

Article / Artigo

## Morbidity-mortality in sickle cell disease

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*The high morbidity-mortality rates in sickle cell disease (SCD) led us to study the epidemiological profile and respective clinical complications of patients seen at a Regional Blood Center (HR) and a University Clinical Hospital (HC-U) between 1998 and 2007. In a retrospective study, 151 patients were evaluated regarding age, gender, skin color, origin, diagnosis, reason of visit to HR or reason and length of stay in the HC-U, and cause and age in cases of death. Simple descriptive statistical analysis was performed. The mean age was 17.7 years, 52.4% of the patients were female, 58.2% were from the city and no information regarding skin color was available in 92.2% of the records. Sickle cell anemia was present in 82.5% of cases. The most frequent reason for the 910 visits to HR and 589 hospitalizations in HC-U were afebrile pain episodes (61.9% and 25.3%, respectively). The mean age of the 11 patients who died was 33.5 years with one patient being younger than 10 years old, and multiple organ failure was the most frequent cause. The epidemiological profile shows a predominance of children and young adults, women, and the SS genotype. The rates of hospitalization in HC-U and of visits to HR and the low mean age at death confirm the high morbidity and mortality related to SCD. However, a large number of children do not present with complications or require hospitalization which reflects the efficacy of preventive measures provided by the early diagnosis implemented over the last 10 years.*

**Keywords:** Anemia, sickle cell; Morbidity; Mortality

### Introduction

Sickle cell disease (SCD) is one of the most common genetic disorders in Brazil<sup>(1-4)</sup> and worldwide.<sup>(2)</sup> It is estimated that there are from 25,000 to 30,000 individuals with SCD in Brazil with a further 3,500 new cases each year.<sup>(4)</sup>

Data from the Neonatal Screening Program of Minas Gerais, established in 1998, show an incidence of 72 cases per 100,000 live births and a sickle cell trait carrier for every 30 live births.<sup>(2)</sup> SCD involves a set of phenotypes with the commonest being the hemoglobin S (Hb S) gene.<sup>(2,3,5)</sup> Hb S

essentially originated in Africa and was introduced to Brazil by the forced immigration of Africans. Through interbreeding, this gene spread<sup>(1,3)</sup> and the trait (heterozygous) and disease are found in both non-whites and whites. Hb S is a mutation in the beta globin gene in which the sixth amino acid chain, glutamic acid, is replaced by valine thus changing the structure of the molecule.<sup>(2,3)</sup>

The commonest forms of SCD are: sickle cell anemia (Hb SS), Sickle-Hb C disease (Hb SC), heterozygous for Hb S and Hb C and sickle cell plus thalassemia (Hb Sβ+) in which there is an interaction of Hb S with beta-thalassemia.<sup>(3,6,7)</sup> With the sickle cell trait (Hb S), there is

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production of hemoglobin A (Hb A) and Hb S and thus this is a benign condition.<sup>(2,3)</sup>

Manifestations of SCD are due to the presence of Hb S, the molecules of which, when deoxygenated, form polymers, giving red blood cells an elongated rigid form known as "red cell sickling".<sup>(5,6)</sup> Apart from deoxygenation, a high concentration of Hb S inside the erythrocyte is necessary for the sickling of red blood cells to occur, as well as a delay in the circulation, as, if hemoglobin become oxygenated in time, the sickling disappears.<sup>(2-6)</sup> Once the cell has sickled, the red blood cell becomes rigid, the membrane proteins change and there is an increased expression of adhesion molecules. Consequently, erythrocytes adhere to the endothelium triggering an inflammatory process, activating coagulation and causing hypoxia, ischemia and local infarction, as well as a reduction in erythrocyte survival. The repercussions of these changes are the main signs and symptoms of SCD: pain, hemolytic anemia and progressive impairment of multiple organs.<sup>(2-6)</sup>

