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Avascular necrosis of the femoral head in sickle cell disease in pediatric patients suffering from hip dysfunction

Osteonecrosis de la cabeza femoral en pacientes con anemia de células falciformes y disfunciones de la cadera en la infancia

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ABSTRACT

Objective The aim of this study is to verify the prevalence of avascular necrosis (AVN) in pediatric patients with sickle cell anemia and hip dysfunction, and to evaluate the presence of associated risk factors.
Method A cross-sectional study was conducted in a group of 92 patients with sickle cell disease and hip dysfunction. Clinical and sociodemographic characteristics were collected, and laboratory variables were evaluated. All the subjects underwent radiographic and clinical evaluation of the hip. The participants were divided into two groups: the “AVN Group” consisting of patients with AVN, and the “Comparison Group” without AVN. Both groups were evaluated in search of factors associated with osteonecrosis of the femoral head.
Results 43 (46.7 %) out of 92 individuals presented hip dysfunction, and 13 were diagnosed with AVN (30.2 %). Comparison between groups showed significant differences in time of diagnosis, previous trauma, presence of pain, and mean values of functional scores. Higher percentage rates of fetal hemoglobin, higher platelet counts and lower rates of total hemoglobin were perceived in the Comparison Group.
Conclusions Pediatric patients with sickle cell anemia with hip dysfunction present a prevalence of 39.4 % of osteonecrosis of the femoral head. This was associated with a longer time of diagnosis (97 months), previous trauma in 92 % of patients, and a mean Charnley score of 15 points. Also, an association with lower rate of fetal hemoglobin (7.2 versus 11.8) was found, which supports the hypothesis that fetal hemoglobin may function as a protective factor against avascular necrosis.

Key Words: Hip, sickle cell, osteonecrosis (*source*: *MeHS, NLM*).

RESUMEN

Objetivo El objetivo de este estudio es confirmar la prevalencia de necrosis avascular (AVN) en pacientes con anemia de células falciformes, así como disfunciones de cadera en la infancia, además de evaluar la presencia de factores de riesgo en estos individuos.
Métodos Se realizó un estudio de corte transversal en un grupo de 92 pacientes con enfermedad falciforme y disfunción de cadera. Se hizo una recolección de características clínicas y sociodemográficas, y se realizó un análisis de las variables encontradas en laboratorio. Todos los sujetos se sometieron a evaluación clínica y radiográfica de la cadera, y fueron divididos en dos grupos: el "Grupo AVN" que consistía de pacientes con AVN y el "Grupo Comparativo" sin AVN. Se evaluó ambos grupos con el fin de encontrar factores asociados con la osteonecrosis de cabeza femoral.
Resultados 43 (46.7 %) de los 92 individuos presentaron disfunción en la cadera y 13 de ellos recibieron un diagnóstico de AVN (30.2 %). La comparación entre los dos grupos mostró diferencias importantes en el tiempo de diagnóstico, trauma previo, presencia de dolor, y media de valores en los puntajes funcionales. El Grupo Comparativo evidenció valores porcentuales más altos de hemoglobina fetal, así como un conteo de plaquetas más alto y valores menores de hemoglobina total.
Conclusiones Entre los pacientes pediátricos con anemia falciforme y con disfunción de cadera se presenta una prevalencia de 39.4 % de osteonecrosis de cabeza femoral, lo que está asociado a un tiempo mayor de diagnóstico (97 meses), trauma previo en 92 % de los pacientes, y valores de puntaje medio de Chanrley de 15 puntos. También se encontró una asociación con valores menores de hemoglobina fetal (7.2 versus 11.8), lo cual respalda la hipótesis de que la hemoglobina fetal puede funcionar como un factor de protección contra la necrosis avascular.

Palabras Clave: Cadera, anemia, anemia de células falciformes, osteonecrosis (*fuente*: *DeCS, BIREME)*.

Sickle cell disease (SCD) is the most common hereditary blood disorder in the world, and also the most prevalent in Brazil (1,2). It is estimated that 3 % of the Brazilian population carry the sickle cell trait, and this number represents at least two million people (1,2). Among the Brazilian states, Bahia has the highest prevalence of the disease (5.48%), followed by Alagoas (4.83 %), Piauí (4.77 %) and Pará (4.40 %) (2).

