Clinical and demographic characteristics of sickle cell disease in Colombian children

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ABSTRACT

Introduction: To describe the clinical and demographic characteristics of pediatric patients with sickle cell disease.

Material and methods: A descriptive observational study was performed. Included were patients under 18 years with a diagnosis of sickle cell disease, who joined the "Ruta de la Vida" Program at the Hospital Universitario del Valle from February 2015 to October 2018. The data was analyzed with descriptive statistics in SPSS.

Results: Reviewed were 153 medical records corresponding to pediatric patients. 54.2% were male and 45.8% female. All the patients were from the Pacific Colombian Region. The median age of the patients at the time of diagnosis was 2.1 years, and the median age of admission to the program was 9 years. Diagnosis by electrophoresis of hemoglobin was performed in 92.2% of the patients, the distribution of polymorphisms was: hemoglobin SS (72.3%), hemoglobin SC (19.9%), hemoglobin Sβ+ (5.0%) and hemoglobin Sβo (2.8%). 76.9% of patients had crises in the last year, the main crises were pain and hemolysis. 6.1% of the patients had cerebrovascular disease diagnosed by cerebral magnetic resonance imaging.

Conclusion: The population studied has sickle cell disease with characteristics of a severe phenotype, with a high frequency of crisis and chronic complications such as cerebrovascular disease. This is the first study conducted in Colombia that describes the characteristics of the pediatric population with sickle cell disease.

Keywords: sickle cell anemia, sickle cell disease, sickle cell crisis, pediatrics, hemoglobin S

INTRODUCTION

Sickle cell disease is the most common hemoglobinopathy in humans, and hemoglobin S (Hb S) is the most common monogenic disorder. It is associated with high rates of complications leading to disability and death. The symptoms can be acute from an early age or chronic with sequelae on white organs in the long term; these manifestations can be controlled, or sometimes avoided, by reducing the factors that trigger the crisis and the early management of complications. The integral approach has increased the survival of a more significant percentage of patients during the pediatric age. However, in many cases, adulthood is reached with some degree of disability or sequelae [1–5].

Sickle cell disease has a high impact on public health in Colombia, especially in the Afro-descendant population concentrated in the coastal areas of the country [6]. The Hospital Universitario del Valle (HUV) is a referral center for these patients, where the "Ruta de la Vida" Program has established routes that allow early and adequate intervention, improve treatment adherence, and reduce complications [7]. The population that integrates the "Ruta de la Vida" Program was included in this study to describe the clinical and demographic characteristics of pediatric patients with sickle cell disease.

So far, no descriptions of sickle cell anemia have been found in Colombian pediatric patients. This study seeks to determine the behavior of sickle cell disease and the characteristics of the affected population as a starting point for the construction of early detection and monitoring programs.

MATERIAL AND METHODS

Type of study

A descriptive observational study was performed.

Inclusion criteria

Included were patients under 18 years diagnosed with sickle cell disease with clinical suspicion and/or confirmation by hemoglobin electrophoresis who joined the "Ruta de la Vida" Program at the HUV from February 2015 to October 2018.

Variables

Variables measured were demographics (department and city of origin, gender, age of diagnosis, age of admission in the program, and number of siblings) and clinical variables (type of hemoglobin, symptoms at the time of diagnosis, type of crisis, cardiac alterations, degree of anemia, ferritin level, presence of visceromegalies, presence of biliary lithiasis, presence of cerebrovascular event, presence of bone necrosis of the hip, alterations in transcranial Doppler, number of transfusions, vaccination status and type of treatment).

Data analysis

The data was analyzed in the SPSS Statistics program. The qualitative variables (nominal and ordinal) were shown in proportions and absolute numbers, and the quantitative variables (continuous and discrete) in medians and interquartile ranges, considering the normality analysis.

Ethical considerations

All the principles of ethics in national and international research were fulfilled.