SCD is a chronic inflammatory disease permeated by painful crises,<sup>(8)</sup> leading to high morbidity and mortality.<sup>(1,2,9)</sup> The clinical manifestations affect the quality of life of patients, causing difficulties for work, study and leisure, as well as psychological repercussions such as low self-esteem.<sup>(2,10)</sup>

Faced with the severity of SCD, the Brazilian Ministry of Health has taken significant steps to improve the quality of life and increase the survival of this population. In 2001, the testing of hemoglobinopathies became compulsory (decree # 822/01) in the National Neonatal Screening Program.<sup>(11)</sup>

This national program was preceded by the Newborn Screening Program established in 1998 by the Health Department of Minas Gerais.<sup>(2)</sup> Decree 1391 of August 2005, established a national policy of comprehensive care for individuals with SCD and other hemoglobinopathies in order to structure a care network for these individuals.<sup>(12)</sup> Such measures aim to reduce morbidity and mortality in SCD. However, there are few published studies about this screening program, in particular in Minas Gerais, where the introduction of neonatal screening began more than ten years ago.

Thus, the current study aimed to epidemiologically characterize patients with SCD treated at the Regional Blood Center (BC) and University Hospital de Clínicas (UHC), to analyze the reasons for consultations and hospitalizations and to assess the causes of deaths in the period from 1998 to 2007.

## Methods

This was a retrospective cross-sectional study. The sample consisted of all SCD patients treated at BC and UHC from 1998 to 2007. The research was approved by the

Research Ethics Committee of the University (Protocol # 1060). Data were collected from June to October 2008 from the medical charts of SCD patients in BC and UHC, in two stages: the first involved evaluating the records of BC filed by diagnosis, and the second assessed the records of the medical archive service of UHC.

A total of 151 SCD patients were identified in BC. Of these, 103 were considered active, 30 inactive (five years or more without treatment in BC) and 18 had died. Of the 103 active patients, the age (in complete years), gender, ethnicity (black, mulatto or white), city of origin, diagnosis (Hb SS, Hb SC and Hb S/beta-thalassemia), and date and reason for treatment in the BC service (painful crises, infections, fever, increased pallor or jaundice, etc.) were recorded. Follow up consultations, preparation for surgery, and sessions of hypertransfusion and iron chelation were not taken into account. The medical records of the 103 patients active in the BC were also checked on the UHC system and data collected in respect to the date, reason and number of days of hospitalization and cause of death.

Of the 30 patients considered inactive, two deaths that occurred during hospitalization in the UHC were identified. Of the 18 cases of deaths that appeared in BC, 9 had occurred during hospitalization in the UHC.

Data were subjected to a simple descriptive analysis (mean, absolute frequencies and percentage).

## Results

The epidemiological profile of the SCD patients in this study included: a mean age of 17.7 years with 60.2% under 20 years old, 52.4% women, 58.2% lived in the city of Uberaba, 82.5% were Hb SS and 92.2% of the patients' records did not state the skin color (Table 1).

Of the 103 patients' records analyzed in BC, there were no reports of complications in 35. The remaining 68 patients suffered 910 complications (mean = 13.4; range: 1-97). The most common reason for consultations was afebrile painful crises in 61.9% of the cases (Table 2).

Eighty-three of the 103 medical records of active patients in BC were also located on the UHC system, with a total of 589 admissions corresponding to an average of 7.1 hospitalizations for each of these SCD patients (range: 1-51) in the period from 1998 to 2007. Hospitalization time ranged from one to 51 days with a mean of 6.2 days. The most common reason for hospitalization (25.3%) was afebrile painful crises, followed by lower respiratory tract infection in 12.4% of cases (Table 3). It is worth mentioning that 80% of the patients without history of complications in BC and 60% of those not hospitalized in UHC were under 10 years old.

