SICKLE CELL ANEMIA: DELAYED DIAGNOSIS IN BAHIA, BRAZIL - A LARGELY AFRO-DESCENDANT POPULATION

Angela Maria Dias Zanette, MD; Marilda de Sousa Gonçalves, PhD; Regina Célia Santos Bahia, MD; Luciana Vasconcelos Araujo Nogueira, MD; Sérgio Marcos Arruda, MD

Hemoglobinopathies are the most common genetic disorders in the world and include sickle cell anemia (SCA), which is a public health problem in Brazil. Nevertheless, the disease is highly unknown among health professionals, and delayed diagnosis constitutes an important cause of concern for caretakers of SCA patients. The purpose of this study was to compare the clinical and laboratory history of SCA patients whose diagnosis was established during the first year of life to those of other SCA patients who had delayed SCA diagnosis. Demographic, clinical, and laboratory data were all reviewed from 99 steady-state SCA patients who were followed in a public hematology and hemotherapy clinic in Salvador, Brazil. The patients were aged ≥12 years and attended the outpatient unit at least once from November 2008 to June 2009. The data were analyzed in 2010. For all patients, the mean age (± SD) at diagnosis was 12.7(± 12.1) years, ranging from 0 to 47 years. Mean age was higher in patients whose SCA diagnosis was established after age 5 (32.9 ± 11.9 years, P=.005). Increased unconjugated bilirubin, stroke and splenic sequestration were more prevalent in patients who were diagnosed in the first year of life (P=.043, .024 and .026 respectively).

The data suggest that stroke, splenic sequestration and unconjugated bilirubin level may be influenced by age at SCA diagnosis. (*Ethn Dis*. 2011;21(2):243–247)

Key Words: Sickle Cell Anemia, Sickle Cell Disease, Hemoglobinopathy, Delayed Diagnosis

From Outpatient Unit, Hematology and Hemotherapy Center of Bahia, Brazil (AMDZ, RCSB, LAVN) and Gonçalo Muniz Research Center, Fiocruz Foundation, Bahia, Brazil (MdSG, SMA).

Address correspondence to Angela Zanette, MD; Alameda dos Umbuzeiros; 510 – Caminho das Arvores; Salvador, Bahia, Brazil; CEP 41820680; +55 (71) 3116-5675; +55 (71) 3116-5680 (fax); angelazanette@gmail.com

INTRODUCTION

Sickle cell disease (SCD) constitutes a group of diseases characterized by the presence of hemoglobin S; the homozygous form, SS, is called sickle cell anemia (SCA).[1] This mutant hemoglobin, in which a glutamic acid residue is replaced by a valine at position 6 of the beta globin chain, can combine with other abnormal hemoglobin molecules; the double heterozygous form is known as SC hemoglobinopathy.[1] Under low oxygen pressures, hemoglobin S polymerizes inside red blood cells (RBC), which assume a sickle shape that obliterates small vessels. Chronic hemolysis and vaso-occlusive phenomena characterize the disease. Ischemia and inflammation resulting from recurrent vaso-occlusive episodes cause the associated painful crises and progressive failure of multiple organs and systems.[1,2] A higher prevalence of the hemoglobin S gene occurs in Equatorial Africa, where it can exceed 20% in countries such as Uganda, Zaire and Cameroon.[3] In Brazil, the hemoglobin S gene was introduced through African slave traffic, which was utilized mainly in the sugar cane trade between the 16th and 18th centuries.[4] The S gene is heterogeneously distributed all over the country but predominately appears in the northeast region. Salvador, the largest city in the northeast Brazilian region (around 3,000,000 people), is the capital of the state of Bahia.[5] It was one of the main Brazilian ports through which African slave ships arrived. Today, Bahia's population has the largest percentage of Blacks outside of Africa.[5]

In Brazil, SCD was recognized by the government health authority as an important public health issue in 1996 through the creation of a Sickle Cell Anemia Program. In 2001, neonatal screening for hemoglobinopathies was implemented by the Brazilian Health Ministry. Since then, the results of neonatal screening have shown that in Bahia, 1 in 650 children are born each year with SCD, a higher prevalence than any other state.[6,7] Despite the high prevalence of SCD in Bahia, patients who were born before 2001 were frequently not diagnosed until adolescence or even later in life. This article compares the clinical outcomes of SCD patients who were diagnosed in the first year of life with those who were diagnosed later in life.