RESULTS

Included were 153 patients diagnosed with sickle cell disease in the "Ruta de la Vida" Program of the HUV in Cali, Colombia. Most of them were male (83 patients, 54.2%). The median age at the time of diagnosis of sickle cell anemia was 2.1 years (range 0 to 14.4), with 17.0% diagnosed before six months of life and 65.4% before three years. The median age of admission to the program was nine years (range 1 to 17).

The patients were from four states, Valle del Cauca (75.2%), Nariño (13.1%), Cauca (11.0%), and Chocó (0.7%). Most of them from Cali (47.9%), Buenaventura (16.2%) and Tumaco (10.6%). 64.1% of the patients had siblings, of which 13.7% had at least one sibling with the disease.

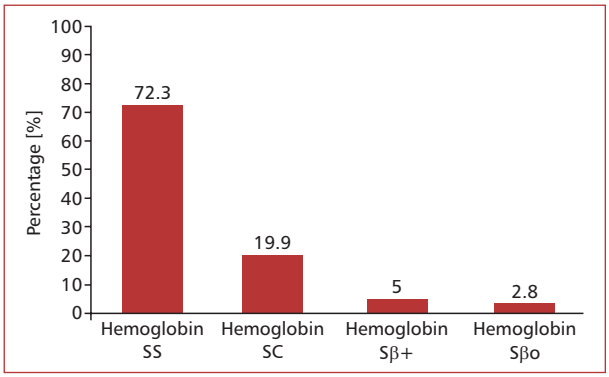

Figure 1. Diagnosis

The diagnosis by hemoglobin electrophoresis was made in 92.2% of the patients. Four different polymorphisms were identified, being the homozygous Hb S pattern the most frequent (*see* Figure 1).

Most patients (143 patients; 76.9%) had at least one complication the previous year before the program admission. 65% had 1 to 3 events, followed by patients who did not have any complications (23.1%), 4 to 6 events (11.2%), and 7 to 10 events (0.7%). The most common type of sickle cell complication the year before entering the "Ruta de la Vida" program was pain, followed by hemolytic and acute chest syndrome (*see* Table 1).

Patients were mainly diagnosed in an external institution. The main complications at the time of diagnosis were: pain (43.8%), hemolytic episodes (32%), dactylitis (14.4%), acute chest syndrome (13.1%), splenic sequestration 7.2%, seizures (2%) priapism (2%) and medullary aplasia (1.3%) (*see* Table 2).

At the time of admission to the "Ruta de la Vida" Program, the most frequent types of complications were pain and hemolysis, followed by acute chest syndrome (24.2%) and infection (23.5%) (*see* Table 3).

The median hemoglobin at admission was 8.8 g/dL, ranging from 2.5 g/dL to 15.2 g/dL, and 8% of the patients had severe anemia (Hb ≤ 7 g/dL). Ferritin levels were obtained in 79.1% of patients, with a median level of 321 ng/mL ranging from 5 to 6,788 ng/mL. 16.5% of patients had ferritin levels > 1000 ng/mL.

Abnormalities on echocardiography at admission were found in 13.1% of the patients. The signs were pulmonary hypertension (2.6%), ventricular hypertrophy (3.9%), and ventricular dilatation (9.8%). The abdominal ultrasound was performed in 97.4% of patients (n = 149); the most frequent disturbances were splenomegaly (15.4%), hepatomegaly (6.7%), and biliary lithiasis (4.7%). 97.4% of the patients had radiography of the hips, with abnormal results suggestive of vascular necrosis in 10.7%.