Of the 11 deaths that occurred during hospitalization in UHC, the mean age was 33.5 years (range: 6-50 years old - mean: 33.7 years old for adult males and 46.5 years old for

Table 1. Epidemiological characteristics of sickle cell disease patients treated at the Regional Blood Center and University Hospital de Clinicas in Uberaba in the period 1998 to 2007

Characteristic	n	(%)
Age (years)		
0 to 9	32	31.0
10 to 19	30	29.2
20 to 29	23	22.3
30 to 39	9	8.8
40 to 49	8	7.7
50 to 59	1	1.0
Gender		
Male	49	47.6
Female	54	52.4
Skin color		
Black	5	4.9
Mulatto	2	1.9
White	1	1.0
Not stated	95	92.2
Origin		
Uberaba	60	58.2
Araxá	13	12.6
Frutal	5	4.8
Uberlândia	4	3.9
Others	21	20.4
Diagnosis		
Hb SS (AF)	85	82.5
Hb SC	15	14.6
Hb S/ B thalassemia	2	1.9
Not stated	1	1.0
<b>Total</b>	<b>103</b>	<b>100</b>

Table 2: Reasons of treatment for complications of sickle cell disease patients at the Regional Blood Center in Uberaba in the period 1998 to 2007

Reasons for treatment	n	%
Afebrile painful crisis	563	61,9
Pain and/or infection of ulcer	74	8,2
Upper airway infection	73	8,0
Gastro-intestinal disorders	35	3,8
Fever	24	2,6
Febrile painful crisis	23	2,5
Priapism	21	2,3
Cough	14	1,5
Drop in hemoglobin	11	1,2
Lower airway infection	10	1,1
Urinary tract infection	7	0,8
Increased jaundice	7	0,8
Dyspnea	3	0,3
Liver enlargement	2	0,2
Reason of visit not stated	13	1,4
Other reasons	30	3,4
<b>Total</b>	<b>910</b>	<b>100</b>

adult females). Only one child, a 6-year-old female, died. The cause of death of six patients (54.5%) was multiple organ and system failure (Table 4).

Table 3: Reasons and time of hospitalization of SCD patients at the University Hospital de Clinicas in Uberaba in the period 1998 to 2007

Reason for hospitalization	n	%	Mean hospital stay	Range of hospital stay
Afebrile painful crisis	149	25.3	3.7	1-11
Lower Airway Infection	73	12.4	8.6	2-27
Febrile Painful Crisis	67	11.4	6.1	2-16
Upper Airway Infection	60	10.2	5.7	1-14
Urinary tract infection	28	4.7	6.3	2-12
Fever	23	3.9	5.1	2-9
Gastrointestinal disorders	21	3.6	5.3	2-23
Surgical procedures	21	3.6	7.4	4-15
Cholecystectomy	10	1.7	8.4	4- 15
Splnectomy	10	1.7	6.7	5-14
Appendectomy	1	0.2	5.0	5
Splenic sequestration	19	3.2	6.0	3-11
Liver complications	19	3.2	3.9	2-10
Cerebral complications	12	2.0	10.4	2-42
Stroke	7	1.1	11.1	2-42
Cerebellar syndrome	1	0.2	8.0	8
Meningitis	1	0.2	23.0	23
Seizure	3	0.5	5.3	3-8
Other infections	10	1.7	7.8	2-24
Cholelithiasise	9	1.5	5.6	2-22
Obstetric/gynecologic reasons	8	1.4	10.8	3-25
Priapism	7	1v2	5.1	2-11
Osteoarticular complications	7	1.1	20.3	3-51
Other reasons *	56	9.5	8.4	1-35
<b>Total</b>	<b>589</b>	<b>100</b>	<b>6.2</b>	<b>1-51</b>

\* Other reasons: dactylitis, acute chest syndrome, infection of ulcer, decompensated congestive heart failure, postoperative complications, sepsis syndrome, jaundice, dehydration, surgical procedure but it was cancelled, coagulation disorders, aplastic syndrome, transfusion reaction, hydroxyurea poisoning, Trauma, Dengue fever, performing examinations for iron chelation

