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Sociodemographic and Clinical Characteristics and the Impact of Hydroxyurea on Laboratory Profile and Healthcare Resource Utilization of Adult Patients with Sickle Cell Disease: An Observational and Retrospective Study of 5 Years of Follow-Up in a Reference Center in Brazil

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Research Article

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Abstract

Sickle cell disease (SCD) is a severe inherited and multisystem blood disorder characterized by hemolytic anemia, vaso-occlusive crises (VOCs), progressive multiorgan damage, and increased mortality. SCD is the most common inherited disorder worldwide, with well over 300,000 children born with SCD yearly, 75% of whom are born in Africa. Based on the Brazilian neonatal screening program, the annual average of new cases of children diagnosed with SCD was 1,087, with an incidence of 3.78 per 10,000 live births and an estimated number of 60,000 to 100,000 individuals living with SCD in Brazil. Our objectives were to describe the sociodemographic and genotype characteristics and clinical complications of patients with SCD and compare the laboratory profile and the impact of healthcare resource utilization between patients with and without hydroxyurea during five years of observation.

Objectives: To describe the sociodemographic and clinical complications, compare the laboratory profile and the impact of healthcare resources utilization between patients with and without hydroxyurea of SCD patients during five years of observation.

Method: This was a retrospective cross-sectional descriptive study conducted at one Brazilian reference center on SCD - Santa Casa de Sao Paulo, in Sao Paulo (Southeast region of Brazil) during a 5-year observation period (2016-2020).

Results: Among a total of 100 eligible adult patients, the main sociodemographic and genotypic characteristics of patients with SCD were: median age of 31 years, 84% of patients between 18 and 45 years of age, only one patient over 60 years of age; the majority were female (59%), Hb SS genotype (91%), black or mixed race, with complete secondary education and low family income; 100% of patients used the SUS insurance plan, although 29% also had private health insurance. VOC,

infection, stroke and priapism, and cholecystectomy and avascular osteonecrosis were the most frequently observed acute and chronic complications, respectively. Most patients used hydroxyurea (71%), 22% were on a chronic transfusion regimen, and 17% used an oral chelator. Patients using HU had a statistically significant improvement in laboratory values (Hb, Fetal Hb, reticulocytes, DHL, bilirubin, leukocytes, and platelets) compared to patients without HU. Despite the improvement in laboratory parameters, patients using HU did not have significantly lower rates of medical care in the emergency room and hospitalization compared to patients without HU.

Keywords: Sickle Cell Disease; Acute And Chronic Complications; Hydroxyurea; Public Healthcare Resources

Abbreviations: SCD: Sickle Cell Disease; Vocs: Vaso-Occlusive Crises; HSCT: Hematopoietic Stem Cell Transplantation; HU: Hydroxyurea.

Introduction

Sickle cell disease (SCD) is an inherited hemoglobin (Hb) disorder characterized by chronic hemolysis and vaso-occlusive episodes, resulting in severe pain, progressive multiorgan damage, and detrimental effects on the psychosocial well-being of those affected, their families, and communities [1,2]. SCD is the most common inherited disorder worldwide, with well over 300,000 children born with SCD yearly, 75% of whom are born in Africa [3]. Based on the Brazilian neonatal screening program, between 2014 and 2020, the annual average of new cases of children diagnosed with SCD was 1,087, with an incidence of 3.78 per 10,000 live births and an estimated number of 60,000 to 100,000 individuals living with SCD in Brazil [4,5].

The pathophysiology of SCD is a result of HbS in low oxygen conditions, giving rise to rigid and fragile sickle-shaped red cells with impaired oxygen-carrying capacity [1,2]. The Hb polymerization leads to hemolysis, anemia, and vaso-oclusion. The sickling and hemolytic characteristics of sickle red blood cells (RBCs) incite an inflammatory cascade through interactions with the endothelium, white blood cells, and platelets. Recurrent RBC sickling and hemolysis, combined with endovascular inflammation, result in acute and chronic organ damage at the cellular level, associated with acute, unpredictable, and potentially life-threatening complications [6-8].

