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Mortality of children with sickle cell disease: a population study

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Abstract

Objective: To describe the deaths of children with sickle cell disease (SCD) in Minas Gerais, Brazil, and followed up at the Fundação Hemominas.

Methods: Cohort of children diagnosed by the Neonatal Screening Program in Minas Gerais (March/1998 – February/2005). Deaths were identified by searching for children who did not attend scheduled consultations at hemocenters. Clinical and epidemiological data were abstracted from death certificates, the newborn screening database, individual medical records, and from interviews with families.

Results: During the period, 1,833,030 newborns were screened; 1,396 had SCD (1:1,300). There were 78 deaths: 63 with SS genotype, 12 with SC genotype, and three with Sβ$^+$ thalassemia genotype. Fifty-six children (71.8%) died before 2 years of age; 59 died in hospitals and 18 at home or during transportation. Causes of death according to certificates (n = 78): infections, 38.5%; acute splenic sequestration, 16.6%; other causes, 9%; did not receive medical care, 15.4%; and not identified on certificates, 20.5%. According to interviews (n = 52), acute splenic sequestration was responsible for one third of deaths, in contrast with 14% recorded on death certificates. Survival probabilities at 5y (SEM) for children with SS, SC, and Sβ$^+$ thalassemia were 89.4 (1.4), 97.7 (0.7), and 94.7% (3.0), respectively (SS vs. SC, $p < 0.0001$).

Conclusions: Even with a carefully controlled newborn screening program, the probability of SS children dying was still found to be high. Causes not identified on death certificates may indicate difficulties recognizing SCD and its complications. Educational campaigns directed at health professionals and SCD patients' families should be boosted in order to decrease SCD mortality.

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Introduction

Sickle cell disease (SCD) is a genetic disorder of great epidemiological and clinical importance. Its hallmark is the inheritance of the S beta-globin gene (gene ßˢ). This gene causes the S variant of hemoglobin to be produced in red blood cells. Vaso-occlusive phenomena and chronic hemolysis are the main causes of the clinical manifestations of SCD and, while the primary abnormalities are restricted to erythrocytes, the result is a systemic disease that can affect any organ.[1]

SCD is an important public health problem in Brazil. It is estimated that the number of people with the sickle trait is 7,200,000, with the prevalence in the general population being between 2 and 8%.[2] The incidence of the sickle trait in Minas Gerais is 3.3% and the incidence of

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SCD is approximately 1:1,400 newborn infants screened, according to data from the - Minas Gerais State Newborn Screening Program (Programa Estadual de Triagem Neonatal de Minas Gerais, PETN-MG), which began screening for hemoglobinopathies in March of 1998. The PETN-MG includes all of the municipal authorities in the state of Minas Gerais, and coverage is 94% of live births.[3]

Although SCD leads to elevated morbidity and mortality, particularly during the first 5 years of life,[4-9] mortality has been reducing among children with SCD less than ten years old.[10-14] In 1970, median survival was 20 years among citizens of the United States with the homozygous form (SS).[15] After initiating programs for neonatal diagnosis, education and integrated patient care, SS children had an 85% chance of survival at the age of 20.[4]

Despite the fact that the majority of SCD genotypes cause reduced life expectancy, sickle cell anemia, which is the presence of homozygosis for hemoglobin S, is the most common genotype and has the most severe clinical presentation. Several different studies have shown that the incidence of deaths is greater and survival is reduced among patients with sickle cell anemia.[4,9,16,17] The primary causes of death before 10 years of age include infections and acute splenic sequestration.[4,16-23]

The objective of this study was to perform a detailed investigation of the causes and circumstances of the deaths of children with SCD identified by the PETN-MG screening program. This is the first time that a population cohort has been used for this purpose in Brazil. Understanding the various different determinants of these deaths should facilitate the planning of public policies and other actions that can contribute towards reducing morbidity and mortality and improving the quality of life of people with SCD.

Methods

The study population comprised children diagnosed with SCD by the PETN-MG screening program and treated at Fundação Hemominas hemocenters who died between the 1st of March of 1998 and the 28th of February of 2005.

The PETN-MG program has screened for SCD and other hemoglobinopathies since March of 1998. All of the state of Minas Gerais' 853 municipal authorities are included and coverage is 94% of live births. Blood samples are taken from newborn infants on their fifth day of life using filter paper and are sent to the neonatal screening laboratory at the Center for Actions and Research in Diagnostic Support (NUPAD - Núcleo de Ações e Pesquisa em Apoio Diagnóstico) at the medical faculty of the Universidade Federal de Minas Gerais (UFMG) in Belo Horizonte, Brazil, where the program's technical and operational headquarters are.