## Discussion

Although there are few studies on life expectancy in Brazil, this work suggests that SCD patients die prematurely as most patients were less than 30 years old (82.5%) and very few were over 40 (8.7%). On the other hand, the high prevalence of under 10-year-old children (31%) and only one death in this age group may reflect the efficacy of neonatal screening and subsequent preventive measures offered to these children; the morbidity and mortality have reduced and the life expectancy increased.<sup>(13)</sup> In a study from Jamaica,<sup>(14)</sup> the median survival was 53 years for men and 58.5 for women with sickle cell anemia (SCA). An investigation in North America<sup>(13)</sup> compared the survival of patients diagnosed after 3 months of age and newborns over a 9.4 year study period; the mortality rates were 8% and 1.8%, respectively. This highlights the importance of neonatal screening.

The higher prevalence of females (52.4%) reflects the profile of the Brazilian population that has a slight predominance of women (50.8%).<sup>(15)</sup>

The almost non-existent recording of patients' race in BC shows the inattention that the clinical staff has with an important epidemiological aspect; SCD is a disease inherited

Table 4. Causes of death according to the death certificate of sickle cell disease patients hospitalized at the University Hospital de Clínicas in Uberaba in the period 1998 to 2007

Year	Age	Cause of death	Due to/as a consequence of	Due to/as a consequence of
2001	34	Cardiogenic shock	Congestive heart failure	Acute lithiasic cholecystitis
2002	6	Stroke	Sickle cell anemia	
2003	34	Multiple organ failures	Decompensated liver disease	
2003	46	Multiple organ failure	Sepsis	Pneumonia
2003	33	Acute respiratory failure	Pneumonia	Sickle cell anemia
2005	47	Multiple organ failure	Anoxic encephalopathy	Stroke
2005	23	Septic shock	Complicated cholecystitis	SC Hemoglobinopathy
2006	50	Multiple organ failure	Sepsis	Toxic epidermal necrolysis
2006	23	Septic shock	Sepsis	Acute cholecystitis
2007	30	Multiple organ failure	Disseminated intravascular coagulation	Sickle cell anemia
2007	43	Multiple organ failure	Sickle cell anemia	

from the black population. However, in a study developed in Brazil, Cunha (personal communication) showed that 45.9% of sickle cell trait carriers are characterized as white, 33.9% mulattos and only 21.0% black, even though 89.0% of the population reported Black ancestry. It has been shown that, because of the high degree of miscegenation in Brazil, ethnic characterization of the population is difficult.<sup>(16)</sup> A total of 41.7% of patients with SCA came from other cities, as Uberaba is a referral center for at least 22 municipalities. The predominance of SCA (82.5%) compared to the other types of sickle cell disease is consistent with other national studies.<sup>(3,17)</sup>

It should be noted that BC is the first institution in which patients with SCA in Uberaba are treated when they suffer complications and only the most serious cases are referred to UHC. Our findings that 80% and 60% of patients that had no history of complications in BC and UHC, respectively were under 10 years old may reflect the early diagnosis and preventive measures. These measures comprise continuous education of the patient and family, extra vaccinations for diseases included in the national immunization program, prophylactic antibiotic therapy and regular outpatient consultations.<sup>(13)</sup>

Painful crises are one of the most characteristic manifestations of SCD.<sup>(2,8,18)</sup> In this study, febrile or afebrile painful crises were the most frequent reason for treatment in BC (64.4%) and for hospitalization (36.7%). Pain is the result of obstruction of the microcirculation caused by the sickling of red blood cells and fever may be secondary to the pain, probably as a result of tissue ischemia and release of endogenous pyrogens, which is not always due to an infection.<sup>(2,5,6,19)</sup> According to Serjeant, the severity of pain varies greatly, ranging from mild and transient episodes (5 to 10 min) to those that last for hours or days and require hospitalization.<sup>(8)</sup> Hospital stays for painful crisis ranged from one to 16 days with means of 3.7 and 6.1 days for

afebrile and febrile episodes, respectively. In under 5-year-old children, dactylitis - a painful crisis of hands or feet due to the inflammatory process initiated by bone marrow necrosis in the distal portions of the extremities - can be the first manifestation of the disease.<sup>(6,8,19)</sup> In this study, dactylitis was the cause of six hospitalizations with an average of 5.8 days in hospital.