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PATIENTS AND METHODS

This is a retrospective study, undertaken at an outpatient unit of a public hematology and hemotherapy clinic, which is a referral center for hemoglobinopathies, in Salvador, Bahia, Brazil. Among children and adults, there are more than 2000 registered patients with hemoglobin diseases, and most of them have sickle cell anemia (SCA). Ninety-nine steady state SCA patients, who were aged ≥12 years and attended the

Table 1. Main patient's clinical and laboratory data

Variables	Sickle Cell Anemia (*N*=99)			*P*
	Diagnosis during first year of life (*n*=15)	Diagnosis between 13 and 60 months of life (*n*=26)	Diagnosis after 60 months of life (*n*=58)	
Sex,*n*; m/f	12/3	14/12	21/37	
Chronologic age, years	23.9±5.6	27.4±9.5	32.9±11.9	.005*
Age at diagnosis, years	–	2.9±1.4	20.4±10.2	
Hemoglobin, g/dL	8.0±1.1	8.7±1.3	8.2±1.5	.185
White blood count, /mm^3	14150±6038	11127±4209	11353±3802	.073
Neutrophils, /mm^3	6743±2432	6043±3200	6345±2912	.789
Platelets, /mm^3	413071±178904	379360±86329	399018±166149	.779
Reticulocytes, %	9.6±8.3	6.6±3.4	7.5±4.2	.593
Lactate dehydrogenase, U/L	1001.4±388.1	607.9±22.4	821.3±585.9	.106
Fetal hemoglobin, %	6.8±4.4	7.6±4.4	8.5±5.9	.593
AST, U/L	47.7±20.6	48.0±18.2	48.1±21.5	.979
Unconjugated bilirubin, mg/dL	3.8±2.3	2.5±2.4	2.1±1.6	.043*
Creatinin, mg/dL	0.6±0.2	0.6±0.2	0.7±0.4	.346
Ferritin, ng/mL	411.6±531.5	316.7±294.3	395.9±357.7	.657
Stroke, *n* (%)	4/15 (26.6)	4/26 (15.4)	4/58 (6.9)	.024*
Osteonecrosis, *n* (%)	1/15 (6.6)	6/26 (23.0)	8/58 (13.8)	.211
Splenic sequestration, *n* (%)	2/15 (13.3)	1/26 (4.0)	0	.026*
Retinopathy, *n* (%)	1/15 (6.6)	0	8/58 (13.8)	.088
Cardiopathy, *n* (%)	0	2/26 (7.6)	9/58 (15.5)	.109
ACS, *n* (%)	0	1/26 (3.8)	2/58 (3.4)	.839
Leg ulcer, *n* (%)	7/15 (46.6)	5/26 (19.2)	21/58 (36.2)	.137
Cholelithiasis, *n* (%)	6/15 (40)	13/26 (50.0)	30/58 (51.7)	.582
Priapism, *n* (%)	2/12 (13.3)	2/14 (14.3)	4/21 (19.0)	.869
Pulmonary hypertension, *n* (%)	0	1/26 (3.8)	2/58 (3.4)	.600
Renal disease, *n* (%)	1/15 (6.6)	0	7/58 (12.0)	.266
Transfusional hemosiderosis, *n* (%)	2/15 (13.3)	2/26 (7.7)	3/58 (5.2)	.504
Hydroxyurea, *n* (%)	0	4/26 (15.4)	5/58 (8.6)	.251

Data shown are mean ± SD unless noted otherwise.
* Significant at <.05.
AST: aspartate aminotransferase; ACS: acute chest syndrome.

clinic for at least one hematologic consultation between November 2008 and June 2009, were enrolled in the study. Clinical, laboratory, and transfusional records of all patients were assessed. Before data collection, participants provided informed written consent. The study was approved by the Ethics Committee of the Bahian Foundation for Sciences Development under protocol no. 47/2007.

