ORIGINAL ARTICLE

Most prevalent clinical complications in patients with sickle cell disease from a medium-sized town in Minas Gerais, Brazil

Complicações clínicas mais prevalentes em pacientes portadores de doença falciforme de uma cidade de médio porte de Minas Gerais, Brasil

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ABSTRACT

Introduction: the patient with sickle cell anemia presents many clinical complications during his lifetime, which affect his quality of life. **Objective:** to learn about the profile of the patient with drepanocytosis and its most frequent clinical complications and estimate the prevalence of chronic ulcers in these patients. **Methods:** this was a cross-sectional study including all patients with sickle cell anemia registered at the Hemominas Foundation in Divinópolis, Minas Gerais. **Results:** repeated infections and pulmonary and hepatobiliary complications were the most frequent complications and 5% of the patients presented active leg ulcers at the time of the study. **Conclusion:** there is a great variety in the presentation of the disease among patients, which requires a standardization of protocols for services, improved training of health network professionals, and training of families for better monitoring their patients.

Key words: Sickle Cell Anemia; Bacterial Infections; Ulcer, Prevalence; Hemotherapy Service.

RESUMO

Introdução: *o paciente portador de anemia falciforme apresenta durante sua vida diversas complicações clínicas que afetam muito sua qualidade de vida.* ***Objetivo:*** *conhecer o perfil do paciente com drepanocitose e de suas complicações clínicas mais frequentes e estimar a prevalência de úlceras crônica nesses pacientes.* ***Métodos:*** *trata-se de estudo transversal incluindo todos os portadores de anemia falciforme cadastrados na Fundação Hemominas de Divinópolis, Minas Gerais.* ***Resultados:*** *as infecções de repetição, complicações pulmonares e hepatobiliares foram as mais frequentes e 5% dos pacientes apresentavam úlcera de perna ativa no momento da pesquisa.* ***Conclusão:*** *há grande variedade na apresentação da doença entre seus portadores, sendo necessária padronização de protocolos pelos serviços, melhor capacitação da rede de saúde, bem como do preparo das famílias para que haja melhor acompanhamento dos doentes.*

Palavras-chave: *Anemia Falciforme; Infecções Bacterianas; Úlcera; Prevalência; Serviço de Hemoterapia.*

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INTRODUCTION

Sickle cell anemia is a disease that is characterized by changes in the normal shape of red blood cells. This alteration is the result of a substitution of glutamic acid by valine (gene mutation GAG> GTG) in the sixth amino acid of the β-globin chain forming the S hemoglobin. Erythrocytes that contain mostly S hemoglobin in

hypoxic conditions take the form of a scythe, which explains the name origin.[1] This is the most common monogenic inherited disease in Brazil with higher occurrence among african-descendents.[2] In addition to the sickle cell anemia (SS), the term sickle cell disease involves the combination of Hb S with Hb C (hemoglobin SC disease) and other less frequent subtypes (S-beta-thalassemia, SD, and others).

In Southeastern Brazil, the mean prevalence of heterozygote individuals is about 2%, reaching 6-10% in the African descendent population. Cançado et al.[2] reported 25-30 estimated thousand cases of sickle cell disease, with expected 3,500 new cases per year.[2] In Minas Gerais, the incidence of sickle cell disease is 1:1,400 newborns screened by the State Neonatal Screening Program.[3] A study conducted in Minas Gerais using data from the Core for Action and Research in Support to Diagnostics (NUPAD) by the neonatal screening of 1 833 030 newborns found during the study period, 1,396 children with a hemoglobinic profile compatible with sickle cell disease; of these, 764 presented the SS genotype or Sß0-talassemia.[3]

The change in the shape of red blood cells underlies the two major pathophysiological mechanisms: hemolysis and vaso-occlusion, which will account for alterations in various organs and systems, and consequently, the clinical manifestations of the disease.[4] One of the key characteristics of this disease is its great clinical variability: some patients express countless complications and frequent hospitalizations while others have a more mild evolution.[5]

