8%) of the patients died with a mean age of 28.1 years, eight with Hb SS and two with Hb SC; 60% of the deaths occurred in patients not taking HU. The main causes of death were acute respiratory failure (40%), multiple organ failure (20%), cardiogenic shock (20%), stroke (10%) and septic shock (10%).<sup>26</sup>

A prospective cohort of 104 pregnant women with SCD registered in the Fundação Hemominas in Belo Horizonte showed that one-third of pregnant women had near misses and 4.8% died (five deaths); the causes were ACS ( $n=4$ ) and sepsis ( $n=1$ ).<sup>23</sup>

## Discussion

The increases in the rates of hospitalization and death after the implementation of neonatal screening in the state of Maranhão suggest that previously there was an underdiagnosis of SCD and that screening, along with other factors, increased 'visibility' of the disease in the state. Possible explanations for an increase both in hospitalization and mortality rates after implementing neonatal screening are under-reporting of the disease due to difficulty of diagnosis, insufficient hospital care, incorrect use of the international disease classification (ICD) code and lack of hospital registry.<sup>19</sup> The authors from Bahia concluded that there is a lack of studies correlating mortality in this genetic disorder and they highlighted the need for filling out death certificates correctly.<sup>20</sup>

It was evident that infection (including pneumonia and septicemia) and ASS were the main causes of infant mortality. Moreover, the incidence of death was higher in patients with sickle cell anemia, the most common genotype and the most severe clinical presentation of the disease.<sup>21</sup> The results of Minas Gerais showed that neonatal screening for SCD was not sufficient to significantly reduce child mortality. Economic and social development and increase of the knowledge about SCD among healthcare professionals and family are needed to overcome the high mortality rate.<sup>21,22</sup>

The studies conducted in the states of Rio de Janeiro<sup>25</sup> and Mato Grosso do Sul<sup>26</sup> reported that hydroxycarbamide therapy decreases mortality among patients with SCD. HU is an agent that stimulates fetal hemoglobin (Hb F) production and contributes by diminishing the inflammatory and vaso-occlusive phenomena thereby reducing mortality.<sup>17,18,26</sup> This drug is provided free of charge in Brazil to patients with SCD who meet the criteria defined by the Brazilian Ministry of Health Hydroxyurea Clinical Treatment Protocol. The inclusion criteria are the following: (1) documented diagnosis of SCD (any genotype), (2) adults  $\geq 18$  years and children  $\geq 3$  years with parental consent, (3) ability to fulfill clinical and laboratory

monitoring and (4) at least one of the following in the preceding 12 months:  $\geq 3$  painful events requiring medical treatment,  $\geq 1$  episode of ACS, prior stroke or transient ischemic attack, one serious or recurrent episodes of postpubertal priapism, or a Hb concentration  $< 6$  g/dL on three separate occasions.<sup>27</sup> Data from a longer (17 years of follow-up) non-randomized prospective study of adults with SCD registered 13 (9.9%) deaths in the HU group and 49 (24.6%) in the group not treated with HU. The probability of 10-year survival was 86% and 65% for HU and non-HU patients, respectively.<sup>17</sup> Hydroxycarbamide therapy was also associated with decreased mortality among children with SCD.<sup>25</sup>

Pregnant women with SCD have a higher risk of maternal and fetal mortality when compared to those with SCT or the population in general.<sup>23,28,29</sup> A research that assessed the evolution of pregnancies in 34 women with SCD for a period of 12 years reported 26.6% of miscarriages, seven fetal losses (3 stillbirths and 4 miscarriages) and only one maternal death (2.9%) in the postpartum period due to ACS.<sup>28</sup> A study carried out in France, aiming to describe maternal mortality in women with SCD from 1996 to 2009 reported 15 deaths, with two of them by septic shock during pregnancy and 13 occurring in the postpartum period, with the same number of deaths being attributed directly to SCD. Ten women were homozygous (Hb SS) for SCD, and five were composite heterozygotes.<sup>29</sup> A recent review of the literature showed that maternal and fetal mortality rates during pregnancy can reach 11.4% and 20%, respectively.<sup>30</sup>