Statistical Analysis

The statistical software SPSS version 15.0 was used for data management and analysis. Differences among clinical outcomes were analyzed by the chi-square test, and the Fischer exact test was applied whenever there were less than five observations. The Student *t* test was used for continuous variables with normal distributions, such as hemoglobin, white blood count, and platelets. The Kruskal-Wallis test was used to compare means among two or more groups when analyzing continuous variables with non-normal distributions, such as fetal hemoglobin. Multivariate analysis was not performed. A $P \leq .05$ was considered statistically significant.

RESULTS

All 99 patients from the study had SCA, and 52 were female (52.5%). The majority lived in Salvador, the capital of Bahia, Brazil (49.5%), whereas 11.1% lived in adjacent cities and 39.4% lived in the countryside.

Patient ages varied from 12 to 63 years with a mean ± SD of 30.2 ± 10.8 years; the mean age at diagnosis was 12.7 ± 12.1 years and ranged from 0 to 47 years. In males, the mean age at SCA diagnosis was 9.4 ± 11.3 years, while in females it was 15.8 ± 12.1 years, a statistically significant difference (P=.009). The majority were diagnosed following an acute event.

According to the age at SCA diagnosis, the patients were divided into 3 groups: 1) diagnosis in the first year of life (n=15); 2) diagnosis between age 13 and 60 months (n=26); and 3) diagnosis after age 60 months (n=58). The mean age at SCA diagnosis was 2.9 ± 1.4 years in group 2 and 20.4 ± 10.2 years in group 3. Given that all patients in group 1 had the disease diagnosed during the first year of life, the mean age at diagnosis was not calculated for that group. Table 1

summarizes the main clinical and laboratory data.

The mean age was higher in group 3 (32.9 ± 11.9 years) compared to the mean ages of the other two groups (23.9 ± 5.6 years in group 1 and 27.4 ± 9.5 years in group 2), which was a statistically significant difference (P=.005). The following values were not significantly different between the 3 groups of SCA patients: hemoglobin, white blood count, neutrophils, platelets, reticulocytes, lactate dehydrogenase, fetal hemoglobin, alanine aminotransferase, creatinin, and ferritin. The mean unconjugated bilirubin level was significantly higher in group 1 patients (P=.043), as shown in Table 1.

Splenic sequestration crises occurred in two patients from group 1, one from group 2 and in no patients from group 3, which was a statistically significant difference (P=.026). Differences in other complications, such as acute chest syndrome (ACS), leg ulcers, cholelithiasis, pulmonary hypertension, renal and cardiac disease, retinopathy, priapism, and transfusional hemosiderosis, did not reach statistical significance based on the patient's age at SCA diagnosis. The use of hydroxyurea also did not show a statistical difference among the 3 groups of patients.

When SCA diagnosis was established in some female patients, they already had one or more pregnancies with or without miscarriages, premature deliveries or other gestational complications.

DISCUSSION

Living in Salvador, the capital of Bahia in Brazil, or in nearby cities did not result in access to an early diagnosis of SCA in 59.7% of cases, even though the referral centers for the diagnosis and management of SCD in Bahia were located in Salvador. Neonatal screening has shown a high prevalence of hemoglobinopathies in Brazil, especially SCA.[6] Nevertheless, the unfamiliarity of health professionals with the disease remains an important cause of delayed diagnosis of SCA in Bahia. This Brazilian state is largely populated with people of African descent.[5] When Paiva e Silva, Ramalho and Cassoria studied 80 SCA patients from another Brazilian state who were aged 18 to 44 years, they showed that the majority of these cases were diagnosed in adolescence or in early adult life.[8] Hutz's study indicated that the mean survival of Brazilian SCA patients was 16.4 ± 12.1 years.[9] More recent studies have estimated a mean survival of these patients at 45 to 55 years in North America, Europe and Jamaica.[10] In the present study, the oldest patient was aged 63 years. The available data does not allow the determination of a longer survival tendency in SCA patients in Bahia as well. Serjeant et al published a study of 102 SS patients in Jamaica, who were all aged >60 years, in which the longest survival was associated with female sex and a higher fetal hemoglobin level.[11]

