

Artigo / Article

Acute clinical events in patients with sickle cell disease: epidemiology and treatment

Eventos agudos em doença falciforme: epidemiologia e tratamento

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*Sickle cell disease is a hereditary illness of high prevalence in black population, and involved patients frequently have multiple hospitalizations. Our objective was to describe and to analyze the clinical course of hospitalizations in patients with sickle cell disease. Cross-sectional study of 78 patients submitted to 230 hospital admissions due to acute complications of sickle cell disease, from 2000 to 2004 in a public teaching hospital in Rio de Janeiro city, RJ, Brazil. Outcomes variables were length of hospital stay and death. Main covariables were age, gender, chronic renal failure, causes of hospitalization and use of medicines. Proportions were compared using the chi-square or the Fischer test, and for the continuous variables, Mann-Whitney test was used. The median age in years was 20.3 (15-53) and the most frequent clinical event was acute painful episode (73.5%). Mean length of stay was significantly higher in admissions caused by different reasons than acute painful episode ($p < 0.001$), in those with chronic renal failure ($p = 0.006$) or with bacterial infection ($p = 0.002$). The number of deaths was higher in admissions with bacterial infection ($p = 0.049$) or chronic renal failure ($p = 0.014$). Gram-negative bacteria isolated from febrile patients included *Pseudomonas* sp and *Acinetobacter* sp. This study allowed a larger knowledge concerning morbidity and mortality among adolescent and adult patients hospitalized with sickle cell disease. As few studies with data from hospital admissions are available, the findings can be useful in public health area, especially on healthcare planning to the population with sickle cell disease. Rev. bras. hematol. hemoter. 2008;30(2):95-100.*

Key words: Sickle cell anemia; epidemiology; hospitalizations; treatment.

Introduction

Sickle cell disease is the most common hereditary illness in the world, affecting mainly people of black ethnicity.¹ In the Brazilian Southeast area, incidences vary from one case of illness to each 1.196² to 2.800³ births. The illness is characterized by a mutation in the 6th codon of the beta hemoglobin⁴ gene which results in the substitution of valine for glutamic acid in position six of beta chain of the hemoglobin, with the resulting abnormal hemoglobin (HbS)

responsible for alterations in the erythrocytes that culminate with the obstruction of the microcirculation, ischemia, tecidual necrosis and organic dysfunction^{5,6}

Sickle cell disease or, more specifically, sickle cell anemia (homozygote SS), is characterized by a high mortality, especially among youths.⁷ In Brazil, about 80% of the deaths by sickle cell disease happen under 30 years of age.⁸ Sharp pain, also called acute painful episode, is the clinical stamp of the disease and its more frequent clinic manifestation.⁹ Acute pain onset can happen after the first six months of life

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with an unpredictable course of pain crisis. A life of intense pain episodes and the need for recurrent hospitalizations turn sickle cell anemia into a unique disease.¹⁰ In Brazil, data on the admissions of patients with sickle cell disease, as well as their epidemiological and clinical characteristics, are scarce.

The objective of the study was to describe the frequency of acute clinical events and the characteristics of the treatment, as well as investigating the correlation between demographic and socioeconomic characteristics and the evolution of patients admitted with sickle cell disease in a Brazilian population.

Patients and Method

The studied population was composed by all patients bearers of sickle cell disease in a public teaching hospital that belongs to the Unified Health System in the Rio de Janeiro city, a reference hospital in the treatment of the disease, and that assists patients of 12 years of age or more. The acute clinical events associated to sickle cell disease were analyzed, in the period from 2000 to 2004. The identification of the clinical records was made from the computerized hospital database, for morbidity, in agreement with the 10th revision of the International Classification of Diseases, being selected the cases classified as D57 (sickle cell disease). All the clinical records were revised, and the non-hospitalized patients in the period were excluded. Seventy eight patients had at least one admission by acute events, in which the patient remained in hospital for, at least, 24 hours. A total of 230 admissions were analyzed. The cases with 13 to 19 years of age were defined as adolescents and those with 20 years, or more, as adults.