The information on patient deaths originates from investigations into the reasons why patients did not attend their consultations at the hemocenter. The NUPAD actively follows-up all patients who are diagnosed with SCD as part of the screening program and are being treated at the Fundação Hemominas, making it unnecessary to design a sampling strategy, since it can be stated with confidence that all deaths during the study period have been accounted for.

Data were extracted from the PETN-MG database and also from death certificates, from the Brazilian National Health Service's database (DATASUS), from the Brazilian Institute of Geography and Statistics' database (Instituto Brasileiro de Geografia e Estatística, IBGE), from medical records from outpatients clinics at the Fundação Hemominas and from interviews with children's carers. Cause, date and location of death were extracted from the 78 death certificates.

The NUPAD database was the source for information on family location and compliance with the follow-up protocol, since a copy of the notes from every consultation at the hemocenters is sent to the Control and Treatment Team at NUPAD. Since this was a retrospective study, there was no specific data collection phase designed to investigate compliance with prophylactic anti-infection measures (specific vaccines and antibiotics).

A semi-structured interview was conducted with each deceased child's parent or guardian during 2006, which was between 1 and 8 years after the child had died. The researcher responsible (APPCF) was obliged to visit 41 different towns, traveling around 10 thousand kilometers. Despite her best efforts, 24 families could not be located, primarily from the subset whose children had died more than 5 years previously. A further two families refused to be interviewed. The median duration of interviews was 25 minutes and four subjects were covered: 1) the circumstances relating to death; 2) SCD follow-up care and acute events other than that leading to death; 3) socioeconomic and cultural status; and 4) subjects' impressions of their experience of living with a child with SCD. All interviews were conducted after interviewees had read and signed an informed consent form that explained the study's objectives, procedures and possible benefits and costs.

A dedicated Microsoft Access database was designed specially for this study and used to input the data from Fundação Hemominas medical records.

For the statistical analysis, the frequencies of nominal variables were compared using the chi-square test, without correction for continuity, or Fisher's exact test when necessary. Survival curves were plotted using the Kaplan-Meier method, and curves were compared using the logrank test. All 78 deaths were defined as adverse events, irrespective of whether they were related to SCD or not. All children who were still alive on the 15th of February of 2005 (n = 1,318) were "censored" on that day. Results were considered significant if the probability of alpha error was ≤ 0.05.

This study was approved by the Research Ethics Committees at UFMG and the Fundação Hemominas and was awarded financial support by the Conselho Nacional de Desenvolvimento Científico e Tecnológico as part of an MCT/CNPq/MS-SCTIE-DECIT grant, number 026/20.

Results

During the period studied, 1,833,030 newborn infants were screened by the PETN-MG, and 1,396 children had a hemoglobin profile compatible with SCD: 764 SS or Sß^0-thalassemia, 555 with hemoglobin SC disease, 10 with hemoglobin SD disease and 67 with Sß$^+$ thalassemia (incidence of 1:1,313 for all forms, 1:2,400 for SS/Sß^0-thalassemia and 1:3,300 for SC).

There were 78 deaths during the 7-year period. Forty-one (52%) of the children who died were male and 37 (48%) were female. The majority of the deceased children lived in urban areas (78%) and in small towns with populations of up to 50,000 inhabitants (56.4%).

The median age at the time blood was taken for the screening test was 9 days, with 75% of the children being screened by 18 days. The median age at first consultation at the hemocenter was 2.1 months. Three children died before attending their first consultation at the hemocenter, aged 19, 55 and 57 days. The cause of death was septicemia in two cases and was not identified in the third.

Figure 1 illustrates the distribution of deaths by age group. The majority of deaths (71.8%) were before 2 years of age. Median age at death was 13.7 months.

Broken down by the hemoglobin profile detected by neonatal screening, 63 of the children who died had SS/Sß^0 (80.8%), 12 had SC (15.4%) and three had Sß$^+$ thalassemia (3.8%).