The clinical phenotype of SCD varies widely; some individuals have a severe disease with frequent vaso-oclusive complications and early morbidity and death at a very young age, whereas others can go unnoticed until adulthood. Homozygosity for the sickle mutation (i.e., Hb SS disease) is responsible for the most common and most severe genotype of SCD, and differences in frequency and severity of clinical events exist even within the same family [1,2]. Vaso-occlusive crises (VOCs) are one of the hallmarks of SCD, the most frequent acute complication among children and adults, and a substantial cause of morbidity, hospitalization, and increased mortality [2,8].

The management of SCD patients may include using hydroxyurea (HU), folic acid, blood transfusion, iron chelation, antibiotic therapies, vaccination, hematopoietic stem cell transplantation (HSCT) and gene therapy [2,8-10]. For nearly 20 years, HU was the only therapy approved worldwide for adults and children with SCD. Three new drugs for HU - L-glutamine, crizanlizumab, and voxelotor – were approved in the US in 2017 [2]. HSCT is a potentially curative procedure. However, its use is restricted for a few patients due to the high cost, toxicity, and limited availability of suitable donors [1,7]. In addition to HSCT, gene therapy is being explored as a curative option for SCD. Gene therapy aims to replace a patient's abnormal gene with new genetic material; it offers a potential cure for SCD without the need for a bone marrow donor or the toxicity associated with traditional conditioning regimens for HSCT [7]. However, these therapies may not be available or affordable for all living with SCD [2].

Considering the high frequency of SCD in Brazil and the lack of a national SCD registry, our objective was to bring information from a population of people with SCD followed at an SCD reference center in Brazil in order to better understand their sociodemographic, genotypic, clinical and laboratory aspects and provide a real-life evidence data with a clearer picture of SCD in our country.

Material and Methods

Study type

This was a retrospective cross-sectional descriptive study conducted at one Brazilian reference center on SCD from Santa Casa de Sao Paulo (SCSP) in Sao Paulo (Southeast region of Brazil) during a 5-year observation period (2016-2020).

Study Participants

The SCD patients from SCSP had to meet all of the following criteria to be enrolled in this study: male or female patients ≥ 18 years, diagnosis of SCD (genotype HbSS, HbSC, HbSβ0/+-thalassemia), with at least three ambulatory visits during the first year of the observation period and written informed consent obtained prior to any study procedures.

Design

The investigators collected the SCD patient's data from the patient's electronic medical records from the hospital, preserving the confidentiality of information. A random sampling method was used to enroll the patient in the study and minimize selection bias. The eligible patients were initially identified based on medical records review at the site, with a unique code being attributed to each patient. Random samples were selected sequentially using the Excel randomization function (RAND) in all sheets. The research was approved by the Research Ethics Committee of the Hospital (CAAE nº 57326521.5.0000.5479)

Data Analysis

Descriptive analysis of the data was performed with the Statistical Package for Social Sciences software (SPSS, version 20.0, Chicago, IL, USA) and expressed as percentages, minimum and maximum values, median, and mean. The Mann-Whitney test was used for continuous variables and the Chi-square or Fisher's exact test for categorical variables. The significance level was 5% for the decision on differences between groups.

Results

One hundred and five patients were included in the study database. Five patients did not meet the eligibility criteria and were excluded. Thus, a total of 100 patients were enrolled and analyzed. The socio-demographic and genotype profiles are summarized in Table 1.

VOC, infection and stroke, cholecystectomy and avascular osteonecrosis were the most frequently observed acute and chronic complications, respectively (Table 2). All 100 patients had at least one VOC during the study period. The numbers and percentage of VOCs/patient/year over the five years evaluated were: 1 to 10 VOCs, 65%; 11 to 20, 15%; and ≥ 21, 1%. Ten percent of the patients had ≥3 VOCs every year in the five years of the study.