Studies carried out in other countries also presented data about mortality by SCD. One of them, carried out in Africa, reported 86 deaths (5.7%;  $n=20$  and 23.3% hospital deaths) among 1516 patients with SCD. Two deaths occurred in children under the age of two, 22 in children under five, 47 deaths in the 5–19 age range and 15 in over 20-year-old individuals.<sup>31</sup> Another study carried out in Amsterdam, before the Neonatal Screening Program in the Netherlands, identified 298 children with SCD (189 with Hb SS, 72 with Hb SC, 20 with Hb S/ $\beta^+$  and 17 with Hb S/ $\beta^0$ ) between 1985 and 2007. During the observation period, 12 patients (4%) died, with sepsis/meningitis ( $n=4$ ; 33%) and stroke ( $n=3$ ; 25%) being the main causes. Three deaths occurred by meningitis (Hb SC, Hb S/ $\beta$  and Hb SS), one by sepsis (Hb SS) and three fatal strokes occurred in over 10-year-old patients (two with Hb SS and one with Hb SC). Concerning the age at death, four children (33%) under the age of 3 died, three (25%) were between 3 and 18 years old and five (42%) were over the age of 18.<sup>32</sup> This study showed that the mean age at death was 11.3 years and one out of 40 children with SCD in the Netherlands does not survive until adulthood.<sup>32</sup> In Jamaica, of 75 young adult patients with SCD, 11 (14.7%) died, with sepsis being the main cause of death.<sup>33</sup> The Neonatal Screening Program in New York identified 21 (1.1%) deaths after the diagnosis of SCD from 2000 to 2009. Of these, 14 occurred in under 2-year-old children and seven in children aged between 2 and 9 years old. Of the total deaths, 16 occurred in children with Hb SS or Hb S/ $\beta^0$  and ten were related to SCD. The deaths of the other five children with Hb SC were not related to the pathology in question. Another interesting finding of this research was that SCD was mentioned on the death certificate in only 57% of the cases ( $n=12$ ).<sup>34</sup> A recent study in the USA about the mortality rate



of children and adults with SCD showed a decrease in the first group (3%) and an increase in the second (1%) during the same period of 26 years (1979–2005).<sup>35</sup> Between 1990 and 2010 in Iran, the overall deaths attributed to hemoglobinopathies decreased from 0.51% to 0.36% of total deaths.<sup>36</sup> A retrospective study showed that infections were the commonest cause of death in Nigerian SCD patients.<sup>37</sup> The mean age at death was 21.3 years (range: 1–47 years) with peak mortality in the 2nd and 3rd decades of life. Infections and thromboembolic phenomenon were the main causes of death, in 78% and 37% of the cases, respectively. This was followed closely by anemia alone or in combination with acute sequestration crises in 31% of patients.<sup>37</sup>

## Conclusions

In summary, there are few published studies on mortality by SCD in Brazil, most of which are from the state of Minas Gerais. This study shows the importance of developing more studies on death related to SCD, so that it may be possible to profile the gene carrier and give health professionals more data so that they can strategize to provide more effective assistance to these individuals. The main causes of death are infection, ASS and ACS.

Infections are the most common causes of death in SCD patients in Brazil with the majority occurring in patients with sickle cell anemia, the most common genotype and the most severe clinical presentation of the disease. Studies show that despite the early diagnosis of SCD by the Neonatal Screening Program and the use of preventive and therapeutic measures (penicillin, immunization and hydroxyurea), mortality by SCD on the world stage is still significant. Variables such as frequency, death rates or mortality coefficient, age and causes of death were not totally investigated by all researchers. This makes it impossible to perform a more accurate analysis of mortality by SCD in the world.

## Conflicts of interest

The authors declare no conflicts of interest.

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