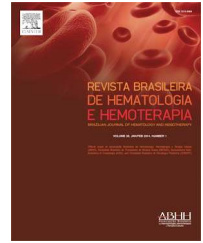




Revista Brasileira de Hematologia e Hemoterapia Brazilian Journal of Hematology and Hemotherapy

www.rbhh.org



Original article

Socioeconomic and demographic characteristics of sickle cell disease patients from a low-income region of northeastern Brazil



Thales Allyrio Araújo de Medeiros Fernandes^{a,*}, Tereza Maria Dantas de Medeiros^b, Jayra Juliana Paiva Alves^b, Christiane Medeiros Bezerra^b, José Veríssimo Fernandes^b, Édvis Santos Soares Serafim^c, Maria Zélia Fernandes^d, Maria de Fatima Sonati^e

^a Universidade do Estado do Rio Grande do Norte (UERN), Mossoró, RN, Brazil

^b Universidade Federal do Rio Grande do Norte (UFRN), Natal, RN, Brazil

^c Hemocentro Dalton Cunha (HEMONORTE), Natal, RN, Brazil

^d Hospital Infantil Varela Santiago, Natal, RN, Brazil

^e Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil

ARTICLE INFO

Article history:

Received 27 October 2014

Accepted 27 February 2015

Available online 14 April 2015

Keywords:

Anemia

Sickle cell

Socioeconomic factors

Hydroxyurea

Vaccination

Penicillin

ABSTRACT

Objective: To characterize the socioeconomic and demographic aspects of sickle cell disease patients from the state of Rio Grande do Norte (RN), Northeast Brazil, and their adherence to the recommended treatment.

Methods: This cross-sectional descriptive study was performed at referral centers for the treatment of hematological diseases. One hundred and fifty-five unrelated individuals with sickle cell disease who went to these centers for outpatient visits were analyzed. All the patients, or their caregivers, were informed about the research procedures and objectives, and answered a standardized questionnaire.

Results: The patients were predominantly younger than 12 years old, self-declared as mulatto, lived in small towns fairly distant from the referral center, and had low education and socioeconomic levels. Individuals who were ten or younger were diagnosed at an earlier age. Almost 50% of the patients were taking hydroxyurea, 91.4% reported having received pneumococcal/meningococcal vaccinations and 76.1% received penicillin as antibiotic prophylaxis. However, the majority of them reported having difficulties following the recommendations of the physicians, mainly in respect to attaining the prescribed medications and transportation to the referral centers.

Conclusion: These individuals have a vulnerable socioeconomic situation that can lead to an aggravation of their general health and thus deserve special attention from the medical and psychosocial perspectives. Thus, it is necessary to improve public policies that provide Brazilian sickle cell disease patients with better access to medical treatment, living conditions, and integration into society.

© 2015 Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. Published by Elsevier Editora Ltda. All rights reserved.

* Corresponding author at: Rua Miguel Antônio da Silva Neto, S/N, Aeroporto, 59607-030 Mossoró, RN, Brazil.

E-mail address: thalesallyrio@yahoo.com.br (T.A.A.d.M. Fernandes).

<http://dx.doi.org/10.1016/j.bjhh.2015.03.013>

1516-8484/© 2015 Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. Published by Elsevier Editora Ltda. All rights reserved.

Introduction

Sickle cell disease (SCD) is one of the most common severe monogenic disorders worldwide.¹ The underlying molecular defect is a single nucleotide substitution (β^S – HBB; GAG>GTG; glu → val; rs334) in the gene that encodes the β -globin chain of hemoglobin. The resulting hemoglobin S (Hb S) polymerizes when deoxygenated, causing polymer-associated lesions of the red blood cells.^{1,2} SCD includes several different genotypes including sickle cell anemia (Hb SS) and compound heterozygotes of Hb S with β -thalassemia (Hb S/ β -thal) or with other types of hemoglobinopathies.³

The World Health Organization recognized SCD as a global public health problem, as the overall number of babies born with SCD between 2010 and 2050 is estimated at about 14.24 million.⁴ Data from the Ministry of Health estimates that around 3500 children are born with sickle cell anemia each year in Brazil and the number of cases of the disease is between 25,000 and 30,000.⁵