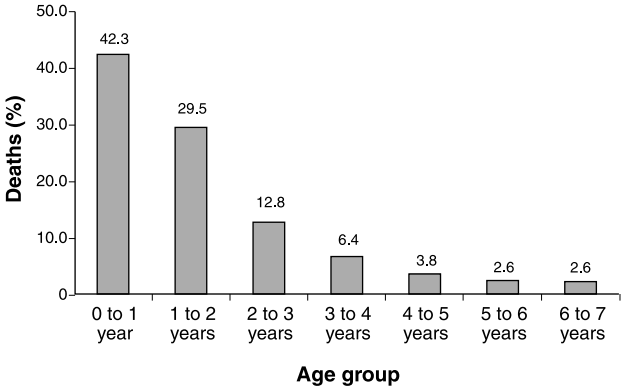

Figure 1 - Distribution by age group of 78 children with sickle cell disease who died between March of 1998 and February of 2005 (Minas Gerais State Neonatal Screening Program - PETN-MG)

According to the death certificate data, there was a higher prevalence of deaths in hospital (59 cases), but 15 deaths were at home, three in transit and one at a basic healthcare center.

Infection (including pneumonia and septicemia) was the predominant *causa mortis* registered on the death certificates, followed by acute splenic sequestration. Where records stated "no medical care" the cause of death was defined as unknown (Figure 2).

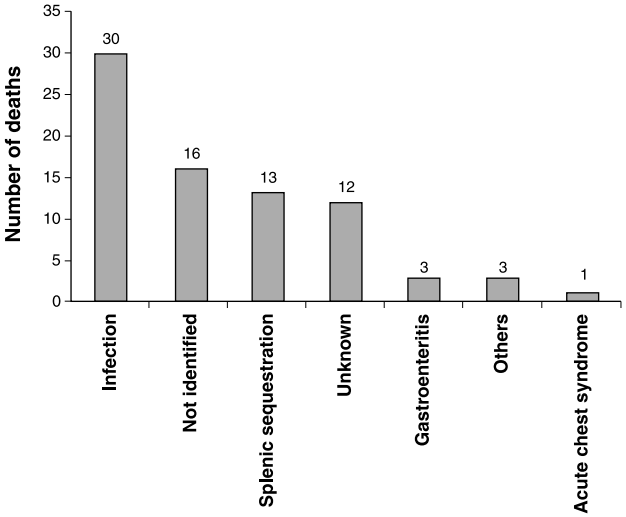

Figure 2 - Causes of death according to the death certificates of 78 children with sickle cell disease who died between March of 1998 and February of 2005, (Minas Gerais State Neonatal Screening Program - PETN-MG)

There was a certain degree of disagreement between the registered causes of death and the information provided by family members during the interviews (n = 52). For example, according to the death certificate data splenic sequestration caused seven of the 52 deaths (13.5%), but according to the interviewees splenic sequestration was responsible for 16 of the 52 deaths (30.8%).

Figure 3 illustrates the survival curves for children with hemoglobin SS disease or Sß^0-thalassemia, SC, SD and Sß$^+$ thalassemia. The survival curve for children with SS/Sß^0-thalassemia is significantly lower than the curve for children with SC ($p < 0.0001$). The survival curve for children with SS/Sß^0-thalassemia does not differ significantly from the curves for children with Sß$^+$ thalassemia or SD ($p = 0.21$ and $p = 0.36$, respectively). It was also observed that, during their first 5 years of life, children with SS/Sß^0-thalassemia exhibited a more rapid reduction in their probability of survival than did children with SC and Sß$^+$ thalassemia (Table 1).

Out of the total number of consultations scheduled for the 78 children who died (580 consultations), 77.3% were attended and 22.7% were not.

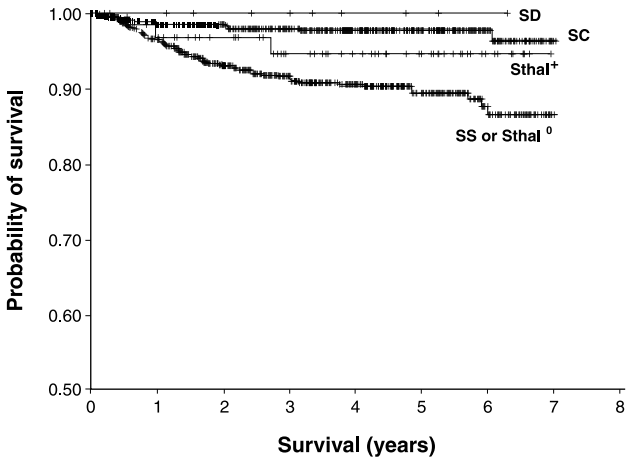

Figure 3 - Curves illustrating the estimated probability of survival of 1,396 children diagnosed between March of 1998 and February of 2005, broken down by type of hemoglobinopathy (Minas Gerais State Neonatal Screening Program - PETN-MG). The survival curves for children with SS/Sß^0-thalassemia are significantly different from the curves for children with SC (Kaplan-Meier method, logrank test, $p < 0.0001$)