Variables	Total n (%)100 (100)
Age (years), mean (SD)	33 (11.7)
Median age (min.-max.)	31 (18.0-71.0)
Age group	
18-30 years	48 (48)
31-45 years	36 (36)
46-64 years	15 (15)
65+ years	1 (1)
Sex, %	
Female	59 (59)
Male	41 (41)
Genotype	
Hb SS	91 (91)
Hb SC	3 (3)
Hb S/Beta^{+} thalassemia	2 (2)
Hb S/Beta^{0} thalassemia	4 (4)
Race/Ethnicity	
White	6 (6)
Mulatto	39 (39)
Black	55 (55)
Educational level	
Elementary school	11 (11)
High school	80 (80)
University education	6 (6)
Do not know	3 (3)
Marital status	
Single	70 (70)
Married/living as married	15 (15)
Divorced	15 (15)
Employment	
Employed	55 (55)
Unemployed/retired	45 (45)
Health resource insurance	
SUS health insurance	100 (100)
Private health insurance	29 (29)
Income	
< 1 BMW	34 (34)
From 1 to 2 BMW	50 (50)
From >2 to 5 BMW	16 (16)

Table 1: Patients' sociodemographic characteristics and genotype.

Parameter	SCD patients (n=100)	
	n	%
VOC*	100	100%
Cholecystectomy	52	52%
Infection	42	42%
Stroke	21	21%
Avascular osteonecrosis	21	21%
Iron overload	17	17%
Splenectomy	14	14%
Leg ulcers	12	12%
Hypothyroidism	8	8%
Heart complications	5	5%
Retinopathy	3	3%
Chronic kidney disease	1	1%
Chronic liver disease	1	1%
Pulmonary hypertension	1	1%
Others	10	12%

Table 2: Most frequent acute and chronic clinical during the study period.

Hydroxyurea	Yes (n=71)		No (n=29)	
	n %		n %	
Age (years)				
18-30	36	51%	12	41%
31-45	24	34%	12	41%
46-64	10	14%	5	17%
≥65	1	1%	0	0%
On regular blood transfusion	**Yes (n=22)**		**No (n=78)**	
	n	**%**	**n**	**%**
Age (years)				
18-30	11	50%	37	47%
31-45	8	36%	28	36%
46-64	3	14%	12	15%
≥65	0	0%	1	1%
Iron Chelation	**Yes (n=17)**		**No (n=83)**	
	n	**%**	**n**	**%**
Age (years)				
18-30	7	41%	41	49%
31-45	7	41%	29	35%
46-64	3	18%	12	14%
≥65	0	0%	1	1%

Table 3: Treatment with hydroxyurea, blood transfusion and iron chelation.

HU was prescribed to 71 patients (71%); 75% received a single dose of 20 to 25 mg/kg/day and 35% between 25 and 35 mg/Kg/day. The indications for HU treatment included a history of VOCs (≥3 crises) that required medical support, recurrent ACS, stroke, recurrent priapism, and severe persistent anemia (Hb< 7g/dL) in the previous 12 months. All patients had received at least one blood transfusion during their lives; approximately 27% were on a chronic blood

transfusion regimen, mainly due to secondary prevention of stroke, and 17% were on regular use of deferasirox (Table 3). The comparative analysis of the main laboratory tests studied between the group of patients without and with HU (average of 3 values for each test per year over the five years of the study) showed a statistically significant difference for all parameters, except ferritin, urea, creatinine, AST and ALT (Table 4).

Parametro	Without HU	With HU	p
	Mean (DP)	Mean (DP)	
Hemoglobin (g/dL)	8.7 (1.1)	9.8 (1.1)	0.03
MCV (fl)	92.5 (12.6)	101.3 (11.5)	0
Leukocytes (10^3/mm^3)	10.3 (2.9)	8.5 (2.5)	0.03
Platelets (10^3/mm^3)	476.8 (118.2)	387.1 (100.2)	0.05
Fetal Hb (%)	9.2 (8.9)	15.9 (8.0)	0
Ferritin (ng/mL)	2,172.2 (2,049.4)	1,735.1 (1,624.0)	0.62
Lactate dehydrogenase (U/L)	868.8 (484.0)	490.2 (132.1)	0
Reticulocytes (%)	11.8 (5.9)	5.2 (5.1)	0.01
Urea (mg/dL)	21.0 (7.2)	22.7 (12.9)	0.83
Creatinine (mg/dL)	0.6 (0.2)	0.7 (0.4)	0.79
Total bilirubin (U/L)	3.6 (2.4)	2.7 (1.8)	0.04
Indirect bilirubin (U/L)	2.8 (2.1)	2.1 (1.6)	0.03
AST (U/L)	43.4 (19.1)	37.4 (17.6)	0.13
ALT (U/L)	34.1 (17.1)	31.2 (17.6)	0.22

Table 4: Comparative analysis of the main laboratory tests between the group of patients without and with Hydroxyurea.