The outcomes variables were length of hospital stay and death. The covariables were age, gender, ethnicity, education, city of residence, phenotype, chronic renal failure, causes for admission, opioids and antibiotics use.

Acute painful episode was defined as an acute pain in the extremities, in the thorax, in the abdomen or in the lumbar area, for which there was not another explanation. Acute thoracic syndrome was defined by thoracic pain, a new pulmonary infiltrate at radiography, fever and respiratory symptoms (cough, dyspnea). Stroke was defined by the presence of a neurological syndrome secondary to the occlusion of an artery or to a hemorrhage, evaluated by a computerized brain tomography. The infections were defined according to the clinical features in patients with fever, submitted to an extensive evaluation of infection that included medical history, physical examination, hemogram, hemocultures and other exams, such as, urinoculture, thorax and paranasal sinuses radiographies, or abdominal ultrasonography, in patients with specific signs and symptoms.

Data were collected retrospectively by medicine students, using standardized forms.

Statistical analysis

Length of stay was analysed as quantitative variable (median); age and opioid use as categorical as well as quantitative variables (medians) and the rest as categorical variables. The differences among the subgroups were evaluated using chi-square or the Fisher exact test for proportions and the Mann-Whitney test for quantitative variables. All P values were two-sided and a P value equal to or smaller than 0.05 was considered significant. The analysis was performed using Statistical Package for the Social Sciences (SPSS), version 10.0.

The study was conducted in agreement with the Helsinki Declaration (1964) and approved by the Ethics and Research Committee of the Escola Nacional de Saúde Pública/Fundação Oswaldo Cruz, Rio de Janeiro.

Results

One hundred and eight patients with sickle cell disease had been attended regularly in the hospital and were in the computerized hospital database. Seventy eight patients were admitted at least once in the time frame of this study. There were 230 hospitalizations due to acute events related to the disease from 2000 to 2004.

Sixty eight patients (87.2%) presented up to five admissions, five (6.4%) presented ten or more admissions and one patient (1.3%) presented twenty admissions. The median age, in years, was 20.3 (13-53) and 95% of the patients were 40 years old or less. Patients' characteristics are presented in Table 1. The sex ratio was similar and most of the cases were black or brown. Almost 60% of the patients had an elementary school education. Most patients (62.8%) lived in the Rio de Janeiro city. The most frequent phenotype was SS (80.8%).

The most frequent clinical event observed in the 230 admissions was acute painful episode (73.5%). Bacterial infections were diagnosed in approximately a third of hospitalizations (30.4%). (Table 2) Simultaneous presence of acute painful episode with bacterial infection took place in 35 cases (15.2%).

Opioids were prescribed in 195 hospitalizations (84.8%) and parenteral morphine in 181 (78.7%). In the 222 admissions in which some analgesic was prescribed, the first analgesia administered after hospital admission was morphine or mepheridine, in 171 cases (77%).

Mean length of stay in days was 6.0 (1-79). Among the adults, it was significantly lower in hospitalizations due to acute painful episode (5.0 x 14.0; $p < 0.001$), and in those who died (2.0 x 6.0; $p = 0.001$) but it was higher in those with bacterial infection; among adults, mean length of stay was significantly higher in those with bacterial infection (8.5 x 5.0; $p = 0.001$), and in those with chronic renal failure (17.5 x 5.0; $p = 0.006$). Independently of the age group, those who received antibiotics stayed longer in hospital (7.0 x 5.0; $p < 0.001$) (Table 3).