The complications of this disease are numerous and can affect every organ and tissue in the body. The most common complications are pain crises, chronic anemia and its acute exacerbations, stroke, acute chest syndrome, infection, priapism, leg ulcerations, osteonecrosis, and cardiac and renal problems.⁶ Complications can be acute, producing dramatic clinical findings, or chronic, disabling, and cause premature death.²

Specific phenotypic manifestations of the disease vary considerably in frequency and severity between patients and even in the same patient over time.⁶ Both genetic and acquired factors contribute to this clinical variation. Among the acquired factors, the most important is the patient's socioeconomic conditions.⁷

Knowledge of the demographic and socioeconomic profile of SCD patients is essential to identify their needs, to contribute to improving resource allocation and to create and implement public health policies that benefit this population.⁸ However, studies that address these aspects of the disease are relatively scarce in both the Brazilian and international literature.

Thus, this study aimed to characterize the demographic and socioeconomic aspects of SCD patients from the state of Rio Grande do Norte (RN), a socioeconomic vulnerable area of northeastern Brazil, and their adherence to the recommended treatment.

Methods

A cross-sectional descriptive study was performed at referral centers for the treatment of hematological diseases in RN: Hemocentro Dalton Cunha (Natal), Hospital Infantil Varela Santiago (Natal), and the Centro de Oncologia e Hematologia de Mossoró (Mossoró). The participants were unrelated SCD patients without cognitive impairment, who went to these centers from March 2011 to October 2013 for outpatient visits.

All the patients, or their caregivers, were informed about the research procedures and objectives, and those who agreed to participate in the study signed an informed consent form and answered a standardized questionnaire. When the patient

was younger than 18 years old, it was answered by the caregiver.

The questions were orally asked by the interviewer without inducing responses. Questions aimed to collect medical history and the demographic and socioeconomic data of the patient, including age, ethnicity, ancestry, residence, schooling, employment situation, family income, age at diagnosis, use of hydroxyurea, prophylactic penicillin, immunization, and difficulties in following treatment, among others. Clinically relevant data were also taken directly from the patient's health records.

Data were collected in single individual interviews, and after collection they were input into a Microsoft Excel 2010 spreadsheet. Frequency distribution tables were used for the descriptive analysis of the categorical or nominal variables and the significance of differences between clinical characteristics by age group were estimated using the Chi-squared (χ^2) or Fisher exact test, as appropriate. The comparison of the age at diagnosis of SCD in age groups employed the Kruskal-Wallis analysis of variance (ANOVA) test, followed by multiple comparisons of mean ranks, using the Statistica software (version 7). Differences with a p -value ≤ 0.05 were considered statistically significant.

This study was conducted in accordance with the Helsinki Declaration as revised in 2008, and was approved by the Research Ethics Committee of the Universidade Federal do Rio Grande do Norte (UFRN, under protocol number 193/09) according to resolution 196/96 of the Conselho Nacional de Saúde, Brazil.

Results

One hundred and seventy-seven patients with clinical and laboratory diagnosis of SCD were interviewed. However, 22 were first- or second-degree relatives of other patients participating in the study and were therefore excluded from the analysis. Among the remaining 155 individuals, 109 (70.3%) had Hb SS, 23 (14.8%) were heterozygous for Hb S and β -thalassemia, 21 (13.5%) were heterozygous for Hb S and Hb C, and two (1.3%) presented the association between Hb S and hereditary persistence of fetal hemoglobin (HPFH).

The ages of the patients ranged from seven months to 48 years, with a median age of 12 years; the highest frequency of individuals was in the age group ≤ 5 years (29.0%), followed by the 11- to 15-year-old group (18.7%). The majority of the individuals were male (52.9%), and self-declared as mulatto (65.8%), but with no information about their ethnic ancestry (83.9%). However, indigenous ancestry was predominant (12.3%) among patients who informed their ancestry. A high percentage of the patients (43.2%) lived in small towns, at least 60 km away from the referral centers (Table 1).

