



## Clinical and care profiles of children and adolescents with Sickle Cell Disease in the Brazilian Northeast region


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### Abstract

*Objectives: to describe the clinical epidemiological and care profiles of pediatric patients with sickle cell disease.*

*Methods: a descriptive study of all (48) children and adolescents with sickle cell disease, assisted at a public referral hospital in Paraíba State. The information were obtained from the patients' medical records and interviews were analyzed by using the Epi-Info program 7.2 version, frequency tables were built for the categorical variables and the central measurements and dispersion tendencies were calculated for the variables related to age and hospitalizations.*

*Results: the patients' age ranged from 15 months to 19 years old (median 8.6 years old); 91.7% considered their skin color mixed/black; 81.3% belong to D and E social class; 48% of the responsible guardians reported to have less than nine years of schooling; 70.9% lived in other cities; 93.8% received late diagnosis and 87.5% had irregular outpatient follow-up, 62.5% had an incomplete or outdated vaccination record. There were 226 hospitalizations; painful crises were the most common causes (55.7%). Each patient was hospitalized, about 5.2 times in the period; the median of total days for being hospitalized was 28. There were no deaths. Cardiac (56.2%) and hepatobiliary (54.3%) were the most common chronic complications.*

*Conclusions: sickle cell disease is a neglected clinical condition in the Brazilian Northeast region, where the appropriate political support for the patients is not fulfilled.*

**Key words** *Sickle cell disease, Complications, Epidemiology, Child health, Adolescent health, Neonatal screening*



## Introduction

Sickle cell disease (SCD) is a term used to define the clinical forms associated with the presence of a mutant hemoglobin (Hb), the HbS, in homozygosis or in association with other variant hemoglobin diseases or thalassemia, such as SC disease and beta S thalassemia, respectively. It presents variable clinical expression, from mild to severe conditions, with high mortality rates; the most severe and common form of SCD is sickle cell anemia, in which individuals have homozygous (SS) in the HbS.<sup>1,2</sup>

The pathological Hb polymerizes when it is exposed to a low pressure of oxygen, it results into multiple changes: red blood cells become rigid, they are destroyed prematurely and presents specific properties that promote inflammation, obstruction of the vasculature and injury to the endothelium, with ischemia and progressive damage to most of the vital organs.<sup>3</sup>

The phenomena vaso-occlusive and anemia can cause acute and chronic complications – painful crisis, acute chest syndrome, asplenia, a predisposition to infections, splenic sequestration, spinal aplasia, stroke, priapism, bone necrosis, lower limb ulcers, retinopathy, hepatobiliary alterations, heart, respiratory, and renal failure - which all increase the need for medical care and compromise of quality and life expectancy of the individual.<sup>1-4</sup>

The prevalence of SCD varies according to region and ethnic composition of the population. In Brazil it is the most common monogenic hereditary disease,<sup>3</sup> affecting 0.1 to 0.3% of the African-Brazilian population,<sup>2</sup> with an estimated 3,000 births per year of children with SCD, in a ratio of 1:1,000 live births.<sup>1</sup> There is no official data on the incidences of SCD in Paraíba State where this study was conducted.

The ethnic group most affected is at the base of the social pyramid and has the worst socioeconomic indicators, with poor clinical outcomes and prognosis<sup>5</sup>; this social factor is strongly associated with the genetic determinant, contributing decisively to the impact of morbidity and mortality.<sup>6</sup> However, early diagnosis, preventive and prophylactic measures<sup>3,7,8</sup> and appropriate medical care can prevent premature mortality even in an unfavorable socioeconomic context.<sup>7</sup>

The vast majority of births of children bearing SCD occur in developing countries,<sup>9</sup> where improved sanitation, nutrition and public healthcare have contributed to a reduction in childhood mortality.<sup>10</sup> In a study conducted in Benin, after creating strategies to improve care for patients with

SCD, the mortality rate in children under 5 years of age was 15.5 per 10,000 newborns who underwent the neonatal screening test.<sup>11</sup> In Brazil, there are few publications on mortality caused by SCD.<sup>12</sup>

In a systematic review published in 2016, the following data were observed: in Maranhão the median age of deaths was 14 years old; in Bahia, 42% of the deaths occurred in adulthood; in Minas Gerais, 76.7% of the deaths affected children under five years of age, with 56.5% of those in the first two years of life. In all the regions, the most common causes of deaths were caused by infectious processes.<sup>12</sup> In developed countries, over 90% of the individuals reached adulthood,<sup>8,13</sup> while in Brazil, life expectancy at birth is 53.3 years old, 23.3 years younger than the general population.<sup>14</sup>

Due to sickle cell being a disease of genetic, biochemical, hematological, clinical, anthropological and epidemiological importance, with a broad spectrum of presentation, whose prognosis is strongly associated with the socioeconomic context and the level of medical care offered, it is important to know its progress and the quality of care available in our region. The objective of this is to prepare intervention measures aimed to control the disease and reduce morbidity due to SCD.