Table 1. Clinical features of patients with sickle cell disease, admitted to a teaching hospital, adolescents and adults. Rio de Janeiro, 2000 to 2004 (n = 78)#

Patients features	Age, years		
	13 to 19 n = 33 (%)	20 or more n = 45 (%)	Total n = 78 (%)
Gender			
Female	17 (42.5)	23 (57.5)	40 (51.3)
Male	16 (42.1)	22 (57.9)	38 (48.7)
Ethnicity*			
Black or brown	26 (41.9)	36 (58.1)	62 (79.5)
White	6 (40.0)	9 (60.0)	15 (19.2)
Education**			
Elementary school	19 (42.2)	26 (57.8)	45 (57.7)
Other	4 (25.0)	12 (75.0)	16 (20.5)
Adress (city)			
Rio de Janeiro	22 (44.9)	27 (55.1)	49 (62.8)
Other***	11 (37.9)	18 (62.1)	29 (37.2)
Phenotype			
SS	25 (39.7)	38 (60.3)	63 (80.8)
Other****	8 (53.3)	7 (46.7)	15 (19.2)
Chronic renal failure!			
Yes	1 (33.3)	2 (66.7)	3 (3.8)
No	32 (42.7)	43 (57.3)	75 (96.2)
Death			
Yes	5 (41.7)	7 (58.3)	12 (15.4)
No	28 (42.4)	38 (57.6)	66 (84.6)

#P value for differences between strata was not significant

*1 case without information; **17 cases without information

*** Most of the municipalities are located in Baixada Fluminense

**** SC, S β ; ! all cases were related to sickle cell disease

Table 2. Causes of admissions for patients with sickle cell disease, admitted to a teaching hospital, adolescents and adults. Rio de Janeiro, 2000 a 2004 (n = 230)

Causes of admission*	Age, years		
	13 to 19 n = 106 (%)	20 or more n = 124 (%)	Total n = 230 (%)
Acute painful episode	76 (71.7)	93 (75.0)	169 (73.5)
Bacterial infection**	30 (28.3)	40 (32.3)	70 (30.4)
Acute thoracic syndrome	11 (10.4)	8 (6.5)	19 (8.3)
Chronic renal failure***	3 (2.8)	7 (5.6)	10 (4.3)
Priapism	1 (0.09)	3 (2.4)	4 (1.7)
Hemorrhagic stroke	0 (0)	2 (1.6)	2 (0.9)
Isquemic stroke	1 (0.09)	0 (0)	1 (0.4)

*More than one cause could have occurred simultaneously;

**Pneumonia, cellulitis, sinusitis, osteomyelitis, meningitis, bacteremia, cholecystitis, urinary tract infection, dialysis catheter infection. Bacteria were isolated from blood and/or urinary tract in 18 cases, and in 15 were gram-negative *Acinetobacter sp* (1), gram-negative not identified (1), *Enterobacter sp*(3), *E. Coli* (4), *Pseudomonas sp* (3), *Salmonella sp* (2), *Citrobacter sp* (1).

***All cases of chronic renal failure were related to sickle cell disease

Within the observation period, 12 out of 78 followed patients died (15.4%). Death proportion among admissions was of 5.2% (12/230) and there was no significant difference among adolescents (4.7%) and adults (5.6%). Table 4 displays a significantly higher death proportion in

hospitalizations with bacterial infection (p = 0,049), in those in whom mechanical ventilation was used (p < 0.001) and in those patients with chronic renal failure (p = 0.014). There was no difference between the age of the patients who died and the ones who didn't. Length of stay and the period of opioid usage were smaller among those who died (2.0 X 6.0; p = 0.02 and 2.0 X 4.0; p = 0.009, respectively) (Table 4).

Discussion

Only half of the patients with sickle cell disease regularly followed up were hospitalized during the period of the study, meaning that while some of them were hospitalized many times, others never were. This finding are compatible to the known phenotypic diversity of patients with sickle cell disease, which varies from the absence of symptoms to several clinical complications and hospitalizations, in spite of a single molecular alteration.¹

The studied sample was constituted by adolescents and adults, with a median age below 30 years. As the mortality among the young population decreases due to the adoption of measures such as prevention and early treatment of bacterial infection in childhood,¹¹ the adult population with chronic organic dysfunctions increases, so it's important, in studies with patients with sickle cell disease, to distinguish adults from children and adolescents.