Of the over 18-year-old patients, 51.9% had not completed high school, 50.0% were unemployed, and 19.2% were retired or receiving social security benefits. Most of the caregivers of the under 18-year-old patients only completed primary school education and the majority (55.3%) were working in regular jobs. Most of the patients (52.7%) had a household income of up to one minimum wage in Brazil, about US\$ 240.00, and one third (34.2%) did not receive any social benefits from

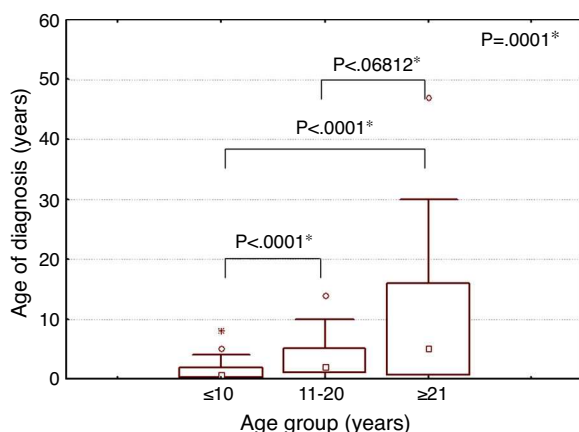
Table 1 – Demographic characteristics of sickle cell disease patients.

Demographic characteristic	n (%)
Age group (years)	
≤5	45 (29.0)
6–10	22 (14.2)
11–15	28 (18.7)
16–20	23 (14.2)
21–30	23 (14.8)
≥31	14 (9.0)
Gender	
Male	82 (52.9)
Female	73 (47.1)
Ethnicity	
White	46 (29.7)
Mulatto	102 (65.8)
Black	7 (4.5)
Ancestry^a	
African	10 (6.5)
Indigenous	19 (12.3)
European	4 (2.6)
Did not know	130 (83.9)
Residence	
Natal	45 (29.0)
Other towns in Natal Metropolitan region	27 (17.4)
Mossoró	16 (10.3)
Other towns of Rio Grande do Norte	67 (43.2)

^a Four patients reported having indigenous and African ancestry, three reported indigenous and European, and one reported African and European ancestry.

the government. Among those who did receive benefits, the Program of Continuous Cash Benefit for Social Assistance (BPC-LOAS) was the most prevalent (37.4% – Table 2).

The median age at diagnosis of SCD was eight months (minimum: one month; maximum: eight years), two years (minimum: one month; maximum: 14 years) and five years (minimum: one month; maximum: 47 years) for individuals in the under 11-year-old, 11- to 20-year-old, and over 20-year-old age groups, respectively. A statistically significant difference was observed in the median age at diagnosis of SCD between age groups (Figure 1).

**Figure 1 – Median age at diagnosis of sickle cell disease stratified by age group.****Table 2 – Socioeconomic characteristics of the patients with sickle cell disease analyzed in this study.**

Socioeconomic characteristic	Number of patients (%)		
	<18 years ^a	≥ 18 years	Total
Schooling^a			
Never Studied	5 (4.8)	3 (5.8)	8 (5.2)
Incomplete primary school	35 (34.0)	15 (28.8)	50 (32.3)
Complete primary school	26 (25.2)	9 (17.3)	35 (22.6)
Complete secondary education	31 (30.1)	24 (46.1)	55 (35.5)
Complete higher education	3 (2.9)	1 (1.9)	4 (2.6)
Did not answer	3 (2.9)	–	3 (1.9)
Employment situation^a			
Working	57 (55.3)	14 (26.9)	71 (45.8)
Not working	22 (21.4)	26 (50.0)	48 (31.0)
Other	24 (23.2)	12 (23.0)	36 (23.2)
Household Income (Brazilian minimum wage)			
Up to 1		81 (52.3)	
From 1 to 2		13 (8.4)	
From 2 to 3		53 (34.2)	
More than 3		8 (5.2)	
Benefits from the federal government^b			
BPC-LOAS		58 (37.4)	
Family allowance		51 (32.9)	
Others		8 (5.2)	
Did not receive social benefits		53 (34.2)	

^a The schooling and employment situation of the caregivers was considered.

^b 15 patients received both Program of Continuous Cash Benefit for Social Assistance (BPC-LOAS) and family allowance.

The majority of the patients (50.3%) reported having difficulties following the recommendations of the physicians, in particular difficulties to acquire the prescribed medications, especially hydroxyurea, and transportation to the referral centers when needed (Table 3).

Regarding the use of preventive measures against clinical complications, it was observed that hydroxyurea was

Table 3 – Major difficulties reported by patients to follow prescribed treatment.

