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ORIGINAL ARTICLE

Profile of falcemic children hospitalized during crises

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anemia, sickle cell; acute pain; epidemiology; child.

Abstract

Objectives: To describe the profile of patients with sickle cell disease and seizures hospitalized in the pediatric unit between January 2014 and October 2016. **Methods:** Descriptive, retrospective study with analysis and data collection from medical records. Inclusion criteria: ICD on admission of sickle cell anemia (D57.0) and exclusion: ICD of sickle cell anemia without crisis (D57.1). **Results:** There were 99 admissions of 42 patients, 42.9% female and 57.1% male; aged between 1 and 17 years; 45.2% between 6 and 12 years; in 47.6% of the cases, the diagnosis was in the neonatal period; 91% of hospitalizations were due to painful seizures; in 55.5% of cases, the crisis involved more than one pain site simultaneously and 44.5%, single site pain: 14% abdominal pain, 15% lower limb, 5% upper limb pain, 4.5% % headache, 3% chest pain, 1% back pain, 1% low back pain and 1% neck pain; 85.7% of the patients had previous hospitalizations, due to pain attacks and infections; 59.5% used opioid (morphine); 31% used hydroxyurea. **Conclusions:** A predominance of males, most being school-age patients and with diagnosis in the neonatal period. Pain crisis was the leading cause of hospitalization and pain in more than one location was more prevalent.

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INTRODUCTION

Sickle cell disease (SCD) involves a spectrum of diseases that is caused by a mutation in the beta globin hemoglobin gene, resulting in abnormal hemoglobin - hemoglobin S (HbS). It is estimated that in Brazil, there are 2 million HbS gene carriers, more than 8,000 affected with the homozygous form and between 700-1,000 new cases of SCD in the country annually[1].

SCD presents acute complications, being the most common: painful vaso-occlusive crises (affecting limbs and the spine) and Acute Thoracic Syndrome (ATS), according to Gellen-Dautremer et al[2]. Painful crisis are caused by tissue damage secondary to blood flow obstruction caused by sickle cells and are a frequent cause of hospitalization, appearing as the first manifestation of the disease in most cases.

The sites most affected in acute pain crises are: the extremities, lumbar region, abdomen or thorax. The incidence and prevalence vary according to age, gender, genotype and laboratory abnormalities, ranging from moderate to transient episodes, generalized episodes that last for days or weeks, with a variable pain pattern[3].

The approach of these patients should be individualized and optimized through multiprofessional teams, hence the importance of constant study on the subject. The treatment is supportive and based initially on the control of pain and investigation of associated complications, mainly infectious conditions. It is important to look for and correct possible triggering factors, such as hypoxia, acidosis and dehydration. The continuous use of hydroxyurea has been shown to be effective in reducing vaso-occlusive phenomena and constitutes a good continuous therapeutic option[4].

Evaluating the profile of these patients is relevant because it is a pathology that is still a challenge in clinical practice, involving patients who suffer periodic complications, with an impact on their quality of life and family members. The objective of this study is to describe the profile of patients with SCD in crisis, hospitalized in the pediatric ward of a hospital in the state capital of Bahia, from January 2014 to October 2016, observing: age, gender, time of diagnosis, medications used to treat the crisis, previous use of hydroxyurea (and/or other therapeutic/prophylactic medications), previous hospitalizations, regular outpatient follow-up with specialist, hospital stay, associated comorbidities, associated pneumonia, other acute complications of the underlying disease during hospitalization and need for admission to an Intensive Care Unit (ICU).

METHODS

A descriptive, retrospective study was carried out, through the analysis and data collection of medical records of patients with SCD hospitalized with crisis, in the pediatric ward of a hospital in the capital of Bahia, from January 2014 to October 2016. Information was obtained from from the database of the computerized system (MVPEP / PAGU) used in the institution. Subsequently, the data was organized into spreadsheets using the Microsoft Excel 2013 software and files in Microsoft Word 2013, Windows 8, from which we created tables and graphs.