Although most of the patients are resident in the Rio de Janeiro city, more than a third lived in other cities; most of them located in the area of the State of Rio de Janeiro denominated "Baixada Fluminense", the second most populous area of the State, characterized by high poverty and serious social problems.

Considering that all admissions were emergency attendances (not elective), some of the cases that came from cities other than Rio de Janeiro could have been examined closer to the patients' households, especially in the admissions due to non-severe acute painful episode, that need a simple clinical management. Probably, there is a low quality of health system in the cities of origin with lack of proper healthcare units. Besides, patients as well as

professional of other cities, like a teaching hospital better with plenty of resources, in spite of the distance between the households and the Hospital. Additionally, there are not clear healthcare programs for those patients in the State, or even reference systems among healthcare units.

Table 3. Mean length of stay according to clinical characteristics among patients with sickle cell disease, admitted to a teaching hospital, adolescents and adults, Rio de Janeiro, 2000 a 2004 (n = 230)

Characteristics	Mean length time, days (median)		p value	Total n = 230 (range)
	Age, years			
	13 to 19 n = 106 (range)	20 or more n = 124 (range)		
Acute painful episode				
Yes (169)	6.0 (1-35)	5.0 (1-23)	ns	5.0 (1-35)
No (61)	4.5 (1-79)	14.0 (1-65)	0.02	6.0 (1-79)
P value	ns	< 0.001		0.016
Acute thoracic syndrome				
Yes (19)	11.0 (1-35)	9.0 (1-58)	ns	9.0 (1-58)
No (211)	8.5 (1-79)	6.0 (1-65)	ns	6.0 (1-79)
P value	ns	ns		ns
Bacterial infection				
Yes (70)	6.5 (1-79)	8.5 (1-65)	ns	7.5 (1-79)
No (160)	5.0 (1-25)	5.0 (1-37)	ns	5.0 (1-37)
P value	ns	0.001		0.002
Chronic renal failure				
Yes (11)	8.0 (2-17)	17.5 (1-37)	ns	17.0 (1-37)
No (219)	6.0 (1-79)	5.0 (1-65)	ns	5.0 (1-79)
P value	ns	0.006		0.006
Death				
Yes (12)	8.0 (2-35)	2.0 (1-14)	ns	2.0 (1-35)
No (218)	6.0 (1-79)	6.0 (1-65)	ns	6.0 (1-79)
P value	ns	0.001		p = 0.020
Mechanical ventilation				
Yes (12)	5.5 (2-35)	2.0 (1-58)	ns	2.0 (1-58)
No (218)	6.0 (1-79)	6.0 (1-65)	ns	6.0 (1-79)
P value	ns	Ns		ns
Opioid use				
Yes (195)	6.0 (1-79)	6.0 (1-58)	ns	6.0 (1-79)
No (35)	3.5 (1-75)	6.0 (1-65)	ns	4.0 (1-65)
P value	ns	ns		ns
Antibiotic use				
Yes (155)	6.0 (1-79)	7.0 (1-65)	ns	7.0 (1-79)
No (75)	5.0 (1-25)	4.5 (1-23)	ns	5.0 (1-25)
P value	0.021	0.003		< 0.001
Total	6.0 (1-79)	6.0 (1-65)	ns	6.0 (1-79)

Acute painful episode occurred in most of the hospitalizations. This event, besides being the most frequent in sickle cell disease,⁹ is also the main cause of hospital admission,¹² being the most frequent in SS form, what was also observed in this study. Bacterial infections were frequent, with a high prevalence of infections due to gram-negative bacteria, including infections acquired in the community, which is described in literature, as well from hospital setting. As patients with sickle cell disease are immunosuppressed, bacterial infections are an important cause of morbidity and mortality,^{7,13} independent of the age group, particularly between 1 and 3 years of age. It's already known that among adolescents and adults, most infections are caused by gram-negative bacteria. The isolated gram-negative pathogens

ordinary in hospital setting in this study points out another morbidity in these patients. Besides their susceptibility to bacterial infections, when the patients present clinical complications that lead to hospitalizations, they are submitted to complex and invasive procedures, becoming susceptible to infections caused by more aggressive germs from the hospital setting itself, with a different epidemiology from infections characteristic of the sickle cell disease, such as *Streptococcus* infections which occurs in early childhood.