Treatment difficulty	n (%)
Achieve the prescribed medication	49 (31.6)
Transport to referral centers	27 (17.4)
Others	13 (8.4)
Did not have difficulties	77 (49.7)

Six patients reported difficulties to achieve the medication and to go to the referral center, two reported problems in achieving the medications and other reasons, and another three persons claimed to have difficulties going to the referral center and other reasons.

Table 4 – Use of preventive measures against clinical complications, according to age group.

	Use of Hydroxyurea n (5)		Vaccinations ^b n (5)		Prophylactic use of penicillin n (5)	
	Yes	No	Yes	No	Yes	No
Age group (years)						
≤5	5 (11.1)	40 (88.9)	42 (93.3)	3 (6.7)	43 (95.6)	2 (4.4)
6–10	13 (59.1)	9 (40.9)	22 (100.0)	0 (0.0)	21 (95.5)	1 (4.5)
11–15	16 (57.1)	12 (42.9)	28 (100.0)	0 (0.0)	20 (71.4)	8 (28.6)
16–20	9 (39.1)	14 (60.9)	20 (95.2)	1 (4.8)	15 (65.2)	8 (34.8)
21–30	15 (65.2)	8 (34.8)	18 (78.3)	5 (21.7)	15 (65.2)	8 (34.8)
31	9 (64.2)	5 (35.7)	8 (66.7)	4 (33.3)	4 (28.5)	10 (71.4)
Total	67 (43.2)	88 (56.8)	138 (91.4)	13 (8.6)	118 (76.1)	37 (23.9)
p-value	0.000 ^a		0.002 ^a		0.000 ^a	
p-value Comparison of the use of preventive measures among the age groups calculated by Fisher Exact test.						
^a Statistically significant.						
^b Pneumococcal/meningococcal vaccinations (Four patients did not remember if they had ever received pneumococcal vaccinations).						

regularly used by 43.2% of the patients, with this percentage being significantly lower in the youngest age group. Furthermore, it was found that the majority (91.4%) of patients reported having received pneumococcal/meningococcal vaccinations and penicillin as antibiotic prophylaxis (76.1%). However, these percentages were much lower in the oldest age group and it was not possible to verify whether the vaccination was complete or incomplete for all patients (Table 4).

Discussion

SCD is a chronic, degenerative and self-incapacitating disease affecting the patient and their family in an intense and permanent way. The clinical complications and the recurrent hospitalizations and blood transfusions, associated with external domains such as unemployment, low income, and lack of access to health services, negatively influence the life of this population.⁷

People in a vulnerable socioeconomic situation are more exposed to the determining social factors of the disease, which can lead to an aggravation of the patients' general health. Therefore, these individuals deserve special attention in respect to medical and psychosocial perspectives.⁹

Rio Grande do Norte is a low-income area of Brazil, having a Human Development Index of 0.684 (16th of all Brazilian states),¹⁰ an illiteracy rate of 19.8%, and a child mortality of 17.0%. Moreover, 62.6% of families have a monthly per capita income of up to one minimum wage (about US\$ 240.00).¹¹

In this study, patients were predominantly younger than 12 years, self-declared as mulatto and living in towns fairly distant from referral centers for the treatment of SCD. Additionally, more than one third of the patients, or their caregivers, had only finished elementary school, were not working, had a very low household income, and were not receiving any social benefits from the government.

The age group profile of this study was similar to that found by Maximo¹² in Rio de Janeiro, Brazil. The predominance of children and adolescents seems to demonstrate the severity of the disease, with patients presenting low life expectancy, despite important advances that emerged in the last decades

for the prevention and treatment of complications of the disease.

The predominance of mulattoes among patients is related to the ethnic background of the population of the state of Rio Grande do Norte according to the Brazilian Institute of Geography and Statistics (IBGE),¹¹ where the influence of African slaves was not so strong as in some other Brazilian states.¹³ The predominance of indigenous ancestry among the patients who informed any ancestry corroborates this hypothesis. However, many studies worldwide have shown that SCD is more common in individuals of black ethnicity, that is, African descent.^{5,14} Therefore, it is likely that the distribution of this self-reported ethnicity may have been influenced not only by the high degree of miscegenation, but also by a certain degree of bias of the individuals analyzed, who often prefer to declare themselves as mulattoes instead of Blacks.