The aim of this present study is to describe the clinical, epidemiological and care profile of children and adolescents with SCD admitted at a university hospital in the Brazilian Northeast region.

## Methods

This is a descriptive study conducted between January 2014 and December 2017, at *Hospital Universitário Alcides Carneiro* (HUAC) (Alcides Carneiro University Hospital), part of the *Universidade Federal de Campina Grande* (UFCG) (Federal University of Campina Grande), in Paraíba State. Campina Grande is the second largest city in Paraíba, located approximately 130 km from the capital with 385,213 inhabitants; 32.8% of those are between zero and 19 years old. HUAC has its service focused on public healthcare of medium and high complexity cases. It is a reference center to care for children and adolescents with SCD in the region, and follows the guidelines set up by the Ministry of Health for outpatient follow-up and manages SCD complications.<sup>1,4</sup>

The study population was consisted of all children and adolescents with SCD, residing in Campina Grande and the surrounding towns. The sample consisted of patients up to 19 years old, with SCD, who were hospitalized and/or received follow-up at

HUAC during the study period, regardless of the date of registering at the institution.

The main sources of information were from the patient's medical records, from which the data regarding the biological, sociodemographic and clinical variables were taken. Any information missing from the medical records was obtained from the interviews with the parents/guardians, after they had signed the Informed Consent Form and the Assent Form.

A statistical Epi-Info software, 7.2 version was used to carry out the descriptive data analysis, where frequency tables were constructed for categorical variables, and the measurements of the central tendency and dispersion were calculated for data referral of age and hospitalization.

The research was approved by the Ethics and Research Committee at HUAC under CAAE Number: 69332717.1.0000.5182. The authors declared no conflict of interest.

## Results

Of the 48 patients studied, 50% were female, with an age range from 15 months to 19 years of age (mean age was 10 years old and the standard deviation was 2.6 years of age); most identified their skin color as mixed or black (91.7%); for 81.3% of the patients, the monthly family income was equal to or below one minimum wage, as specified in 2017 (R\$ 937.00), of these, 18.7% received up to half a salary; 81.2% came from D-E social classes, according to the classification of the *Associação Brasileira de Empresas de Pesquisas* (ABEP)<sup>15</sup> (Brazilian Association of Research Companies); 45.9% lived in a habitation without any basic sanitation; almost half of the caregivers (48%) reported having less than nine years of schooling and most (70.9%) lived outside the follow-up city. The other sociodemographic characteristics are described in Table 1.

With reference of patients' nutritional stage, the assessment was made both during outpatient follow-up as for hospitalization, 83.3% were eutrophic. One patient with pubertal retardation was registered.

Age at diagnosis ranged from 15 days to 10 years of life (mean 5.5 years old; standard deviation 3.4 years old); 14 (29.2%) underwent neonatal screening for hemoglobinopathies, of which three had access to the diagnosis before two months of age. The predominant type of SCD was hemoglobinopathy SS, found in 70.8% of patients (Table 2).

Considering the norms set up by the Ministry of Health for clinical and laboratory follow-up of patients with SCD,<sup>1,4</sup> of the 48 patients studied,

87.5% did not attend appointments regularly and most performed routine examinations irregularly: blood count, Ferritin and lactic dehydrogenase were performed with inadequate periodicity by 77%, 79.1% and 94.8% the of patients, respectively. Transcranial Doppler (TCD), which was performed in 20.8% of the patients, and showed changes in 40% of these - (30% low conditional and 10% abnormal; data not shown in table).

During the study period, 226 hospitalizations occurred; the most common causes were painful crises (55.7%), presented in an isolated form (61.9%), or associated with other complications, notably to an infectious processes; therefore, in one hospitalization episode, more than one diagnosis may have occurred (Figure 1). Each patient with SCD was hospitalized in an average of 5.2 times during the period analyzed (five patients had no registration of hospitalization). The median days of hospitalization were 28 in total. There were no deaths in this period.