Length of stay is one of the indicators used to evaluate the performance and the productivity of hospitals,¹⁴ and in this study, the mean length of stay was 6 days, similar to the another national study, in which it varied from 4 to 8 days¹⁵ and similar to the Unified Health System national mean (5.98 days).¹⁴ Among admissions due to acute painful episode the expected length of stay it is not long, varying from 4 to 10 days,¹ what certainly influenced the overall estimated length of stay in our study. Mean length of stay did not vary significantly among adolescents and adults, except in admissions due other causes than acute painful episode, being lower among the adolescents. Length of stay in cases with a bacterial infection and prescription of antibiotics was longer, suggesting more complex clinical situation and the use of parenteral antibiotics use. The presence of chronic renal failure, a disease with serious evolution in patients with sickle cell disease, is related to a more complex clinical evolution, what could have contributed to a longer hospitalization.

In this study, the proportion of hospitalizations in which the endpoint was death (5.2%) was similar to the one of another national study with patients hospitalized with sickle cell disease¹⁵ and it didn't vary between adolescents and adults. In relation to the death rate by patient, our estimate (15.4%) was lower than the one reported by Ballas *et al.*¹⁶ (19,1%),

that followed up North American patients for five years, and similar to the one reported by Houston-Yu *et al.*¹⁷ (15.5%), that followed up patients for two years. In the two above mentioned studies the patients had more severe evolution and worse prognosis: in Ballas *et al.*¹⁶ the patients were homozygotes SS (sickle cell anemia) and in Houston-Yu *et cols.*¹⁷ they had been previously hospitalized several times. In the present study, the patients were not selected according to prognosis criteria.

The age at hospitalization was not different among the patients who died and the ones who did not. However, compared to other studies, median age at death was lower, about 21 years. In a national study with hospitalized patients of any age group,¹⁵ the age at death varied, from 26.5 to 31.5

years, depending on the State considered. The age at death found in the present study was about a decade lower than the one reported by Houston-Yu *et al.*¹⁷ in North American patients (33.5 years). The comparison between our study and the one of Houston-Yu *et al.*¹⁷ is possible because, in both, the patients were adolescents and adults (children were excluded).

There was not significant association between death and acute painful episode, acute thoracic syndrome or length of stay. Mortality was significantly higher in those with bacterial infection, reinforcing the importance of the recognition and appropriate treatment of infections in these patients, even out of the age group with higher risk, the childhood. The association between bacterial infection and mortality is known for a long time.^{7,9} Recently, Mancini *et al.*¹⁸ confirmed it, when reported that the infection was the main cause of death in patients with sickle cell disease evaluated by necropsy, independent of the age group. The present study showed a higher incidence of deaths among chronic renal failure cases, which is the main reason of morbidity among chronic organic lesions of sickle cell disease and a known risk factor for early death.¹⁹ Mechanical ventilation is a procedure reserved to patients of high risk and, in this study, it was associated to death, suggesting that this procedure was a marker for cases with a very unfavorable clinical evolution. A shorter length of stay and a smaller number of days with opioid therapeutics were death predictors, suggesting that severity was not associate to prolonged stay or opioid use.

Opioids use for pain management was universal and parenteral morphine was the most prescribed drug, a procedure recommended by American Pain Society²⁰ for cases of moderate-to-severe pain. Unfortunately, pain in most of cases was not measured by a pain score, thus hiding an analysis about the quality of the pain control.