The main complications that the sickle cell disease carrier may present throughout life are: recurrent infections, pulmonary, neurological, renal, hepatobiliary, and ocular complications, priapism, and leg ulcers.[6] The most common infections are pharyngitis, mainly caused by *Haemophilus influenzae* type b. Children under-five years old with sickle cell disease are 30-100 more times at risk to develop infections than healthy children.[4] Complications of the nervous system such as transient ischemic attacks, cerebral infarction, cerebral hemorrhage, unexplained seizures, and coma occur in around 25 % of patients.[6] The acute thoracic syndrome is considered the second leading cause of hospitalization by sickle cell disease patients, with the highest prevalence in young children and those with high rates of recurrence after the first episode. Cholelithiasis occurs in at least 70% of the patients. In young adult males, 5 to 10% suffer from priapism and 45% present some degree of impotence later in life.[6-10]

Another complication that deserves attention in patients carriers of sickle cell anemia are chronic ulcers. They cause painful conditions, long periods of treatment, generate great expenses to health services, and can become a disabling condition for their carriers.[5,11] Ulcers occur preferentially in the lower limbs; they are more frequent in men with a peak in incidence between the second and third decades of life,[12] with a prevalence of 8 to 10% of homozygous patients. However, there are reports of incidence over 50% of individuals in tropical areas.[13,14] They present high recurrence rates, ranging around 25 to 50% after medical treatment, and often progress to chronicity.[11]

Ballas et al.[15] propose a classification based on the definition of phenotypic manifestations of the disease and on its complications in three groups: hematological complications and their sequelae; pain syndromes and correlated situations; and complications of vital organs and their sequelae.[15]

Considering the fact that sickle cell anemia is an incurable condition, the therapeutic priority becomes the prevention and early diagnosis of complications in order to provide improved patient quality of life. The frequent outpatient follow-up, in patients who have many complications and those asymptomatic; involvement of multidisciplinary teams; and assistance to families in recognizing early signs and symptoms of complications help prevent frequent hospitalizations and lessen consequences and possible disease sequelae.[5,16] Thus, there is a need to know the patient's profile and complications for an effective approach to the patient and community where he is inserted.

PATIENTS AND METHODS

A sectional study was developed in patients with SS genotype recorded and identified by hemoglobin electrophoresis until June of 2010 in the clinic of the Hemominas Foundation in the city of Divinópolis, Minas Gerais. The Hemominas Foundation, after approval by its Ethics and Research Committee, provided the list of names and respective hemoglobinic profiles, phone numbers, and addresses of patients, distributed in 24 cities in the macro-region. Home visits were conducted after phone contact in order to invite patients to participate. All participants or their legal representatives who signed the free and informed consent (TCLE) responded to a structured questionnaire containing questions about socioeconomic

data, information about disease complications, and access to health and treatment services. Questionnaires were identified only by numbers in the database, and the obtained information was logged using the EpiData software 3.1® and analyzed through the EPIINFO 2000 3.2® and STATA 11® software.

Patients who moved outside the region surrounding the Hemominas Foundation in Divinópolis were excluded from the study. Patients were considered lost after five unsuccessful contact attempts in different ways and times (letter, telephone, home visits, e-mail) or those who refused to participate.

Socioeconomic questions approached the level of patient education, housing conditions, and family income. The questions related to complications of sickle cell anemia addressed the following events: recurrent infections, neurological complications, pulmonary complications, hepatobiliary complications, renal complications, priapism in male patients, ocular complications, splenic complications, and increased focus on the occurrence of leg ulcers. The questions have four answer categories: no complications throughout their lives, one to five times, six to 20 times, and more than 20 complications. In addition, access to health services and treatment was questioned, if patients usually use the public or private sector for treatment, which medications were being used, and inquiries about blood transfusions and/or surgeries in the past. If active chronic ulcers were present, permission to close observation at the time of the interview was requested.