The inclusion criteria were patients whose ICD upon admission to the Pediatric Emergency Unit (PEU) and/or International Code of Diseases (ICD) upon hospital discharge with a description of sickle cell anemia WITH CRISIS (ICD10: D57.0). However, the exclusion criteria were patients whose ICD upon admission to the PEU and/or ICD upon hospital discharge with a description of sickle cell anemia WITHOUT CRISIS (ICD10: D57.1). The project was approved in November 2016 by the Research Ethics Committee of Bahia Hospital, with Certificate of Presentation for Ethical Assessment (CAAE) number 62046316.0.0000.0048 and under protocol # 1,841,058.

RESULTS

There were 99 hospitalizations of 42 patients in the pediatrics ward, 42.9% (18) of them female and 57.1% (24) male. The patients were evaluated in the age range of 1 year and 2 months up to 17 years (Figure 1).

About the time of diagnosis of SCD, the majority occurred in the neonatal period, through a screening test (foot test), corresponding to 47.6% (20) of the patients evaluated. Three other patients were diagnosed at different periods: 1 (2.4%) of them at 4 months of age, 1 at one year of age and the other at 5 years of age. It was not possible to define the diagnosis timeframe in 45.2% (19) of the patients, because this information was not present in their medical records.

Single-site pain location occurred in 44.5% (40) of the hospitalizations, and was distributed as follows: 14% (12) abdominal pain; 15% (13) lower limb pain; 5% upper limbs; 4.5% (4) headache; 3% (3) thoracic pain; 1% (1) back pain; 1% (1) low back pain and 1% (1) neck pain. Of the patients who experienced pain in more than one location simultaneously, spine pain associated with limb pain prevailed.

Upon analyzing the medical records, 6 patients were hospitalized for other causes, totaling 9 admissions: one was

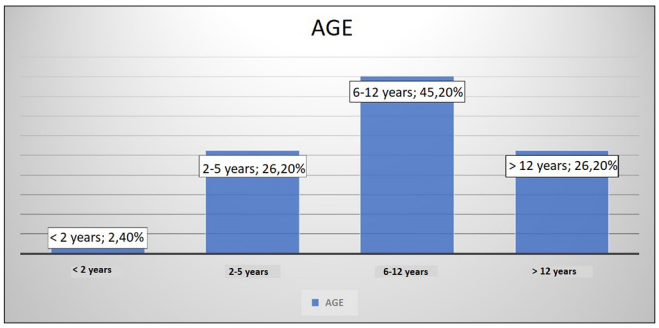

Figure 1. Age range distribution of patients with sickle cell disease and pain crisis.

hospitalized on two occasions, one due to severe transfusion reaction and the other to acute thoracic syndrome (ATS); another, for splenic sequestration and fever to be clarified in two moments; another one, due to hemolysis and associated infection; another patient was hospitalized twice for exchange transfusion, one for pneumonia and the other for syncope.

In 8 of the hospitalizations, there were other acute complications of SCD, in addition to the pain crisis: 3 patients had ATS, 2 splenic sequestrations (in the same patient), one hospitalization hemolysis, one case of bone infarction, and one of venous thromboembolism .

It should be noted that 3 patients presented more hospitalizations when compared to the others in the study. Each had a significant number of hospitalizations in the period, being: 16, 9 and 7, respectively. In the patient who was hospitalized 16 times, 15 hospitalizations were motivated by a pain attack and one for syncope investigation. Similar characteristics were fouind among the 3 patients: female gender, age above 12 years and hospitalizations mainly due to pain crisis, infections (pneumonia more commonly) and surgeries. Two of these children were under regular use of hydroxyurea (HU).

The majority of patients, 85.7% (36) were hospitalized before the period evaluated. Of these, most of them presented more than one hospitalization per year, the main causes being: pain and infection. Pneumonia was the most prevalent infection.

In the three years included in the study, there were 36, 27 and 36 admissions in 2014, 2015 and 2016, respectively. Average of 33 hospitalizations per year. There were 842 days of hospitalization for a total of 1,035 days (34 months), overall. Dividing this total of days by the number of patients (42), it means that each patient remained on average 20 days in a hospital environment in the period studied, that is, an average of 6.6 days per year.