A limitation of this study was the inclusion of patients from a single hospital, a public teaching one, not representative of patients with sickle cell disease as a whole, jeopardizing external validity. Lack of information prevented us from handling patients' socioeconomic profile. There were not registries on income data in most of the clinical records, and the blank supplied to education data was not always filled out.

Conclusions

We considered this study relevant to allow a larger knowledge concerning morbidity and mortality among adolescent and adult patients hospitalized with sickle cell

Table 4. Proportion of deaths among patients with sickle cell disease, admitted to a teaching hospital, according to age and clinical characteristics, Rio de Janeiro, 2000 a 2004 (n =230)

Clinical characteristics	Death		p value	
	N = 230			
		Yes n =12 (%)	No n = 218 (%)	
Age, median (years)		21.4 (13-40)	20.2 (13-54)	ns
Acute painful event				
Yes (169)		7 (4.1)	162 (95.9)	ns
No (61)		5 (8.2)	56 (91.8)	
Bacterial infection				
Yes (70)		7* (10.0)	63 (90.0)	0.049
No (160)		5 (3.1)	155 (96.9)	
Gram negative bacteria				
Yes (16)		3 (18.8)	13 (81.2)	0.041
No (214)		9 (4.2)	205 (95.8)	
Acute thoracic syndrome				
Yes (19)		2 (10.5)	17 (89.5)	ns
No (211)		10 (4.7)	201 (95.3)	
Mechanical ventilation				
Yes (12)		10 (83.3)	2 (16.7)	< 0.001
No (218)		2 (0.9)	216 (99.1)	
Chronic renal failure				
Yes (11)		3 (27.3)	8 (72.7)	0,014
No (219)		9 (4.1)	210 (95.9)	
Length of stay, median (days)		2.0 (1.0-35.0)	6.0 (1-79)	0.020
Length of opioids usage, median (days)		2.0 (0-4.0)	4.0 (0-27.0)	0.009

disease. There are few studies with data from hospital admissions, then the study results can be useful in public health area, especially on healthcare planning to the population with sickle cell disease.

Resumo

A doença falciforme é uma doença hereditária, de alta prevalência na população negra, que leva a múltiplas internações hospitalares. Nosso objetivo foi descrever e analisar o curso clínico de pacientes com doença falciforme hospitalizados. Realizou-se estudo transversal de 78 pacientes submetidos a 230 internações hospitalares devido a complicações agudas da doença falciforme, de 2000 a 2004, em um hospital universitário no Rio de Janeiro-RJ, Brasil. Os desfechos estudados foram tempo de permanência hospitalar e óbito. As principais co-variáveis foram idade, sexo, presença de insuficiência renal crônica, causas de hospitalização e uso de medicamentos. Proporções foram comparadas utilizando-se o teste qui-quadrado ou teste de Fischer; e, para as variáveis contínuas, o teste de Mann-Whitney foi utilizado. A mediana da idade foi 20,3 anos (15-23) e o evento clínico mais freqüente foi o episódio doloroso agudo (73,5%). O tempo médio de permanência hospitalar foi maior nas internações por causas distintas do episódio doloroso agudo

($p < 0,001$), e naquelas com o diagnóstico de insuficiência renal crônica ($p = 0,006$) ou infecção bacteriana ($p = 0,002$). O número de óbitos foi maior nas internações com o diagnóstico de infecção bacteriana ($p = 0,049$) ou insuficiência renal crônica ($p = 0,014$). Os germes gram-negativos isolados nos pacientes com febre incluíram *Pseudomonas sp* e *Acinetobacter sp*. O presente estudo permitiu um maior conhecimento acerca da morbimortalidade entre adolescentes e adultos hospitalizados com doença falciforme. Como poucos estudos sobre internações hospitalares estão disponíveis, os achados podem ser úteis no campo da saúde pública, em especial na área de planejamento de saúde da população de pacientes com doença falciforme. Rev. bras. hematol. hemoter. 2008;30(2):95-100.

Palavras-chave: Anemia falciforme; Tempo de permanência hospitalar; tratamento.

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