A descriptive analysis of variables, comparison of proportions using the chi-square test, and analysis of the prevalence of presented complications were performed. To better understand the concomitant complications in men and women, two descriptive flowcharts were built by gender.

RESULTS

Out of the 85 patients enrolled and eligible for the study, two were interviewed in the pilot project. Given the changes that were required in the collection instrument, the pilot study data were not considered in this analysis. Out of the 83 patients elected for the interview, four were excluded because they moved away from Divinópolis, 14 were considered lost, eight were not found, and four had died. Two patients refused to participate. The remaining 65 patients were interviewed, and their responses were included in the analysis.

Regarding the profile of patients, 52% (34) were females and 48% (31) males. The data in Table 1 shows that more than half of the patients were older than 20 years old, 26 (40%) lived in Divinópolis, and 39 (60%) in 23 municipalities in the macro-region. Regarding the race/color, over 55 (85%) were self-declared mulatto/brown or black. The average monthly family income of 31 (47.7%) patients was less than twice the minimum wage. There was no significant difference between the male and female groups regarding the sociodemographic variables.

Table 1 - Sociodemographic data of the studied population

Variable	Female	Male	Total (%)	P value*
Age				
0-9 years old	8	6	14 (21.5)	0.954
10-19 years old	7	8	15 (23.1)	
20-49 years old	18	16	34 (52.3)	
50 and over years old	1	1	2 (3.1)	
Residence				
Divinópolis	12	14	26 (40)	0.417
Other cities	22	17	39 (60)	
Color				
White	5	4	9 (13.8)	0.27
Brown or mullato	20	13	33 (50.8)	
Black	9	14	23 (35.4)	
Family monthly average				
1 to 2 minimum wages	18	13	31 (47.7)	0.44
2 to3 minimum wages	5	8	13 (20)	
3 to 5 minimum wages	6	7	13 (20)	
More than 5 minimum wages	5	2	7 (10.8)	
Not known	0	1	1 (1.6)	

* Pearson chi-square.

Table 2 - Frequency of recurrent infections according to gender, Divinópolis

Gender	None (%)	1 to 5 (%)	6 to 20 (%)	More than 20 (%)	Total (%)
Female	11 (32.3)	10 (29.4)	2 (5.9)	11 (32.3)	34 (100)
Male	11 (35.5)	8 (25.8)	4 (12.9)	8 (25.8)	31 (100)
Total	22 (33.8)	18 (27.7)	6 (9.2)	19 (29.2)	65 (100)

The main complication found in both genders was recurrent infections (Table 2). Figures 1 and 2 shows that only seven men (26%) and nine women (28%) who had at least one complication had no infection during their lifetime. Pulmonary and hepatobiliary complications were very common in both genders. The latter was reported by 11 (35.4%) male and 18 (52.9%) female patients. The neurologic complications showed similar frequency between the two genders; ocular complications were reported by three male patients. Renal events were more prevalent in women (7 to 20.6%) than in men (2 to 6.4%) according to the data presented in Table 3.

Among all researched complications, the most frequent was the occurrence of recurrent infections, followed by pulmonary (63%) and hepatobiliary (44.6%). On recurrent infections, 66% of patients had already had this problem at least once in their lifetime, and nearly 38% have been affected more than six times throughout life (Table 3). There was no significant difference between the number of infections by age group or gender.

The flowcharts in Figures 1 and 2 show different complications in male and female groups. Out of the total of 31 men, 22 (71%) presented a maximum of three complications, and nine (29%) had four or more. Among women, 30 (86%) had three or fewer complications, and four (14%) had four or more. In the age groups above 22 years, only two men (12.5%) did not have any complications in life. The most frequent combinations of complications were recurrent infections associated with another complication. Another point that stands out is the fact that young patients have reported five or more different complications during their lifetime.