In the cases contemplated by the study in Salvador, 59.5% (25) of the patients used opioid (morphine) during hospitalization. In addition, of a total of 90 hospitalizations per crisis in the period evaluated, in 86.7% (78) of them, morphine was used in association with other analgesic medications.

Regarding the use of hydroxyurea, 13 (31%) patients were using it. Of the 42 patients, 41 were in regular use of folic acid and 21 used penicillin for infections prophylaxis. Four of these patients used other medications for specific conditions: iron chelator (2 patients) due to secondary hemochromatosis, anticoagulant in 1 patient with a history of thromboembolism and vitamin D supplementation in another patient. Only in the case of one of the patients, there was no record of the use of prophylactic drugs.

In our sample, 40 patients had regular follow-up with a specialist (pediatric hematologist) and 2 did not follow up. Four of these patients were also followed by other specialists for associated comorbidities: 1 with gynecologist, 1 with endocrinologist for short stature, 1 with a cardiologist because of interatrial communication (CIA) and 1 with the orthopedist for lumbar hernia.

Of the 42 patients, 26 had no associated comorbidities. However, in 16 of them, pathologies, either isolated or in association, were found: asthma (3), allergic rhinitis (3), scrofulous prurigo (1), short stature (2), obesity (1), lactose intolerance drug allergy (2) - dipyrone (1) and codeine (1), chronic constipation (2), sequelae of stroke in 3 of them, lumbar hernia (1), IAC (1) and Moya-Moya disease .

Considering the 99 admissions, there were associated pneumonia in 18 of them. (1), STA (1), bacteremia (1), venous thromboembolism (1), severe transfusion reaction associated with infection without definite focus (1) (2), pneumonia associated with ATS (2), pneumonia and abdominal pain (1), and without an allergic crisis, to investigate syncope (1). There were no deaths among these hospitalized patients during the study period.

DISCUSSION

There are studies on patients with sickle cell disease, whether in the pediatric age group or in adults, performed worldwide. However, each of them is developed from a different perspective, including: epidemiology, clinical aspects, treatment of the pain crisis and other acute complications of the disease.

The patients hospitalized with an allergic crisis at this hospital in Salvador during the period evaluated were mostly males, they were in the school age group and were diagnosed in the neonatal period. This is in line with the slightly male predominance of studies conducted in Brazil in hospitalized pediatric patients with SCD, as described by Capoulade and Laurindo[5] and Grunewald and colleagues[6], in which 52.5% and 50% of the patients were males, respectively.

Among the acute complications of SCD, the pain crisis was the major cause of hospitalization among these patients and pain in more than one location simultaneously was the most prevalent (Figure 2). According to Field and colleagues[7], painful crises are the most common presentation among patients with SCD, corresponding to more than 80% of hospital admissions. Since 1981, Murtaza and colleagues[8] postulated, through studies with children with SCD in London, that the most common cause of hospitalization in this group was the vaso-occlusive pain crisis.

In addition, in Indianapolis, USA, a study involving pediatric SCD patients concluded that painful vaso-occlusive crises are the most common causes of hospitalization[9]. Likewise, a study conducted in Kuwait by Akar and Adekile[10], who observed for 10 years hospitalizations of children with SCD, found that the main reason for hospitalization was vaso-occlusive crises (63.2%). Also corroborating the findings of the present study, there is a randomized clinical trial carried out with children with SCD in the United States, in which the researchers concluded that vaso-occlusive crisis is an

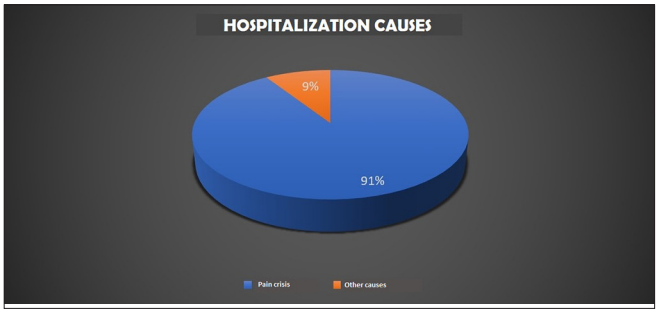

Figure 2. Hospital admission causes of SCD pacientes between January 2014 and October 2016.