Screening for chronic complications was not performed for the entire study population. Cardiac and hepatobiliary alterations were the most frequent, affecting 56.2% (18 of 32 investigated) and 54.3% (25 of 46 investigated), respectively (Table 3).

Due to cardiac complications, enlargement of the left chambers was the most common (eight patients), one case of pulmonary hypertension was diagnosed and two patients were found to have mild pericardial effusion; mild mitral and tricuspid valve regurgitation were also found at a slight degree.

Hepatomegaly and biliary lithiasis prevailed among hepatobiliary alterations affecting ten and five patients, respectively; seven presented both alterations concomitantly; four underwent cholecystectomy and two underwent splenectomy.

The main renal alterations were microalbuminuria and increased renal medullary echogenicity identified by ultrasound.

A mild obstructive breathing disorder was observed, without variation after administering  $\beta_2$ -agonist in four patients. No ulcers on lower limbs were found in the investigated population.

By analyzing the prophylactic care, the vaccination schedule was incomplete/outdated for 62.5% of the patients; prophylaxis antibiotic was used by 68.7% in this population, of which 69.6% used it regularly.

In relation to therapy and adherence, almost all the patients made regular use of folic acid (95.7%); 18 patients (37.5%) used hydroxyurea, but four of them used it irregularly; and one (2.1%) used an iron chelator. In addition, 85.4% received concentrated

red blood cells, with seven (17%) received 10 or more blood transfusions and one patient enrolled in a regular transfusion program.

**Table 1**

Distribution of Sickle Cell Disease patients at a referral hospital according to sociodemographic characteristics. Campina Grande, 2014-2017.

Variables	n	%
Age (years)		
< 5	11	22.9
≥ 5 - < 10	15	3.2
≥ 10	22	45.9
Ethnicity/skin color		
White	4	8.3
Black/Mixed	44	91.7
Socioeconomic class*		
B-C	8	16.7
D-E	39	81.2
Information unknown	1	2.1
School age/grade delay		
Yes	12	25
No	17	35.4
Not applicable**	16	33.4
Information unknown	3	6.2
Years of schooling for the caregiver		
< 5	9	18.8
≥ 5 - <9	14	29.2
≥ 9 - < 12	15	31.2
≥ 12	8	16.6
Information unknown	2	4.2

\*Criteria established by ABEP<sup>15</sup>; \*\* Taking into account children outside of school-age.

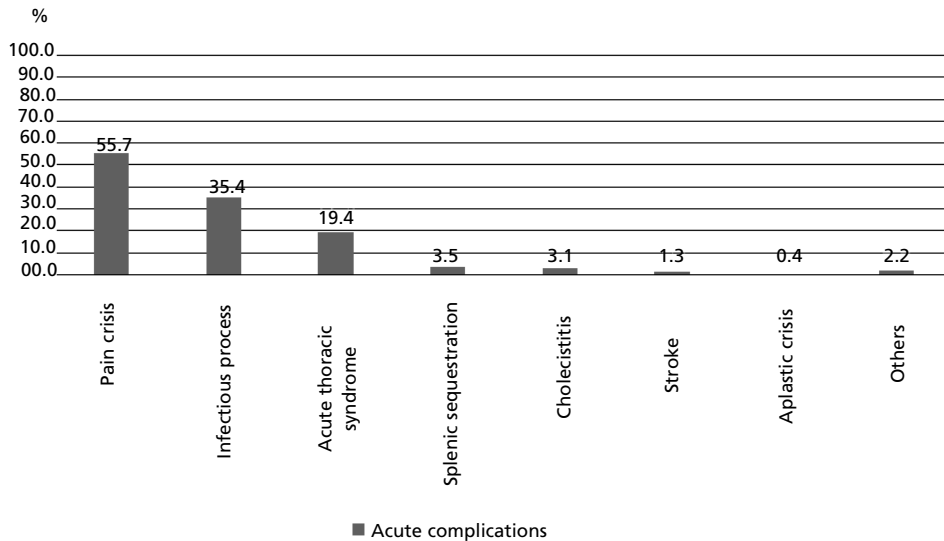
**Table 2**

Distribution of Sickle Cell Disease patients at a referral hospital according to age of diagnosis and electrophoretic pattern. Campina Grande, 2014-2017.