According to information from the interviews (n = 52), 57.7% of these children were seen within 6 hours of onset of the symptoms related to the event that caused their deaths, while 71.2% were seen within 24 hours and 17.3% died without receiving any medical care. In this subset, death occurred within 12 hours of the onset of symptoms in 55.8% of cases and within 24 hours in 67.3. According to the interviewees, fever, pain, vomiting and prostration were the most common symptoms related to the event leading to death. Nineteen children were taken straight to hospital by their families (36.5%), while basic healthcare centers were the first service sought by 12 (23%) families and another six families first presented at walk-in centers (11.5%). Forty-three families (82.7%) reported that their children had been given antibiotic prophylaxis regularly, and 47 families (90.4%) said their children were taking folic acid regularly. Twenty-one families (40.4%) reported that their children had been given special immunobiologicals regularly. With relation to the children's clinical condition prior to death, 65% of the children had been admitted to hospital at least once previously and 19% of them had been admitted more than three times, while 67.3% of them had already suffered a pain crisis previous to death and 14 children (27%) had already suffered acute splenic sequestration, with two of these suffering the event more than once.

With relation to the social and economic situation of the families who were interviewed (n = 52), 58% had a monthly *per capita* income of less than R$ 100.00 (R$ 2.00 = US$ 1.00) and for 20% of them this figure was less than R$ 50.00. The lowest reported *per capita* income was zero and the highest was R$ 380.00. At the time of the interview the national minimum monthly wage was R$ 350.00. The mean number of family members was 5.6 and 76.8% of the mothers and 86.8% of the fathers had not completed primary education and 13.5% of the mothers and 19% of fathers were illiterate.

Discussion

The patient population studied here reflects the overall health status of children with SCD born in the Brazilian state of Minas Gerais, since the PETN-MG has a coverage of 94% of all infants born in 100% of the state's municipalities. All deaths among the subset of children diagnosed with SCD and being treated at the hemocenters were included in the analyses, meaning that the cases include all deaths from within this group of children that occurred within the study period, as is characteristic for a population-based study.

As has been observed in other reports, in this study there was no significant difference between the incidence of deaths in each sex within the age groups studied.[4,23] The greatest incidence of death (80.8%) was among patients with Hb SS which is both the most common genotype and responsible for the most severe clinical presentation; and this has also been observed in other studies.[4,9,16,17]

Table 1 - Estimated probabilities of survival (% ± SE) of 1,396 children diagnosed between March of 1998 and February of 2005, broken down by type of hemoglobinopathy and survival (1, 3 and 5 years)

Type of hemoglobinopathy (n diagnosed)	Estimated probability of survival		
	1 year	3 years	5 years
SS or Sß^0-thalassemia (n = 764)	96.6 (0.7*)	91.6 (1.1*)	89.4 (1.4*)
SC (n = 555)	98.7 (0.5*)	98.0 (0.6*)	97.7 (0.7*)
Sß$^+$ thalassemia (n = 67)	96.8 (2.2*)	94.7 (3.0*)	94.7 (3.0*)
SD (n = 10)	100.0	100.0	100.0
All (n = 1,396)	97.5 (0.4*)	94.3 (0.7*)	93.1 (0.8*)

* Standard error of the mean.

When deaths were distributed according to the child's age at death, a concentration of deaths can be observed before 2 years, in common with reports published by other authors.[4,16,19,21] Follow-up data on children with SCD diagnosed by the neonatal screening programs of three US states and published by the Centers for Disease Control and Prevention (CDC) showed that the median age at death was 22 months.[24] This elevated mortality during the first 5 years of life may be because of the greater incidence of severe acute events during early childhood. Three children died before reaching 2 months, and before attending their first consultation, from causes that were probably not related to the underlying diagnosis.