The low education level and socioeconomic status of the patients were similar to those found in studies conducted in England,¹⁵ the USA,¹⁶ Nigeria¹⁷ and other states of Brazil.^{7,8,18,19} This generates a condition of social vulnerability that affects the quality of life of patients and makes them more dependent on government programs for financial benefits and health care. Additionally, one third of the analyzed patients were not receiving any social benefits, a situation that impairs their living conditions even further. These vulnerable conditions also influence adherence to the treatment recommended by the physician.²⁰

Despite the complexity and multifactorial pathophysiology of the disease, relatively straightforward measures have greatly improved outcomes for children with SCD. Such measures include early identification of SCD by neonatal screening programs and the prompt establishment of preventive measures with prophylactic penicillin and immunizations, and therapeutic interventions, such as transfusions and hydroxyurea.²¹

This study showed that individuals who were under 11 years old were diagnosed at an earlier age. These results demonstrate that the relatively recent implementation of health policies have had a positive impact on the lives of patients. It was also found that approximately half of the patients (43.2%) were taking hydroxyurea. This percentage

is higher than that reported by other studies conducted in Brazil^{18,22} and the USA,^{23,24} and demonstrates good adherence of the patients to treatment and the healthcare team's confidence in the efficacy of the medicine. However, only 11% of under 5-year-old children were taking hydroxyurea, which seems to reflect the concerns about the overall safety of this medicine, mainly in very young children. The results of the Pediatrics Hydroxyurea Phase 3 Clinical Trial (Baby HUG) demonstrated both safety and beneficial effects of hydroxyurea in asymptomatic and symptomatic young children with SCA, and suggests that clinicians should consider changing their practice to prescribe hydroxyurea therapy for all very young children with SCA, rather than treating only those most severely affected.²⁵

The rates of vaccination (91.4%) and prophylactic use of penicillin (76.1%) found in this study also demonstrate good adherence of health staff and patients to general recommendations for the treatment of SCD. Improved immunization against *Streptococcus pneumoniae* and *Haemophilus influenza*, and the use of penicillin prophylaxis have dramatically reduced the frequency of serious bacterial infections and mortality of infants with SCA.^{26,27}

This immunization coverage of patients with SCD was similar to those obtained by Frauches et al.²⁸ in the state of Espírito Santo, Brazil, and by Hardie et al.²⁹ in patients from Jamaica. On the other hand, the prophylactic use of penicillin was higher than the rate reported by Warren et al.³⁰ in the USA, and similar to those described in others studies carried out in Brazil³¹ and Jamaica.³² However it was not possible to directly assess the vaccination record card of all individuals, nor verify adherence to prophylactic penicillin by other methods; it is possible that our results are overestimated. Lower rates of adherence to these practices in the older age groups can be explained by the fact that these recommendations were established in the 1980s and 1990s.

Despite this adherence to treatment and use of preventive measures, a significant percentage (31.6%) of patients reported problems in achieving the prescribed medications, especially hydroxyurea. The high costs of these medicines and low socioeconomic status of patients make them dependent on public programs for dispensing medicines. Therefore, the occurrence of financial and administrative problems in these programs can make access to the recommended therapy quite difficult.

The distance to reference centers constitutes a barrier to the implementation of a comprehensive care program for SCD patients, as it generally restricts transportation to health services.³³ Added to this, the need to travel to get treatment endangers patients' lives. A study conducted by Fernandes and Viana³⁴ pointed out difficulties in getting transportation to the health center as a contributing factor for premature deaths of these individuals. In our study, almost half of the analyzed individuals lived in towns fairly distant from the referral centers and 17.4% reported difficulties in arriving at the centers to perform the recommended treatment.

Therefore, it is necessary to improve public policies for these individuals, taking into account their low socioeconomic status, demographic characteristics, and difficulties in achieving the recommended treatment. And to be effective, these measures need to provide psychosocial counseling necessary

for the development of the patient's integration into society, as well as access to medical treatment, allowing favorable improvements in the reality experienced by Brazilians with this disease.