Variables	n	%
Age of diagnosis		
< 2 months	3	6.2
≥ 2 months to < 2 years	23	47.9
≥ 2 years to < 5 years	16	33.4
≥ 5 years	6	12.5
Type of Hemoglobinopathy		
SS	34	70.8
Sβ+	9	18.7
SC	3	6.3
Sβ <sup>0</sup>	2	4.2

**Figure 1**

Causes of hospitalization in Sickle Cell patients at a referral hospital. Campina Grande, 2014-2017.



The causes can co-exist, soon the sum is greater than 100%.

**Table 3**

Absolute and relative distribution of investigation and detection of chronic complications in patients with Sickle Cell Disease at a referral hospital. Campina Grande, 2014-2017.

Chronic complications	Investigated		Altered results	
	n	%	n	%
Hepatobiliary	46	95.8	25	54.3
Kidney	45	93.7	9	20.0
Cardiac	32	66.7	18	56.2

## Discussion

This study highlights that SCD in Campina Grande, Paraíba and its surrounding cities occurs predominantly amongst the mixed and black populations, and evidence shows a clear social vulnerability, which already was demonstrated by other studies.<sup>8,16-18</sup>

The affected population occupies the base of the social pyramid and exhibits the worst socioeconomic, epidemiological and educational indicators; it gains the lowest salary, it has the highest unemployment rate, the worst access to healthcare and the lowest participation of GDP, and for this reason it is a victim of the institutional racism, with differenti-

ated distribution of services, benefits and opportunities, generating inequalities and inequities.<sup>16</sup>

The predominance of SCD among the underprivileged is well documented in many studies on the subject,<sup>18-21</sup> as well as the low schooling level of caregivers; in some publications, more than 50% of the responsible guardians did not concluded the elementary level of education.<sup>22,23</sup>

It could be seen that a considerable portion of patients were behind in their school-age level. These children prematurely experience situations of suffering due to acute complications, with frequent hospitalizations and a high rate of school absenteeism.<sup>19</sup> They also experience the worst school performance associated with their low intelligence

quotient<sup>18</sup> and their worst socioeconomic status.<sup>18,24</sup>

The psychosocial consequences faced by these individuals must be taken into consideration; they are victims of stigmatization resulting from a triple association between skin color - social class - chronic and severe disease.<sup>16</sup> Low self-esteem, social isolation and feelings of hopelessness may occur, contributing to the onset of depression, which also contributes to the increase in pain crises, missed appointments and poor adherence to the treatment.<sup>19</sup>

We would like to highlight the high prevalence of SCD cases among patients who are resident outside the follow-up city. This is connected to the worst prognosis data, since the territorial distance impairs outpatient follow-up, leading to poor adherence to the treatment and inadequate management of acute complications.<sup>5,6,25</sup>

The absence of early diagnosis, in most cases, may be explained by the late implementation of screening for hemoglobinopathies in Paraíba State and by the organization of the service network.

Paraíba State was certified to carry out hemoglobinopathy screening through the Neonatal heel prick test in July, 2013. Even among those diagnosed after this date, most patients received late the test result (after 60 days since birth) and some received the diagnosis after the disease had manifested itself. These facts indicate, aside from the delay in implementing it, that the test was inadequately carried out, from the initial collection of the samples, taken in the city maternity hospitals, up to the distribution of the test results.

The established process is still the same since its initial implementation: blood samples are sent to the state reference laboratory in the capital (João Pessoa) 130 km from Campina Grande and, if alterations are detected, the children are summoned to go to João Pessoa. If the diagnosis is confirmed, the patient is requested to move to the state capital for follow-up at a referral unit, regardless of the patient's origin. Thus, the likelihood of missed consultation increases, leading to the discontinuation of the follow-up.