Regarding the use of healthcare resources – ER visits (stay < 24 hours), hospitalization (stay ≥ 24 hours), and days of hospitalization - during the five years of follow-up, the average rate (min.-max.) was 7.58 (2-22) and 1.52 (0-17) and 8.64 (0-106), respectively. There was no statistically significant difference between the groups without and with HU.

The leading causes for medical care in the ER were VOC alone (46%, 70% of which were painful crises, 22% acute chest syndrome, and 8% priapism), VOC and infection (35%), and infection only (19%). Most infections were related to airway infections (sinusitis, tonsillitis, and pneumonia) or urinary tract infections.

Discussion

Sociodemographic and Genotype Data

A population's lifestyle and health conditions characterize how the person locates themselves within the social world. Such ways are corroborated by socioeconomic, political, and cultural factors that affect these people's environment, behavior, and biology, influencing their health/illness and, consequently, their well-being and quality of life. These social determinants significantly influence the lives of people with chronic illnesses, such as those with SCD, as they present significant vulnerability. In this situation, these people require care and monitoring by health services to protect them and improve their quality of life [11].

The sociodemographic and genotype data observed in our study highlight the severity of SCD evidenced by the predominance of the Hb SS genotype, which is associated with the more severe clinical course, and the low life expectancy of patients since, in a cohort of 100 patients, only 1 was older than 60 years of age.

The HbSS genotype is the most frequent in Brazil, although its prevalence may vary according to the Brazilian state. Results of a clinical and genetic ancestry profile of a large multi-center SCD Cohort in Brazil analyzed a total of 2,795 participants at six sites from 4 Brazilian states (Minas Gerais, Pernambuco, Rio de Janeiro, and São Paulo) observed that the Hb SS genotype was the most common SCD genotype (70.7%), followed by HbSC (23%), Sβ0 thalassemia (3.0%) and Sβ+thalassemia (2.9%) [12].

In our current study, SCD mainly affected patients of Afro-descendant ethnicity, with low educational levels and low

per capita income, which is usually associated with greater socioeconomic vulnerability, worse health conditions, and more difficult medical access. The vast majority were single, which undoubtedly reflects the disease's negative impact on the patient's self-care and family dynamics and the quality of life from the psychological perspective, which is worse in SCD patients who live alone. All these data were in accordance with other Brazilian studies [11-14].

The current study observed that 45% were unemployed/retired, showing the significant impact of the disease concerning this setting. More information on the employment status of individuals with SCD is needed in Brazil. Two studies observed a rate of SCD patients unemployed ranging from 31% to 68.8% [11-14]. The unpredictable nature of SCD symptoms, including fatigue and VOCs, the need for frequent medical visits, and hospitalizations, can make it challenging for patients to maintain regular employment. Employers and policymakers need to recognize SCD individuals' unique challenges and provide supportive measures such as flexible work arrangements to ensure their inclusion in the workforce [13,14].

All patients used public healthcare insurance (SUS), although 29% also had private health insurance. Patients with private insurance coverage usually have easy access to healthcare utilization (laboratory and imaging tests, consultation with doctors of different specialties, emergency room, and hospitalization), which can positively influence the control of the underlying disease [15]. Interestingly, even those with private health insurance continue to be followed at our service. One of the explanations for this is likely due to the security and better health care that patients may perceive by being followed up at referral services for SCD patients, remembering that most of these centers are located in the public health sector.