The brain magnetic resonance imaging (MRI) was performed on 96.1% (n = 147), of which 12.9% presented alterations. It was found that silent stroke (2.7%) and

Table 1. Complications number the year before admission

Number of crisis	Pain [%]	Hemolysis [%]	Splenic sequestration [%]	Acute chest syndrome [%]
0	66.00	75.20	96.10	81.70
1	23.50	16.30	3.30	13.70
2	2.60	3.90	0.00	2.60
3	3.90	2.00	0.00	0.00
4	2.00	1.30	0.70	1.30
5	0.70	0.00	0.00	0.00
6	1.30	0.70	0.00	0.00
7	0.00	0.70	0.00	0.00
8	0.00	0.00	0.00	0.00
9	0.00	0.00	0.00	0.70

Table 2. Type of complications at diagnosis

Crisis	Frequency	[%]
Pain	67	43.8
Hemolytic	49	32.0
Dactylitis	22	14.4
Splenic sequestration	11	7.2
Seizures	3	2.0
Priapism	3	2.0
Medullary aplasia	2	1.3

Table 3. Type of complications at the time of admission

Crisis	Frequency	[%]
Pain	83	54.2
Hemolytic	55	35.9
Acute chest syndrome	37	24.2
Infection	36	23.5
Cerebrovascular stroke	13	8.5
Splenic sequestration	11	7.2
Medullary aplasia	6	3.9
Priapism	5	3.3

asymptomatic and symptomatic stroke (3.4%). Transcranial Doppler results were obtained in 65.4% of patients (n = 100), of which 77% were normal, 14.0% were conditional, and 9.0% were abnormal.

A vaccination scheme was obtained in 96.7% of the patients (n = 148). The patients had been vaccinated for *Streptococcus pneumoniae* (66.2%), *Neisseria meningitis* (51.4%), *Haemophilus influezae* (58.8%), hepatitis A (24.3%), and hepatitis B (60.8%).

Regarding the treatment, it was found that 65.4% of the patients had received at least one transfusion of red blood cells, with a median of two transfusions, with a range of 0 to 56. At the admission to the program, 96.7% (n = 148) reported receiving some medication, 55.4% of patients received hydroxyurea, 84.5% folic acid, 46.6% zinc sulfate, 48.0% phenoxymethylpenicillin (PenVK®) and 8.1% deferasirox.

DISCUSSION

Sickle cell disease is a systemic disease worldwide impacting public health. There are 300,000 children homozygous for Hb S [8], most found in sub-Saharan Africa, the Middle East, and India. According to the World Health Organization, 13,000 births are in the Americas region [9].

In Cali, the incidence of hemoglobinopathies reaches 3.7%, and 1 in 10,000 neonates is homozygous for Hb S [10], which increases the risk of having cases with a severe disease phenotype in the city.

Additionally, Colombian patients with sickle cell disease could have a more severe expression of the disease because Benin and Bantu haplotypes appear more frequently [11].

In countries with limited resources, especially in cases of extreme poverty, like some African countries, where access to treatment is limited and neonatal screening is not available, the mortality rate in children under five years is close to 90% [8]. In well-developed countries such as the United States, where there is neonatal screening and established integral attention and follow-up programs, the mortality rate has decreased by 68% in the last 20 years, with a 95% survival until reaching adulthood.

Despite knowing the population impact of the disease and the prevalence of up to 10% of Hb S in the Colombian child population [11], no studies describe the characteristics of the pediatric population.

This descriptive study characterizes a population of Colombian children who attend a follow-up program designed for these patients in a reference III level center in Cali.

The distribution of sex was similar to the results obtained by the Cooperative Study for Sickle Cell Disease in the United States by Gill et al. [12], where they reported 53% male and 47% female. Although patients with sickle cell anemia living in developing countries have different outcomes than those in countries with higher income, the distribution of sex was the same in both scenarios.

The patients in this study had a median age of 2.1 years at diagnosis, and 17% were diagnosed before six months. In the study by Gill et al. [12] carried out in 1978–1988, 100% of

the patients were diagnosed thanks to neonatal screening for hemoglobinopathies in their first six months of age. In the United States, universal neonatal screening includes hemoglobinopathies. In Colombia, there is no routine neonatal screening for hemoglobinopathies or inborn errors of metabolism, which would explain the delay in diagnosis.