Splenic dysfunction is the main cause of the increased susceptibility of SCD patients to infection. This is the result of autosplenectomy caused by recurrent splenic infarctions

because of the blood circulation peculiar to the organ that favors local sickling and tissue hypoxia thereby facilitating local infectious.<sup>(2,6,8,18)</sup> Consequently, infectious complications are common, severe and are an important cause of mortality, especially in children.<sup>(2,6,7,18)</sup> In our study, 31% of hospital admissions were due to infections with an average of ten days of hospitalization. Meningitis was the cause of hospitalization with the longest mean hospital stay (23 days).

At least ninety of the consultations in BC were for infections. In our study, septic shock was the cause of two (18.2%) of 11 deaths with another two (18.2%) related to sepsis, thus a total of 36.4% of deaths were caused by infection. In a study on the death of 52 children, infection was the cause of 19 deaths (36.5%) and splenic sequestration in 17 (32.7%).<sup>(20)</sup> In another study of 78 SCD children who died, infection was the cause in 30 (38.5%) and splenic sequestration in 13 (16.6%).<sup>(21)</sup>

Splenic sequestration is a major complication of SCD with rapid and progressive drops in hemoglobin and, not infrequently, a course to fatal hypovolemic shock if the condition is not treated quickly.<sup>(2,7,8,22)</sup> Splenectomy is indicated after two attacks of sequestration or after the first severe episode.<sup>(2,7,22)</sup> In this series there were 19 hospitalizations of 13 patients for splenic sequestration with a mean of 6.0 days. Ten patients underwent splenectomy with ages between 8 months and 27 years (mean 5.9 years). Despite the severity and high mortality reported, no deaths due to splenic sequestration or splenectomy were identified. The 27-year-old splenectomized patient had Sickle-Hb C disease and the other nine had SCA.

SCD patients are prone to developing gallstones.<sup>(2,7,23)</sup> In a comprehensive review of the literature on cholelithiasis in SCD,<sup>(24)</sup> four of seven authors indicated cholecystectomy in patients with asymptomatic cholelithiasis to prevent possible complications such as choledocholithiasis,

pancreatitis, perforation of the gallbladder, bile peritonitis and sepsis. The other three authors indicated the procedure only in symptomatic patients. In our study, three deaths were related to complications resulting from cholecystitis and nine patients were hospitalized for cholelithiasis, a number that may be underestimated due to the variable symptomatology of this complication. Abdominal pain may be attributed to vasoocclusion, cholecystitis or other complications and symptoms such as nausea and vomiting may be related to other gastrointestinal disorders.<sup>(7,23)</sup> Over ten years, ten cholecystectomies were performed in UHC due to SCD. These patients were hospitalized for an average of 8.4 days and no deaths occurred related to the procedure. Two other studies reported up to 25% of deaths of patients after cholecystectomy.<sup>(23,24)</sup>

Strokes are one of the most serious complications of SCD.<sup>(2,7)</sup> In one review article on central nervous system complications,<sup>(25)</sup> SCA was identified as the most common cause of strokes in childhood with an incidence of from 5% to 10% of under 17-year-old SCD patients. A Brazilian study found that 9% of deaths involved the brain.<sup>(26)</sup> In our study, seven patients were hospitalized due to strokes, with hospital stays ranging from 2 to 42 days, and two patients died (18.18%).

With a total of seven hospitalizations, osteoarticular complications, including femoral head necrosis, septic arthritis, osteomyelitis and bone infarction, were the reason for the second longest mean hospital stay (mean 20.3 days; range: 3 to 51 days) in this study. These complications result from vasoocclusion and progressive degeneration of blood vessels in bone with osteonecrosis of the femoral head affecting 10% to 30% of SCD patients.<sup>(27)</sup>

Priapism is a prolonged and painful penile erection not accompanied by sexual stimulation.<sup>(2,7,8)</sup> It affects 20% to 38% of SCD patients and is responsible for high rates of impotence (> 50%), even when treated.<sup>(8,28)</sup> Episodes of priapism were responsible for 21 visits to BC and seven hospitalizations in UHC with an average stay of 5.1 days.