Although the majority of deaths occurred in hospital, it is nevertheless important to point out that almost one quarter of these children died at home or on their way to a healthcare service. Certain factors, such as living in rural areas and difficulties preventing families from identifying situations in which their children were at risk, may have contributed to this situation. A study conducted in England reported seven deaths at home out of a group of 11 SCD patients less than 20 years old. These authors stressed the need for rapid recognition of acute events and seeking medical attention promptly in order to counteract the rapidity with which the severe signs and symptoms of the disease develop.[25]

The predominant cause of death in this study was infection, followed by acute splenic sequestration. Similar data have also been published by other authors.[4,17-21,26,27] Notwithstanding, the numbers of unidentified and unknown causes of death were elevated. An unidentified cause of death suggests that healthcare teams have a certain difficulty in recognizing SCD and its acute complications, since the majority of certificates where the cause of death was not identified took place in hospital. The majority of cases in which cause of death was unknown were related to children who died before receiving medical care.

Comparison of the death certificate data with information provided in the 52 interviews revealed discrepancies, primarily with relation to acute splenic sequestration as cause of death. The apparent difficulty that healthcare teams have in recognizing splenic sequestration is noteworthy since this is one of the primary severe acute events characteristic of SCD in early childhood and its history and clinical presentation are very obvious.[26]

Analysis of the survival curves showed that the probability of survival of children with SS/Sβ^0-thalassemia dropped more sharply during the first 5 years than the curve for SC children. The failure of the comparison between Sβ$^+$ thalassemia and SD groups to attain statistical significance is probably due to the small number of children in each category.

The general mortality rate for under-5s in the state of Minas Gerais was 30.4 per thousand in 2000,[28] which, subtracted the early neonatal mortality rate, results in an estimate of 18 per 1,000 for the purposes of making comparisons with the estimated probability of survival to 5 years in this study. The estimated mortality rate for SS children was 106 per 1,000 (10.6%), i.e., around six times greater than the rate for the state. The survival curve for 310 SS children who took part in a Jamaican cohort study showed that first-year mortality was 6%.[5] In the Dallas cohort the probability of death by 6 years of age for SS/Sβ^0-thalassemia children was 5%.[29] It should be pointed out, however, that the area covered by the study was restricted to the Northeast of Texas and that enrollment on the study only took place after attendance at a first consultation at the Comprehensive Sickle Cell Center (median of 4.2 months) rather than after laboratory diagnosis of the newborn (with sensitivity close 100%), which obviously underestimates the true probability of death in the population.

In the majority of cases, medical care was received within the first 6 hours after onset of symptoms. There was, therefore, no major delay in seeking medical attention. Twenty-three percent of these cases were seen at basic healthcare centers, which is because of the large number of children who live in small towns. The high reported compliance with antibiotic prophylaxis should be treated with skepticism since a study was undertaken into this specific subject at the Hemocenter de MG and found that compliance is well below this figure.[30] It can be concluded that the most significant difficulties that may have contributed to these deaths are related to the medical attention itself, i.e. the healthcare teams' levels of capacity and training for dealing with acute SCD events and the resources available at the health services where patients first present. Another factor that should be considered is the speed with certain clinical presentations progress. The low educational level of parents and low family incomes are further obstacles.

The most important limitation of this study is its retrospective nature, since the clinical follow-up protocol was designed for treatment and not for research. The failure to interview families in one third of the cases was also a result of the retrospective cohort design, since the more time has passed, the more difficult it becomes to locate them. Since the main objective of the interviews had been to ask how the deaths took place, adding a qualitative element to the study that is more refined and humanized than merely inspecting death certificates and medical records, we do not believe that failing to interview 26 of 78 families compromised the study objectives.

These results indicate that in SCD social factors are strongly associated with the biological determinants and make a decisive contribution to the morbidity and mortality of the disease. The problems related to SCD are not therefore limited to technical issues, but are, indeed, also a social and political issue. The Ministry of Health's program to provide integrated healthcare for people with SCD is an ideal

towards which patients, their families and the professionals involved in treating them must work in order to achieve the objective of improving the current living conditions and health status of these people.

It was concluded that even in the context of a neonatal screening program with rigorously controlled treatment, during the 7 first years of the PETN-MG the probability of death before 5 years of age was much greater among SS children than the overall mortality rate for this age group. Unidentified causes of death indicate that there are difficulties in recognizing SCD and its complications. Educational campaigns aimed at health professionals and at SCD patients' families should be stepped up in order to reduce the mortality and morbidity caused by SCD. Capacitating the basic healthcare centers should be made a priority, since simple interventions, such as neonatal screening, prophylactic penicillin, immunization and education can have a great impact on public health. Many deaths could be avoided through educating and by improving the social, economic and cultural conditions of the families of children with SCD.

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