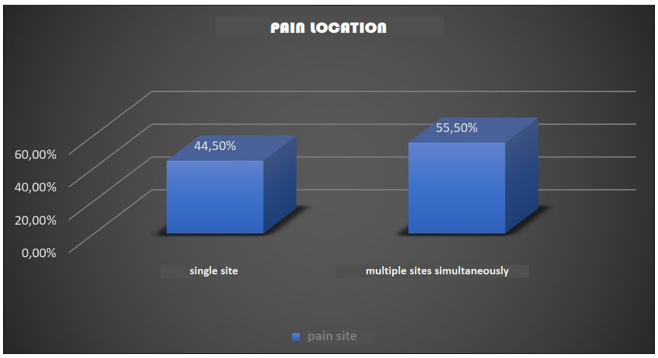

Figura 3. Pain location (pain crisis).

important cause of pain and was considered the most common complication in SCDF[11].

Augier et al.,[12] in a study carried out in Jamaica involving patients with SCD and pain, described 8 different pain sites, the most common being the lower limbs (44.6%), although the majority (60.3%) experienced more than one site in the same period; similar to the present study, in which the majority (55.5%) of patients presented pain in more than one site simultaneously (Figure 3). Babela and colleagues[13] postulated that the sites of major involvement in painful SCD episodes are: long bones, abdomen and thorax, a result similar to the one in the present study that showed pain distribution (in an isolated location) with a higher prevalence in the lower limbs (15% of patients) and abdominal pain (14%).

Debaun et al.,[4] analyzed a series of cases, containing 145 adults with hospitalized SCD, and reported on the prevalence of pain in the following places: dorsal region (63%), left arm (61%), right arm (30-40%), thorax (26%), abdomen (26%) and lumbar region (12%). Differently, in the study conducted in Salvador, a lower proportion of such sites were reported: 5% (5) upper limb pain, 3% (3) thoracic pain, 1% (1) back pain and 1% (1) low back pain.

On the other hand, studies carried out in the 1980s in the United States and Europe with children and adults with SCD showed that preschoolers had predominantly limb pain, while schoolchildren and young adults complained of more pain in the trunk[8,14,15]. This distinction of location in relation to age was not found in the present study.

According to Babela et al.[13], the most prevalent hospitalizations were caused by painful musculoskeletal crises (58.6%), followed by abdominal pain, ATS, Stroke (stroke) and priapism. In the present study, the other acute complications of SCD found were: Acute Thoracic Syndrome, splenic sequestration, hemolysis, bone infarction and venous thromboembolism.

Almost all patients were followed up by a specialist, less than half used hydroxyurea (31%) and half of the patients used penicillin for infection prophylaxis (1 to 12 years of age). According to a study carried out in Brasília with children with SCD and an allergic crisis, HU was used in 15.8% of the patients[5]. In another study, Grunewald and co-workers[6] showed that among 24 children with SCD, hospitalized with an allergic crisis in a Minas Gerais hospital, only 3 of them used HU continuously (12.3%).

In 2012, a randomized placebo-controlled clinical trial in Alabama, called BABY HUG, was developed to evaluate the use of hydroxyurea (HU) in children with severe sickle cell anemia. This demonstrated that HU reduced the rates of acute complications of the disease, reducing the incidence of episodes of pain and hospitalization rates[16]. Another study showed that the benefits of using HU in children include increased survival and reduced risk of ATS[7]. Clinical trials have shown that HU reduces the number of hospitalizations in patients with SCD, but there are specific criteria for its use.