The prevalence of chronic leg ulcers found in this study was 5% while 17% have reported ulcer at some point in life. Of the latter, seven (10.8%) were males and four (6.2%) were females. The areas most affected by ulcers were the medial malleolus, and the total healing time ranged from one month to three years. As for treatment, a wide variation was observed among the participants, most of whom held semi-occlusive dressings with the use of lubricant ointments and topical antibiotics associated with daily cleaning and monitoring in primary care units. Out of the three patients who had an ulcer at the time of the interview, only one was not being monitored in any health service, and the other two were followed-up in the basic units of the Unified Health System (SUS).

The progression time of ulcers in activity was three weeks, two months, and five years for each of the patients. None of the ulcers had an aspect of infection; they presented irregular edges and no odor or non-physiological secretion. All were classified as superficial, not exceeding the dermis, and showed signs of central granulation tissue. The patients used saline for local cleaning, and only one patient occluded the lesion and changed the dressing every other day. All used topical compounds to aid in hydration and combat local loss of moisture.

DISCUSSION

This study analyzed 65 patients with sickle cell anemia in the macro-region of Divinópolis with emphasis on complications manifested throughout life. The results are similar to the consulted literature. Among the identified complications, recurrent infections were the most frequent, followed by lung and hepatobiliary. The prevalence of chronic ulcer was 5%. Most patients belonged to low-income families and resided in the municipality of Divinópolis, possibly because this is the largest city and a hub in the Midwestern macro-region of Minas Gerais.

Table 3 - Frequency of percentage of occurrence according to the type of complication, Divinópolis

Complications	None (%)	1 to 5 (%)	6 to 20 (%)	More than 20 (%)	Total (%)
Recurrent infections	22 (33.8)	18 (27.7)	6 (9.2)	19 (29.2)	65 (100)
Neurological	54 (83.1)	8 (12.3)	0	3 (4.6)	65 (100)
Renal	56 (86.1)	5 (7.7)	2(3.1)	2 (3.1)	65 (100)
Pulmonary	24 (36.9)	27 (41.5)	7 (10.8)	7 (10.8)	65 (100)
Hepatobiliary	36 (55.4)	24 (37)	1 (1.5)	4 (6.1)	65 (100)
Ocular	62 (95.4)	3 (4.6)	0	0	65 (100)
Priapism	45 (69.2)	19 (29.2)	0	1 (1.5)	65 (100)
Priapismo	22 (71)	4 (12.9)	0	5 (16.1)	31 (100)*

* Excluding the female gender.