Leg ulcers are common in SCD adults with a mean incidence of 25%; they can be spontaneous or the result of trauma.<sup>(2,5,6,29)</sup> Recurrence occurs in 25% to 50% of cases after medical treatment and often become chronic.<sup>(7)</sup> Pain or infection of the ulcer was the second leading cause of complications in BC (8.2%). It is noteworthy that 81.1% of these visits were just by one single patient. Infection of ulcers was the cause of six hospitalizations with an average stay of 9.3 days.

In a study on hospitalization for complications associated to SCD<sup>(9)</sup> the median hospital stay was 5.0 days in Bahia and Rio de Janeiro and 4.0 days in Sao Paulo. In this study the average stay was 6.2 days, which is justified by an efficient emergency service in BC; the patient is treated and observed for up to 12 hours, and hospitalizations occur only with severe complications.

In a Brazilian study on mortality due to SCA, 75% of deaths occurred by the age of 27.8 years.<sup>(1)</sup> In another Brazilian study, the median age of cases that progressed to death was 26.5 years in Bahia, 31.5 years in Rio de Janeiro and Sao Paulo 30.0 years.<sup>(9)</sup> In this study, the mean age at death was 33.5 years if only adults are considered; for women it was higher (46.5 years) with the majority due to acute events. These findings are similar to those described in published reports that show a trend towards higher survival rates for women.<sup>(14)</sup>

## Conclusions

In summary, painful crises were the commonest reason for treatment in BC and for hospitalization in UHC. The epidemiological profile shows the predominance of children and young adults, women and the SS genotype. The high treatment rates in BC and hospitalizations in UHC, the 11.82% death rate over 10 years and the low mean age at death confirm the high morbidity and mortality associated to SCD. However, the large number of under 10-year-old children without reports of complications or hospitalizations and the occurrence of only one death in this age group reflect the effectiveness of preventive measures offered by the early diagnosis of SCD.

## Resumo

*A alta morbimortalidade referida na doença falciforme (DF) levou-nos a estudar o perfil epidemiológico e respectivas intercorrências clínicas dos pacientes atendidos no Hemocentro Regional (HR) e Hospital de Clínicas da Universidade (HC-U), de 1998 a 2007. Estudo retrospectivo de 151 pacientes, avaliados quanto a: idade, gênero, cor da pele, procedência, diagnóstico, causa de atendimento no HR, causa e tempo de internação no HC-U e a causa e a idade em caso de óbito. Foi realizada análise estatística descritiva simples. A média de idade foi de 17,7 anos, 52,4% eram do gênero feminino, 58,2% procediam da cidade de Uberaba e em 92,2% dos prontuários não foram encontrados relatos sobre a cor da pele. A anemia falciforme representou 82,5% dos casos. Dos 910 atendimentos no HR e 589 internações no HC-U, a crise dolorosa afebril foi a causa mais frequente em ambas as instituições (61,9% e 25,3%, respectivamente). A idade média dos 11 óbitos foi de 33,5 anos, sendo apenas um em menor de 10 anos e a falência de múltiplos órgãos a causa mais frequente. O perfil epidemiológico mostra predomínio de crianças e adultos jovens, sexo feminino e genótipo SS. As taxas de internação no HC-U, de atendimento no HR e a baixa média de idade ao óbito confirmam a alta morbidade e mortalidade da DF. Contudo, o grande número de crianças sem intercorrências e/ou internações reflete a eficácia das medidas preventivas propiciadas pelo diagnóstico precoce implantado nos últimos 10 anos.*

**Descritores:** Anemia falciforme; Morbidade; Mortalidade

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