Recurrent splenic vaso-occlusive episodes lead to early functional asplenia, which compromises immunity against some encapsulated bacteria particularly between ages of 0 and 5 years, in SCA patients.[12] Penicillin prophylaxis in patients aged 2 months to 5 years, in addition to anti-pneumococcal, haemophilus influenzae type b and meningococcal vaccines, have decreased the mortality of SCA children.[13] Patients whose disease is diagnosed late are deprived of these prophylactic measures, which places them at high risk for sepsis caused by these infectious agents.

In our study, splenic sequestration crises were significantly more prevalent in SCA patients who were diagnosed during the first year of life. Fernandes et al conducted a study on mortality in SCD, and splenic sequestration was responsible for one-third of the deaths and caused 71.8% of them occurring in children who were aged <2 years.[14] That study was conducted in Minas Gerais, which was the first Brazilian state to establish a neonatal screening program to detect abnormal hemoglobins in 1998; the deaths occurred in hospitals, at home, or on the way to the hospital. Our data are consistent with the literature. Considering the absence of splenic sequestration in patients from group 3, whose SCA diagnosis was established after age 5 years, this observation could suggest that SCA patients in Bahia who had splenic sequestration crises died without an SCA diagnosis.

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In our sample, stroke occurred more frequently in patients who were not diagnosed until 12 months of age. Ohene-Frempong et al reported that approximately 11% of SCD patients have clinically apparent strokes before aged 20 years, with a higher risk in the first decade of life.[15] The highest incidence of stroke among these patients occurred between ages 2 and 5 years, followed by a slightly lower incidence from 6 to 9 years.[15] Transcranial Doppler (TCD), which is used to determine the velocity of cerebral arterial flow, has emerged as a valuable tool in stroke risk evaluation in SCA.[16] Patients who are at high risk for cerebral vascular events as determined by TCD must be included in a hyper-transfusion schedule as established in the STOP study.[16] A schedule for periodic TCD evaluation should be initiated by age 2 years. Taking into account that risk for stroke in SCA is higher in the first decade of life, particularly between ages 2 and 5 years, it becomes evident that, in Bahia, many patients would not have access to proper medical care because of delayed hemoglobinopathy diagnosis.

In our patients, the SCA diagnosis occurred later in the female group, reaching statistical significance. A possible explanation is that iron deficiency anemia (IDA) is more prevalent among women and is considered normal by some physicians. As a consequence, female SCA patients in Bahia might be maintained for longer periods on iron supplementation, with an incorrect diagnosis of IDA. This assertion needs to be confirmed by epidemiological studies that are specifically designed for that purpose. In the present study, 100% of patients were prescribed iron supplements before SCA diagnosis, independent of age, sex and iron status. Iron deficiency is uncommon in SCA; the increased iron absorption from the digestive system and from hemolyzed RBC iron recycling, as well as iron from blood transfusions, provides sufficient quantities for SCA patients.[17]

According to Tran et al, periodic evaluation for early retinopathy should be initiated by ages 6 and 13 years in SS and SC patients, respectively.[18] In our study, there were cases whose first manifestation of the disease was visual deficit, which required medical assistance. Delayed diagnosis of SCD prevented the implementation of early multidisciplinary care in these patients.