Clinical Manifestations

The clinical manifestations of SCD are variable, from mild to severe forms of the disease resulting from sickling of red blood cells, hemolysis, and occlusion of blood vessels, causing acute painful crises and chronic and progressive organ damage. Corroborating the findings of other clinical studies, our study observed that the most frequent acute and chronic complications were VOC, infection, stroke and priapism, and cholecystectomy and avascular osteonecrosis, respectively [11-14].

VOC is one of the hallmarks of SCD, the most frequent complication, and a substantial cause of morbidity, hospitalization, and increased mortality [1,2]. It is important to emphasize that all patients in this study had at least one VOC during the study period, the majority of which were due to a painful crisis; 65% had between 1-10 VOCs, and 10% of the patients had ≥3 VOCs every year in the five years of the study.

The splenic dysfunction observed in SCD patients is responsible for the high risk of bacterial infection, mainly caused by pneumococcus and *Haemophilus influenzae* [1,2]. On the other hand, adopting prevention strategies, including penicillin prophylaxis and vaccination, led to a substantial improvement in survival among patients with SCD, reducing infection and death. Infection is a frequent complication in patients with SCD due to rates [2].

The incidence of stroke in patients with SCD varies between 5% and 10%, occurring mainly in patients with the Hb SS genotype and especially in the first decade of life [1,2]. Most stroke patients in our study came from the SCSP pediatric hematology service and continued clinical and laboratory follow-up and the chronic transfusion regimen in our service.

Blood Transfusion and Iron Chelation

Blood transfusion is a supportive therapy for managing anemia, vasculopathy, VOCs, and organ dysfunction [2,7]. In the current study, all patients had received at least one transfusion during their lives, and approximately 27% were on chronic blood transfusion, mainly due to secondary stroke prevention. Chronic blood transfusion inevitably leads to secondary iron overload that can cause significant damage to many organs, such as the liver, endocrine system, and heart, and is associated with morbidity and mortality in SCD.2 As a result, guidelines recommend initiating iron chelation therapy once serum ferritin levels are >1,000 ng/mL or if patients have received cumulative transfusions of at least 20 units of blood transfusion [1,2]. Regarding iron chelation therapy, 17% regularly used deferasirox (Table 2), Brazil's most used iron chelator [18].

Hydroxyurea and its Impact on the Laboratory and Clinical Profile

Hydroxyurea (HU) improves the clinical severity and the hematological parameters of SCD patients. It reduces episodes of acute pain, acute chest syndrome, hospital admissions, and the need for transfusions, in addition to reducing mortality rates and improving quality of life [10].

HU was prescribed to 71% of patients in our study. Despite the evidence of HU's safety, efficacy, and tolerability in both pediatric and adult age groups, this significant therapeutic advance has been underused in Brazil and many countries worldwide. Lobo et al [18], analyzing 1,144

patients with FD at HEMORIO Rio de Janeiro, observed that HU was prescribed to 40.5% of children and 36.4% of adults. Carneiro-Proietti, et al. [12] reported using HU in 29.3% of children (458 of 1,104 patients) and 36.3% of adults (447 of 1,044 patients). HU remains underutilized partly due to a lack of awareness of its benefits on the part of patients and providers, which compromises patient adherence to medication when available; concerns regarding adverse events (i.e., myelosuppression), need for regular monitoring, uncertainties surrounding possible adverse effects on reproduction and fertility [1,2,17].

By definition, patients who required HU had more severe disease in terms of hemolysis, VOC, and organ damage. The therapeutic success of HU and, therefore, the reduction, above all, of acute complications, is directly associated with three main aspects that may contribute to explaining the discrepancy between the data found to the data published in the scientific literature: dose used, adherence to treatment, access and availability to HU.

The therapeutic success of HU vitally depends on the adequate dose (between 20 mg/kg/day and 35 mg/kg/day) and treatment adherence (continuous daily use) [10,17]. Poor adherence is the primary reason why HU therapy is ineffective in children and adults with SCD [17]. In this study, patients were receiving adequate doses of HU; however, we did not evaluate the treatment adherence rate, although it is our practice to talk to patients about the importance of treatment adherence, showing the benefits concerning improved laboratory tests and reinforcing that one of the main factors that ensure a more favorable clinical course of the disease is treatment adherence [1,2,16,17]

Corroborating the findings of several published studies, the comparative analysis between the group of patients with and without HU showed a statistically significant improvement in the main laboratory parameters of patients with HU, such as increase in Hb, reduction in hemolysis parameters (LDH, bilirubin), increased Fetal Hb and reduced leukocyte and platelet counts [10,16,17].