Since the 1980s, studies by Murtaza and colleagues[8], on drug prophylaxis with penicillin, have been known to be given to patients with SCD at least until 5 years of age. According to Debaun et al.,[4] the benefit of penicillin prophylaxis for patients with SCD was demonstrated in a review of Cochrane clinical trials in 2012, with a decrease in the risk of pneumococcal infections with the adoption of this measure.

In this study in Salvador, there was a mean hospitalization duration of 6.6 days, consonant with a study done in Brasília with children hospitalized with an allergic crisis and patients with SCD, in which the mean length of hospital stay was 6.3 days[5]; the same occurring in the study by Lin and collaborators[17] conducted in New York with adults with SCD, showing a mean of stay of 6 days.

Differently, studies carried out in the United States and England in 2015 with 40 children with SCD hospitalized for an allergic crisis, the mean hospitalization time was 5.1 days[18,19]. Grunewald et al.[6], through studies in Minas Gerais with children with SCD hospitalized with an allergic crisis, found that the mean was 12.07 hospital days, and Murtaza and colleagues[8], through studies in the United States and Europe, showed an average of hospital stay of 7.4 days.

More than 90% of the patients presented frequent hospitalizations, mainly due to pain crises, associated or not with infections - with pneumonia being the most prevalent infection. Since the 1980s, studies in the United States and Europe have pointed to pneumonia as the most common infection in patients with SCD[8,14,15].

Most of the patients in the study in Salvador were initially medicated with common analgesics, mainly dipyrone, in a systematic way, associated with non-steroidal anti-inflammatory drugs (NSAIDs), more commonly ketoprofen. Morphine was reserved for cases in which the association of the medications described was not enough to control pain. Other medications such as codeine were less used (Figure 4).

Similarly, in a study of children with SCD admitted to a hospital in Brasília, dipyrone was the medication most frequently used during hospitalization[5]. In studies in Jamaica and Congo, on the treatment of pain attacks in children and adolescents with SCD, the most commonly used options were opioids and non-opioids[12]. According to Grunewald et al.[6], in a study of children with crisis and SCD admitted to a university hospital in Juiz de Fora, Minas Gerais, the most commonly used medications were dipyrone associated with ibuprofen and morphine (50% of cases).

The present study presented some limitations. Patient genotypes (type of hemoglobinopathy) were not analyzed to determine if there was a higher prevalence of any subtype in the evaluated group, such as HbSS homozygous, which has a more aggressive clinical presentation; baseline hemoglobin levels, which are also sometimes related to more frequent and severe painful crises; and drug therapy used at home before hospital admission.

On the other hand, this study provided knowledge concerning the population assisted by the hospital, including similarities and peculiarities, which may influence discussions and actions to improve the quality of care, especially in the approach to pain, in individuals with SCD. It was possible to analyze a relevant period of time, corresponding to a longer period of time than some studies already performed in Brazil, and to identify associated comorbidities as well as the need for ICUs during hospitalization, factors that had not been evaluated in other studies.

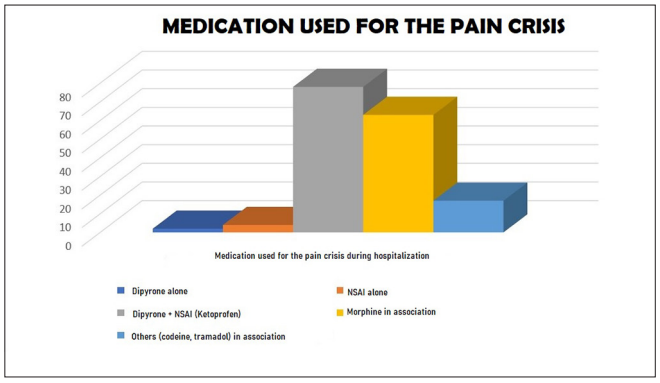

Figura 4. Medication used to treat the pain crisis during hospital stay.

The study concerning the profile of patients with SCD with an allergic crisis is important insofar as such patients frequently use the hospital environment and should be promptly cared for, in order to control pain and to investigate other complications. We believe that this study should serve as a stimulus to new studies on the subject, seeking to ratify the data found and, above all, to elucidate the characteristics not addressed by it.

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