Renal dysfunction begins in infancy in a significant percentage of patients with SCA, although chronic renal insufficiency rarely develops in children with the disease.[19] Marsenic, Couloures and Wiley's study reports that total proteinuria was increased in 46% of SS patients as young as age 3, suggesting that renal damage occurs very early in SCD.[20] The late diagnosis of the disease does not allow preventive measures, such as the use of angiotensin-converting enzyme inhibitors, hydroxyurea, or exchange-transfusion, to be adopted in a timely manner. These measures are valuable tools for preventing or delaying renal dysfunction in SCD.[21–23]

In our study, higher unconjugated bilirubin levels occurred in patients whose SCA diagnosis was established during the first year of life, and this was significantly different from patients who were diagnosed later on. Passon et al, studying 115 North American children with SCA, reported that genetic variations in the uridine diphosphate-glucuronosyltransferase 1A (UGT1A1) promoter significantly influences serum bilirubin levels and the development of symptomatic cholelithiasis.[24] Another study of Jamaican SCA patients showed a highly significant relationship between UGT1A1 polymorphisms and bilirubin levels, despite the less significant association with gallstone formation.[25] In our groups of patients, cholelithiasis prevalence did not reach statistical significance regardless of the bilirubin level and age at SCA diagnosis. More recently, Vilas-Boas et al, studying Brazilian SCA patients, reported a positive and significant association between serum arginase concentrations and laboratory markers of hemolysis, which include unconjugated bilirubin.[26] In that study, arginase was associated with an increased expression of TGF-beta, suggesting that clinical outcomes of SCA patients are complex and influenced by several genetic and acquired factors.[26]

Another cause of concern in our patients is that some SCA patients had one or more pregnancies, with or without obstetrical or hematological complications and without hemoglobinopathy diagnosis. The literature has shown that SCD is associated with a significant risk for complications during the gestational period; this explains why SCD guidelines recommend that pregnant patients be followed in high-risk prenatal care units.[27–29]

The multidisciplinary management of SCD patients has shown considerable impact on reducing morbidity and mortality. Frempong and Pearson's study, which compared the mortality rates in SCD patients aged <15 years before and after the institution of neonatal screening and multidisciplinary assistance, demonstrated that these programs contributed to a remarkable reduction in mortality.[30]

Although some patients in the present study may have had late SCA diagnosis because of less severe disease, the identification of a SS homozygote as late as age 47 years denotes an evident failure of the health system in Bahia.

The present study has limitations, such as its retrospective design and small number of patients. Furthermore, an underestimation of the complications, such as pulmonary hypertension, retinopathy, and osteonecrosis, cannot be excluded considering that some laboratory and imaging tests were performed at different medical clinics, some of which may not have had the necessary expertise to successfully diagnose these complications. Nevertheless, this study addresses a relevant issue given the recent neonatal screening data from Bahia. In a region where one out of 650 newborns has a hemoglobinopathy, mostly SCA, the diagnosis of patients who were born when such neonatal diagnostic testing was not available is equally important and is a highly relevant public health issue. Increasing the survival and quality of life for SCD patients demands high-quality, comprehensive health assistance. Despite some official initiatives for implementing permanent SCD education for Brazilian health professionals by the national and/or local health authorities, there still remains a lot of work to be done.

CONCLUSION

The data suggest that age at SCA diagnosis, among other genetic and acquired factors, might influence SCA clinical outcomes. Recent neonatal screening data in Bahia, Brazil, demonstrated that improving SCA care is an important issue for Bahian public health authorities.

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AUTHOR CONTRIBUTIONS

Design concept of study: Zanette, de Sousa Gonçalves, Bahia, Nogueira, Arruda

Acquisition of data: Zanette, de Sousa Gonçalves, Bahia, Nogueira, Arruda

Data analysis and interpretation: Zanette, de Sousa Gonçalves, Bahia, Nogueira, Arruda

Manuscript draft: Zanette, de Sousa Gonçalves, Bahia, Nogueira, Arruda

Statistical expertise: Zanette, de Sousa Gonçalves, Bahia, Nogueira, Arruda

Administrative: Zanette, de Sousa Gonçalves, Bahia, Nogueira, Arruda