Certain limitations of the current study should be taken into account, especially with regard to adherence to the recommended medical treatment. As it was not possible to analyze the vaccination record cards of all patients, we were not able to assess the adequacy of the vaccine program. Furthermore, the use of hydroxyurea and prophylactic penicillin was evaluated taking into account only the patients' reports. Therefore, their regular and proper use of these drugs could not be proven.

Conclusions

SCD patients from the state of Rio Grande do Norte have a vulnerable socioeconomic situation that can lead to an aggravation of their general health and thus deserves special attention from the medical and psychosocial perspectives. Therefore, it is necessary to improve public policies that provide Brazilians with SCD better access to medical treatment, living conditions, and integration into society.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

This study was supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, grant no. 402022/2010-6) and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, grant no. 08/57441-0). We would like to thank the staff of Hemocentro Dalton Cunha, Hospital Infantil Varela Santiago, and Centro de Oncologia e Hematologia de Mossoró for the access provided to patients.

REFERENCES

1. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. *Lancet*. 2010;376(9757):2018-31.
2. Steinberg M. Sickle cell disease. In: Steinberg M, Forget B, Higgs D, Weatherall D, editors. *Disorders of hemoglobin – genetics, pathophysiology and clinical management*. 2nd ed. Cambridge: Cambridge University Press; 2009. p. 435-6.
3. Steinberg MH, Sebastiani P. Genetic modifiers of sickle cell disease. *Am J Hematol*. 2012;87(8):795-803.
4. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell anaemia in children under five, 2010-2050: modelling based on demographics, excess mortality, and interventions. *PLoS Med*. 2013;10(7):e1001484.
5. Cançado RD, Jesus JA. A doença falciforme no Brasil. *Rev Bras Hematol Hemoter*. 2007;29(3):204-6.
6. Ballas SK, Kesen MR, Goldberg MF, Luty GA, Dampier C, Osunkwo I, et al. Beyond the definitions of the phenotypic complications of sickle cell disease: an update on management. *ScientificWorldJournal*. 2012;2012:949535.