Appropriate medical care, following early diagnosis, is known to be the measure of the greatest impact on reducing morbidity and mortality in SCD in the first years of life.<sup>3,7,8,26</sup> This is when the treatment plan should be outlined, medical tests taken and the process of learning about the disease should be given to the responsible guardians. This process, through a clarification of the chronic and severe nature of the disease, aims to increase patient adherence to the control program and enhance early recognition of complications.<sup>1,4</sup>

In the study population, clinical follow-up was found to be inadequate in most cases, which may be explained by the late diagnosis, poor communication, poor understanding of the chronic characteristics and severity of the disease, structure of the service network and place of residence.<sup>5,22,25</sup>

The high hospitalization rates are connected to the poor socioeconomic status of patients with SCD.<sup>27</sup> In this study was highlighted the multiple hospitalizations, with recurring causes, where pain crises and infectious processes stand out, in agreement with the consulted literature.<sup>4,24</sup>

There is a high number of patients who did not regularly perform routine and screening tests for chronic complications. This is contrary to the norms established by the Ministry of Health for outpatient follow-up and management of SCD complications,<sup>1,4</sup> such as TCD for primary prevention of strokes, which affected two patients, with one case of recurrence; none of them had performed the exam. A detection of an abnormality can lead to therapeutic measures that reduce the risk of an event by 92%.<sup>26</sup>

As a possible consequence of the lack of consultations, there is low vaccination coverage, also seen in the state of Espírito Santo.<sup>25</sup> The importance of the pneumococcal conjugate vaccine must be stressed, especially in children with SCD, because of the high risk of bacteremia, which is a causative agent of sepsis and also of death.<sup>1,26</sup> In the present study, a lack of Pneumo-23 was noted at the *Centro de Referência para Imunobiológicos Especiais* (CRIE) (Reference Center for Special Immunobiological), as it is registered in the medical records.

The adherence to prophylaxis antibiotic cannot be analyzed with greater accuracy and should be treated with some skepticism. This is due to the inquisitive nature of the method, as reported in a study conducted in Belo Horizonte, where researches in medical records found that nearly 90% of the children had regular antibiotic use, in contrast to the presence of antibiotic in the urine. The authors highlighted that there is no clear recommendation for what constitutes an adequate level of penicillin for the appropriate prevention of infections in children with SCD.<sup>23</sup>

Despite the marked irregularity of follow-up and the consequences of this, no cases of death were identified during the study-period.

Since 2013, hydroxyurea has been incorporated into standard treatment norms and is the only medication currently affecting the quality of life of patients with SCD, significantly reducing morbimor-

tality.<sup>4,26</sup> Of the patients in this present study who met the clinical and/or laboratorial testing criteria for the use of hydroxyurea,<sup>28</sup> just over half did so; concluding that inadequate follow-up may deprive some patients of the drug of choice.

A low prescription-rate of iron chelator is also due to the unsatisfactory follow-up treatment; its indication may be underestimated because it depends on the ferritin level, which is not periodically measured.

Therefore, a well-designed and organized neonatal screening program, followed by diligent adherence to basic clinical standards, would be able to impact and modify the natural course of the disease.<sup>7</sup> SCD is still a forgotten clinical condition and hidden from the health professionals and society as a whole.<sup>16</sup>

The lack of awareness of SCD among professionals of the *Unidades Básicas de Saúde* (UBS) (Basic Health Units), which are the gateways to the entire healthcare system, must be highlighted. Taking on the coordinating role in care, the UBS should also be responsible for directing the patient to other levels of care, and ideally be organized within the integrated healthcare networks.<sup>29</sup>

The implementation of a successful SCD control program calls for a substantial effort from its organizers and prolonged government support,<sup>7</sup> as well as committed professionals. However, in the current context of social spending budget, especially with the approval of the *Proposta de Emenda a Constituição* (PEC) 55 (Proposed Amendment to the Constitution) in 2016, which freezes health funding

for the next 20 years, it seems unlikely that prevention and disease control programs will progress any further.<sup>30</sup>

This study presents some limitations such as the focus on cases from one site only; data collected from medical records and the difficulty in accessing relevant participants to conduct additional interviews.

It is important to stress that these limitations do not diminish the importance of the research, but it has contributed to improve the knowledge of the studied population, the details of the healthcare provided, and, mainly, by outlining clear flaws in the political organization of the state and city. In turn, the study has provided tools to improve the action planning aimed in changing the variables that negatively affect the lives of these individuals.

In conclusion, therefore, SCD is a neglected clinical condition in our country, where there is no adequate fulfillment of policies of care set up for the patients.

### Authors' contribution

Marques T participated in the planning, the construction of the method, collecting, analysis, and the writing of the article. Vidal AS participated in the planning of the study, analysis of the results and the final review. Braz AF participated in the planning and the writing of the article. Teixeira MLH performed the bibliographic review, collecting and analysis of the data. All authors have approved the final version of the manuscript.

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