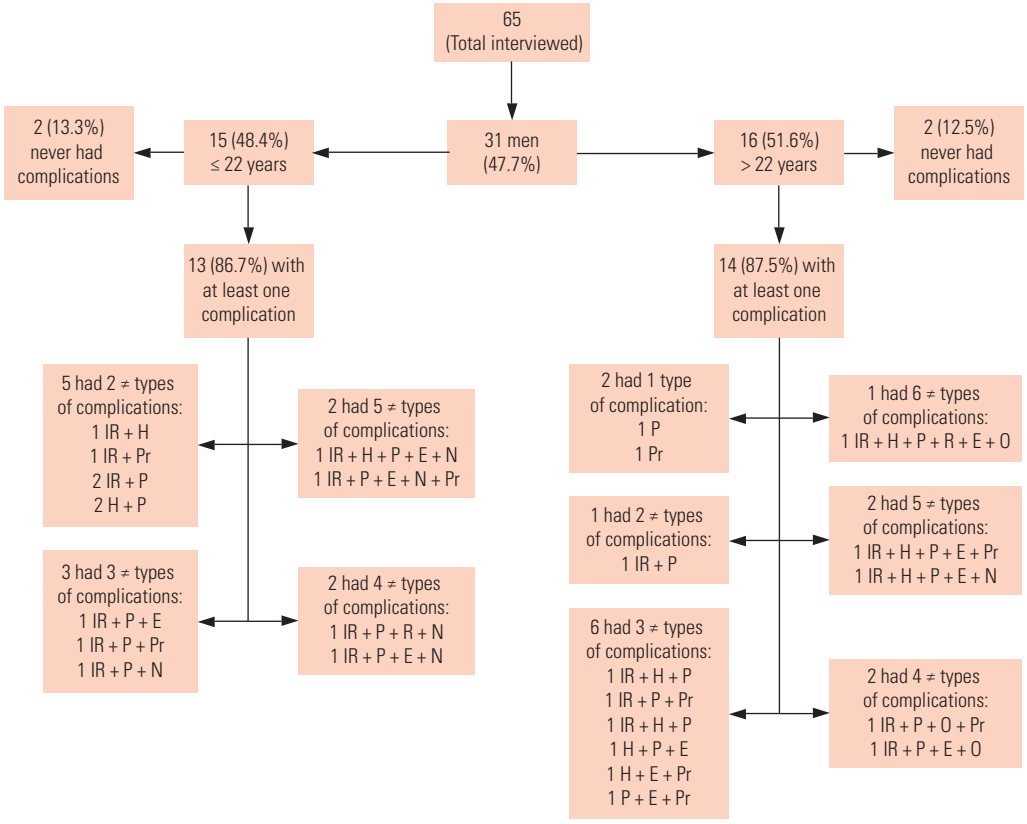

Figure 1 - Flowchart of complications in male patients according to the type of infections - IR = recurrent infections. H = hepatobiliary complications, P = pulmonary complications, E = splenic complications, R = renal complications, N = neurological complications, p = priapism.

It is known that recurrent infections are the most common complications of sickle cell anemia, considering that individuals with the disease have asplenia generated by splenic complications and become more susceptible to infections by mainly encapsulated microorganisms.[4] The appearance of respiratory diseases is justified by the recognition of acute chest syndrome in these patients, which can occur for various reasons such as: pneumonia, fat embolism, pulmonary or chest infarction, and infections in general, although in approximately 50% of cases there is no causal identification. The occurrence of these findings is more common among children but are more serious in adults.[15]

The high incidence of hepatobiliary complications is explained by the frequent occurrence of ischemia and cholelithiasis as a result of vascular obstruction and hemolysis, justifying the appearance of stones and jaundice in these patients. Moreover, hepatomegaly is often observed in these patients caused by hepatic congestion or by the fact that repeated blood transfusions may lead to excess of circulating iron and damage to the hepatic parenchyma.[15]

In analyzing the events occurred, it appears that although there is a similarity between the occurrence or not occurrence of an event, a higher number of different complications is observed among men than in women, which can be related to the finding of priapism, a symptom unique to this gender. Overall, the literature does not show significant differences in the prevalence of complications occurred in patients with sickle cell disease between men and women.[15,17,18] Small variations in prevalence observed between genders, such as in eye and kidney complications, may be due to the small size of our sample.

Regarding the distribution by age groups, some complications are more common in some age ranges. The most frequent complications in the range from zero to five years old were: recurrent infections, painful crises, splenic sequestration, jaundice, and stroke. In addition to these, ocular complications and cholelithiasis were reported in the range between six to 12 years old. Leg ulcers and priapism were also included in the range starting at 13 years old.[19]