7. Pereira SA, Brener S, Cardoso CS, Proietti AB. Sick cell disease: quality of life in patients with hemoglobin SS and SC disorders. *Rev Bras Hematol Hemoter.* 2013;35(5):325-31.
8. Santos JP, Gomes Neto M. Sociodemographic aspects and quality of life of patients with sickle cell anemia. *Rev Bras Hematol Hemoter.* 2013;35(4):242-5.
9. Paiva e Silva RB, Ramalho AS, Cassorla RM. Sick cell disease as a public health problem in Brazil. *Rev Saude Publica.* 1993;27(1):54-8.
10. Nações Unidas Ranking IDHM Unidades da Federação 2010. Available from: <http://www.pnud.org.br/atlas/ranking/Ranking-IDHM-UF-2010.aspx> [cited 30.01.15].
11. Instituto Brasileiro de Geografia e Estatística – IBGE. Síntese de indicadores sociais—uma análise das condições de vida da população brasileira. Rio de Janeiro: IBGE; 2014, 214 pp.
12. Maximo C [thesis] The policy for comprehensive care of persons with sickle cell disease in Rio de Janeiro and the challenge of decentralization. Rio de Janeiro: Fundação Oswaldo Cruz – Escola Nacional de Saude Publica; 2009, 104 pp.
13. Cascudo LC. História do Rio Grande do Norte. Rio de Janeiro: Departamento de Imprensa Nacional; 1955.
14. Brousseau DC, Panepinto JA, Nimmer M, Hoffmann RG. The number of people with sickle-cell disease in the United States – national and state estimates. *Am J Hematol.* 2010;85(1):77-8.
15. Aljuburi G, Laverty AA, Green SA, Pheko KJ, Bell D, Majeed A. Socio-economic deprivation and risk of emergency readmission and inpatient mortality in people with sickle cell disease in England: observational study. *J Public Health.* 2013;35(4):510-7.
16. McCavit TL, Lin H, Zhang S, Ahn C, Quinn CT, Flores G. Hospital volume, hospital teaching status, patient socioeconomic status, and outcomes in patients hospitalized with sickle cell disease. *Am J Hematol.* 2011;86(4):377-80.
17. Adegoke SA, Adeodu OO, Adekile AD. Sick cell disease clinical phenotypes in children from South-Western, Nigeria. *Niger J Clin Pract.* 2015;18(1):95-101.
18. Felix AA, Souza HM. Epidemiologic, Ribeiro S.B. social aspects of sickle cell disease. *Rev Bras Hematol Hemoter.* 2010;32(3):203-8.
19. Loureiro MM, Rozenfeld S, Portugal RD. Acute clinical events in patients with sickle cell disease: epidemiology and treatment. *Rev Bras Hematol Hemoter.* 2008;30(2):95-100.
20. Reiners AA, Azevedo RC, Vieira MA, de Arruda AL. Bibliographic production about adherence/non-adherence to therapy. *Cien Saude Colet.* 2008;13 Suppl. 2:2299-306.
21. McGann PT, Nero AC, Ware RE. Current management of sickle cell anemia. *Cold Spring Harb Perspect Med.* 2013;3(8), pii: a011817.
22. Silva Junior GB, Libório AB, Vieira AP, Bem AX, Lopes Filho AS, Figueiredo Filho AC, et al. Evaluation of renal function in sickle cell disease patients in Brazil. *Braz J Med Biol Res.* 2012;45(7):652-5.
23. Brandow AM, Jirovec DL, Penepinto JA. Hydroxyurea in children with sickle cell disease – practice patterns and barriers to utilization. *Am J Hematol.* 2010;85(8):611-3.
24. Zumberg MS, Reddy S, Boyette RL, Schwartz RJ, Konrad TR, Lottenberg R. Hydroxyurea therapy for sickle cell disease in community-based practices – a survey of Florida and North Carolina hematologists/oncologists. *Am J Hematol.* 2005;79:107-13.
25. Thornburg CD, Files BA, Luo Z, Miller ST, Kalpatthi R, Iyer R, et al. Impact of hydroxyurea on clinical events in the BABY HUG trial. *Blood.* 2012;120(22):4304-10.
26. Gaston MH, Verter JI, Woods G, Pegelow C, Kelleher J, Presbury G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia A randomized trial. *N Engl J Med.* 1986;314(25):1593-9.
27. Halasa NB, Shankar SM, Talbot TR, Arbogast PG, Mitchel EF, Wang WC, et al. Incidence of invasive pneumococcal disease among individuals with sickle cell disease before and after the introduction of the pneumococcal conjugate vaccine. *Clin Infect Dis.* 2007;44(11):1428-33.
28. Frauches DO, Matos PA, Vatanabe JH, Oliveira JF, Lima AP, Moreira-Silva SF. Vaccination against pneumococcus in children with sickle cell anemia in the state of Espírito Santo, Brazil, between 2004 and 2007. *Epidemiol Serv Saude.* 2010;19(2):165-72.
29. Hardie R, King L, Fraser R, Reid M. Prevalence of pneumococcal polysaccharide vaccine administration and incidence of invasive pneumococcal disease in children in Jamaica aged over 4 years with sickle cell disease diagnosed by newborn screening. *Ann Trop Paediatr.* 2009;29(3):197-202.
30. Warren MD, Arbogast PG, Dudley JA, Kaltenbach L, Ray WA, Wang WC, et al. Adherlatic antibiotic guidelines among Medicaid infants with sickle cell disease. *Arch Pediatr Adolesc Med.* 2010;164(3):298-9.
31. Gomes LM, Reis TC, Vieira MM, de Andrade-Barbosa TL, Caldeira AP. Quality of assistance provided to children with sickle cell disease by primary healthcare services. *Rev Bras Hematol Hemoter.* 2011;33(4):277-82.
32. King L, Ali S, Knight-Madden J, MooSang M, Reid M. Compliance with intramuscular penicillin prophylaxis in children with sickle cell disease in Jamaica. *West Indian Med J.* 2011;60(2):177-80.
33. Wolfson JA, Schrager SM, Khanna R, Coates TD, Kipke MD. Sick cell disease in California: sociodemographic predictors of emergency department utilization. *Pediatr Blood Cancer.* 2012;58(1):66-73.
34. Fernandes AP, Viana MB [thesis] Caracterização e circunstâncias da ocorrência de óbitos em crianças com doença falciforme triadas pelo Programa Estadual de Triagem Neonatal de Minas Gerais, no período de março de 1998 a fevereiro de. Belo Horizonte: Universidade Federal de Minas Gerais; 2007, 82 pp.