Patients using HU had a statistically significant increase in HbF and MCV levels. These findings corroborate data from previous studies [10,16,17]. The increase in intra-cellular Hb F signals a response to HU; the greater the increase in intra-cellular Hb F, the better the clinical course of the disease. The increase in the level of Hb F inside red blood cells is responsible for the increase in the volume of these cells and is associated with better intra-cellular hydration. Therefore, the increase in MCV, especially > 100 fl, is an important parameter used in clinical practice to infer satisfactory patient adherence to HU [1,2,17]. HU's cytoreductive effect explains the reduction in leukocyte and platelet counts in peripheral blood. It is related to improving the chronic inflammatory state characteristic of patients with SCD [1,2,17].

Regarding clinical events, we observed that patients using HU did not have significantly lower rates of medical care in the ER and hospitalization than patients without HU. These data are not in line with those published in the literature, which show that patients treated with HU present a reduction in the number of VOCs, rates of emergency care, and hospitalization, in addition to a lower mortality rate [1,2,17].

The fact that patients with HU show improvement in laboratory parameters signals, in a way, treatment adherence. On the other hand, our study analyzed the average obtained from three values of each test per year over the five years of the study, which does not eliminate the possibility that the patient had spent a few weeks without HU, that is, the annual average of each test could have if maintained unchanged. However, the lack of HU, even for a few weeks, could increase the risk of acute complications such as, for example, VOC.

Another relevant fact is access and availability to HU. Access to HU is a process that involves carrying out a list of mandatory laboratory tests and updating a specific form for HU renewal, which takes place every three months. Suppose a single test required for acquiring HU needs to be included, or there is any error in filling out the medication form. In that case, the patient does not receive the medication, which results in the lack of HU, increasing the risk of worsening the disease, i.e., worsening hemolysis and increased VOC rate. The availability and cost of HU can be significant barriers to consistent use in low- and middle-income countries. The lack of HU in state pharmacies in different regions of Brazil is not uncommon.

A possible limitation of our study is that we only analyzed admissions to our hospital (SCSP). Sometimes, due to the distance between the patient's home and a reference hospital or because they have private healthcare insurance, the patient may seek medical care closer to their home. Therefore, the number of hospital ER visits and hospitalization rate may be even greater than that recorded in the current study.

Although it presents essential information about Brazilian patients with SCD, our study had limitations. First, we only included data from one center in Brazil, limiting generalizability. Second, we only analyzed admissions to our hospital (SCSP). Due to the distance between the patient's home and a reference hospital or because they have private health insurance, the patient may seek medical care closer to their home. Therefore, the number of hospital emergency

room visits and the rate of hospitalizations may be even higher than reported in the present study. The strength of our study lies in its scope, as it covers the burden of SCD in the daily lives of Brazilian patients, providing real-life evidence data with a clearer picture of SCD in our country.

Despite multiple statements and calls to action from WHO to recognize and address the global burden of SCD, there remains a crucial lack of data in individual countries or across the highest-burdened regions of the world to accurately quantify this problem and drive resource allocation to improve the diagnosis, management, and awareness of SCD [19,20]. Systematic data collection for SCD through population-wide surveillance, an initiative already taken up in several countries and of which Brazil must be part, can help to facilitate treatment progress, and different types of registries and databases can be complementary to surveillance data, promoting an economy of scale in resource allocation [19,20].

Conclusion

These results emphasize the severity of SCD in the daily lives of patients with SCD, the impact of acute and chronic complications associated with the disease on public healthcare resources, the need for improved therapeutic options to limit or prevent disease progression, the importance of having both a longitudinal clinical registry and a national surveillance program to improve resource utilization and clinical outcomes of patients with SCD and the urgent need to revitalize the current national comprehensive SCD care programs.

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