The median age at admission to the program was nine years, ranging between 1 and 17 years. In the study by Gill et al. [12], patients were admitted to referral centers at the age of 3 ± 1.4 months [average ± 1 standard deviation (SD)], while in the study conducted in Tanzania by Makani et al. [13], the average age was 6.9 years (range 3.3 to 12.8). The results suggest differences in the diagnosis and timely treatment among children from developing countries in contrast to children from high-income countries, which generates a gap in survival and quality of life among the less advantaged [4].

All of the patients belong to the Colombian Pacific Region, which has a high concentration of Afro-descendant population. In the study by Durán et al. [11], a cord sample of 1,200 Colombian children was obtained, from which 33 (2.75%) had hematological alterations associated with Hb S and the Bantu haplotype, suggesting that most of the affected patients migrated from Africa. It possibly explains the high proportion of patients with sickle cell disease in this country's regions.

The majority of case of the diagnosis of sickle cell disease was confirmed by hemoglobin electrophoresis. More than half of the patients were homozygous for Hb S, followed by Hb SC, Hb Sβ+, and Sβo, similar to the findings of Gill et al. [12]. In Tanzania [14], they found that most were homozygous for Hb S, only 4% had Hb βo. A small unpublished of the HUV proportion had a rare polymorphism βS/HPFH. It is interesting how proportions are maintained with the population of the United States despite the difference in the number of patients. It changed in Tanzania, where most patients are Afro-descendant and are the first five countries in the world with sickle cell disease. It could be related to migration and ethnic mixing from Africa and other regions in America.

The main characteristic of the sickle cell disease complications in the study cohort was pain, followed by hemolysis, and the third cause was acute chest syndrome. On the other hand, in the American study [12], the main complications were pain, followed by acute chest syndrome and bacteremia. This last complication has a robust environmental component and is also affected by the socioeconomic conditions of the patients. The presence of acute chest syndrome in both studies could be explained in the study by Gill et al. [12] because in the 1978–1988 decade, hydroxyurea management had not been implemented, and in the present study, because in Colombia, the use of this drug is still irregular.

In the study by Makani et al. [13] in Tanzania, 31% of patients who report Hb S report severe anemia as the leading cause of hospitalization in the previous year, followed by a painful crisis and fever. These data contrasted with the leading causes of hospitalization found in the present study.

In this study, differences were found in the type of complications at the time of diagnosis and upon admission to the program. In both cases, the significant crises were pain and hemolysis, but they differed in that dactylitis was more frequent at diagnosis and acute chest syndrome on admission. The age of the patients could explain this difference since dactylitis is an acute vaso-occlusive complication that occurs mainly in children under one year of age [1], and the median age at diagnosis was 2.1 years. At the same time, admission to the program was late at nine years old. Admission to a follow-up program seven years after the median time of diagnosis implies more significant chronic complications.

Interestingly, priapism was a frequent complication in 2% of the patients at the diagnosis and 3.3% at the time of admission. However, priapism was not reported in the United States [12] or Tanzania [13] and the Kenya [15] studies. In the literature, it is found that the association with thalassemia reduces the risk of priapism, while other genetic markers, such as the KL polymorphism, are associated with more priapism [8]. This finding could be the subject of further studies to determine if the population has a genetic association that explains it.

Among the chronic complications, cerebrovascular stroke (CVS) stands out due to the morbidity and mortality it generates. Before the follow-up with transcranial doppler, CVS occurred in 5–10% of pediatric patients with sickle cell disease [4]. The increase in the flow velocity of the cerebral artery implies a 40% increment in the incidence in the next three years of cerebral infarction, with a reduction of up to 25–30 years in life expectancy [16], become a vital screening to establish the risk of cerebral infarction.

In the present study, 6.1% of patients had a diagnosis of CVS by brain MRI and the transcranial Doppler report was conditional in 9.2% and abnormal in 5.9% of the population. Gill et al. [12] found 13 of 694 with CVS (1.8%) with the highest incidence of 2 per 100 people annually.