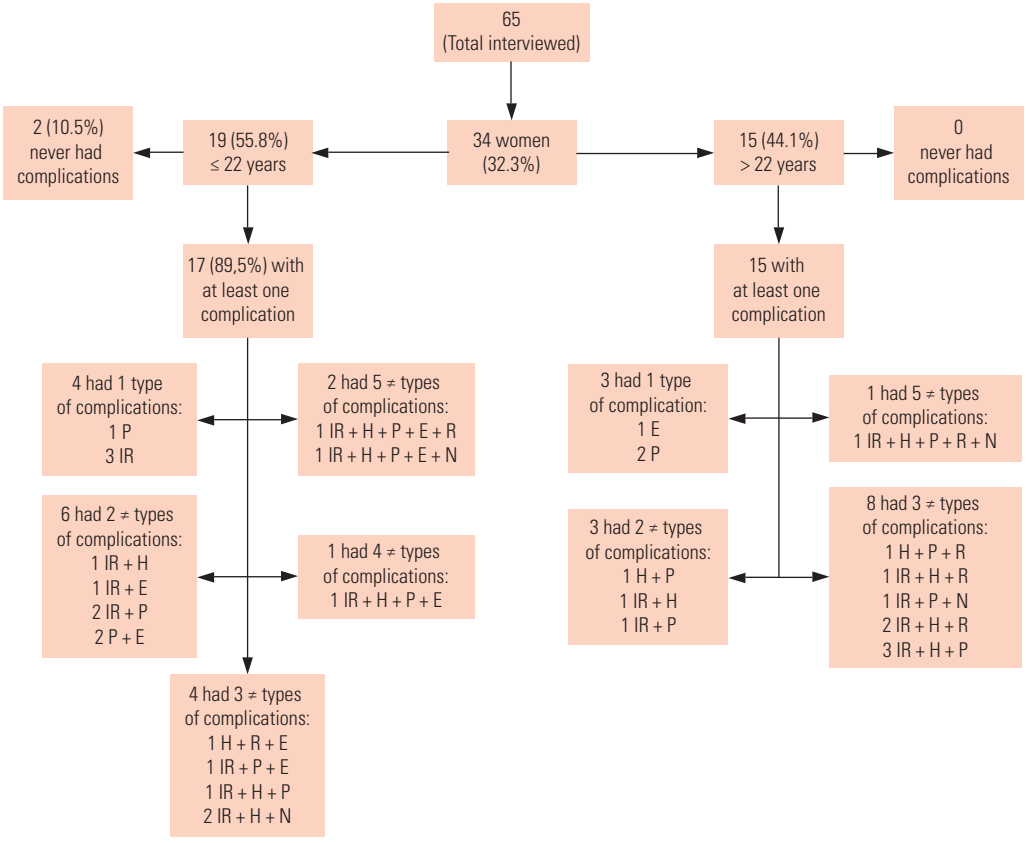

Figure 2 - Flowchart of complications in female patients according to the type of infections - IR = recurrent infections. H = hepatobiliary complications, P = pulmonary complications, E = splenic complications, R = renal complications, N = neurological complications.

Specifically on the occurrence of leg ulcers in our study and from these preliminary analyzes, it can be inferred that the prevalence of chronic ulcers is as expected and with preference for the male gender[12,18], however, there is no homogeneity in the treatments adopted by patients. The literature recommends that the approach to these patients be carried out with the support of a multidisciplinary team, orientation to the patient based on clinical and hematological points of view, correction of vitamin, minerals, and electrolytes deficiencies, dehydration, and malnutrition.[14,20] The observation of patients who have active ulcers for long periods indicates the need for frequent professional supervision in order to reduce its complications.

This study has some limitations that need to be considered. The first is that only patients registered at the Hemominas Foundation were interviewed, which could mean the loss of patients followed in other services. However, it is known that in the SUS network, the Hemominas Foundation constitutes the main follow-up service for these patients, and it is estimated that the registration database of Hemominas Foundation encompasses almost all patients in the region. Another limitation is a possible recall bias considering that patients with more complications may remember more details than those who did not have complications in life.

Despite these limitations, this study brings interesting results that can assist in the discussion of policies for the prevention of complications in patients with sickle cell anemia. Despite the small number of observations, few studies[16,17] evaluated combined complications in patients with the disease, which is a contribution of our study for the planning and raising of hypotheses that support further investigation in this population. Another point to be highlighted is the need for the network capacity to deal with complications and adherence to protocols for the prevention and treatment of complications, particularly in relation to chronic ulcers and care in the preparation of families to identify the problem and immediately search for treatment.

CONCLUSION

This study evaluated patients with sickle cell disease and their complications. The results reveal the need for the standardization of protocols, improved training of the network, and preparation of families. The verified complications possibly affect the quality of life of patients; considering the hereditary character of the disease and inevitability of its occurrence, prevention of complications should be the main target of health policies for sickle cell patients.

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