The analyzed Colombian population showed that despite having a previous type of screening, they had a higher CVS frequency than expected, according to recent literature reports, which would represent in the literature an increase in mortality and long-term disability in the children of the study. It is essential to determine if the follow-up in a specialized program can reduce the incidence of CVS.

Sickle cell disease causes multiorgan dysfunction, whereas cardiopulmonary disease stands out due to pulmonary hypertension and diastolic dysfunction, alterations also associated with increased mortality in adults [4].

The admission echocardiogram reported abnormalities in 13.1% of the population, among them pulmonary hypertension (2.6%), ventricular hypertrophy (3.9%), and ventricular dilatation (9.8%). That shows the importance of follow-up since childhood to diagnose cardiac affection and timely management.

Patients with sickle cell disease can develop functional asplenia at any time, implying a risk of infections by encapsulated microorganisms. All patients with sickle cell disease should be vaccinated against *Streptococcus pneumoniae, Neisseria meningitides*, and *Haemophilus Influenza type B*, as well as for hepatitis B virus and seasonal influenza, in addition to all the standard ones [1]. Despite the above, the present study found that many patients did not have complete vaccination against this type of germs, thus increasing the risk of life-threatening infections such as pneumonia, sepsis, and complicated meningitis [4]. This could also be related to acute chest syndrome being the third type of complication at the time of admission. Among the possible causes of low vaccination, it is believed it is linked to the fact that the participants come from very remote areas where access is limited secondly, not all these vaccines are covered by the PAI of Colombia, which makes their access more difficult.

Transfusions are essential for sickle cell disease patients; however, they are not innocuous. Part of the complications is alloimmunization and iron overload, which can lead to hepatic, cardiac, or endocrine dysfunction. The best test to determine iron deposits is a liver biopsy since there are no new non-invasive techniques, such as quantifying R2* and T2* in cardiac resonance [1]. Considering the difficulties in obtaining such studies, serum ferritin levels are included for follow-up; patients with serum ferritin > 1000 ng/mL should be managed with an oral iron chelator such as deferasirox [17].

In the study, 16.5% of the patients had serum ferritin levels > 1000 ng/mL; of these, only 25% received treatment with deferasirox. It is important to determine during the follow-up of these patients if there is an organic dysfunction associated with iron overload and verify the adherence to the treatment.

Regarding medical management, hydroxyurea has extensive evidence of its effectiveness in the treatment of patients with sickle cell anemia, since December 2017 the Food and Drug Administration (FDA) approved its use in children under two years, and since 2014 the National Institutes of Health in its evidence-based guide for the management of sickle cell anemia recommends the use of hydroxyurea from nine months, based on the results of the BABY HUG study [14].

Despite the above, only 55.4% of the study patients received hydroxyurea treatment, which could be related to the amount and type of crisis with severe organic compromise they presented when they entered the program. It should be evaluated in subsequent studies if adherence to current guidelines impacted reducing the manifestations of the disease.

Since 1986 the use of prophylactic penicillin has been established in two doses per day in children under five years, which has been demonstrated to drastically reduce the rate of invasive pneumococcal disease [1]. 46.4% of the study patients received a prophylactic penicillin treatment, some older than five years, due to incomplete vaccination schemes. The relationship between prophylaxis and the reduction of infections should be evaluated in future studies.

CONCLUSIONS

The population studied has a sickle cell disease with characteristics of a severe phenotype, with a high frequency of crisis and chronic complications such as cerebrovascular disease. This is the first study conducted in Colombia that describes the characteristics of the pediatric population with sickle cell disease. It is the starting point to assess the impact of follow-up programs.

Article Information and Declarations

Data availability statement: Original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics statement: The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

Author contributions: All authors participated in generating the idea, writing the protocol, data collection, statistical analysis, drafting the manuscript and approval the final manuscript.

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Conflict of interest: The authors declare no conflict of interest.

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