Sickle cell disease generates severe anemia associated with thromboembolic and vaso-occlusive phenomena that may affect various tissues and systems. Estimations show that 4 to 12 % of these phenomena occur in the bone microcirculation, favoring painful crises (falcemic crises), infarctions in the bones and osteonecrosis (3-6). Specifically, osteonecrosis of the femoral head has been described as a very frequent condition in these patients, in comparison with the general population (5,6).

Avascular necrosis (AVN) of the femoral head is a clinical entity that generates due to the reduction or interruption of blood flow to the femoral head, leading to bone necrosis, loss of medullary bone trabeculae and subchondral collapse, causing deformity with secondary joint destruction (5,6). This condition produces severe functional incapacity of the hip associated with pain, and consequently, limitations on leisure and daily life activities. At early stages, AVN may be treated in a conservative manner through surgeries that are not very aggressive, which may prevent joint collapse; however, the treatment of the neglected disease or at more advanced stages normally requires highly complex procedures for a long period of time, with poor prognosis and no reversal of the established sequelae (5,6).

AVN in sickle cell anemia has a direct relationship with age and is prevalent in approximately 3 % of children under age 15, increasing from 8.7 to 12.4 % by age 21, and progressing to values higher than 50 % in population over 35 (5-8). The approach to osteonecrosis in the pediatric population would, therefore, be the starting point to prevent the onset and progression of articular disease. In addition, knowledge of the predisposing factors for AVN in this population would be of fundamental importance for identifying patients at risk, leading to the adoption of adequate preventive measures or early therapeutic intervention to minimize sequelae (5-8).

Despite the epidemiological importance of sickle cell anemia in Brazil and the status of AVN as one of the most incapacitating chronic complications of this disease, few studies approach this subject with the intention of creating new prevention and treatment protocols. The aim of this study is to verify the prevalence of AVN in pediatric patients with sickle cell anemia and hip dysfunction, and to evaluate the presence of risk factors associated with AVN in these individuals.

METHODS

Type of study and population

Between December 2008 and February 2009, a cross-sectional study was conducted in a group of patients from the Hematological and Hemotherapy Center of the State of Bahia (HEMOBA y its acronym in Portuguese). In this study, the clinical condition of the hips of 92 individuals under the age of 21 with sickle cell disease was evaluated.

The patients were selected through non-probabilistic sequential sampling, and patients who accepted to participate in the study, and whose parents authorized and signed the Informed Consent, were included. Patients with neuropathies, cognitive deficiency, rheumatic joint diseases, and sequelae of hip fracture or surgery were excluded.

In this group, the hip was clinically evaluated using the Charnley score (9), and considering the following items: range of movement (6 points), pain level (6 points) and capacity of walking (6 points). The normal hip achieves a total score of 18 points, while hips with alterations add up to a maximum of 17 points, and are considered dysfunctional (6,9).

43 patients had dysfunctional hips, that is, with a Charnley score below 18 points. These patients were subsequently invited to undergo orthopedic evaluation in the Pediatric Outpatient Center of Hospital Santa Izabel, with the intention of confirming the presence of avascular necrosis of the femoral head (AVN) through clinical and imaging tests. This re-evaluation was made between July 2010 and November 2011; 33 patients actually attended consultation for evaluation of avascular necrosis of the femoral head, and the remaining 10 patients did not respond to the request.

All the re-evaluated patients were included in the study. There was no sample size calculation because this study used a methodology similar to case control studies that assess diseases with low prevalence, in which the use of all the individuals is essential to provide the sample with greater statistical power.

Study Procedures

The 33 individuals selected were evaluated by anamnesis, clinical exam and standardized questionnaire for sociodemographic data collection in the Pediatric Orthopedic Outpatients Clinic of Hospital Santa Izabel. Laboratory data related to hemogram and leukogram were collected from the record charts of the patients at the Hematological and Hemotherapy Center of the State of Bahia (HEMOBA), considering only those tests performed in a period not longer than three months. The hemoglobin F evaluation in laboratory was also collected in the same manner, taking as a basis, the last exam of this type performed by the patient at HEMOBA.

The clinical characteristics considered were sex, age, height, weight, time of diagnosis, association with trauma, number of infections in the last year, hospitalizations in the last year, and transfusions in the last year. In

addition, hemorrhages, jaundice, venous ulcer in lower limbs, and splenomegalia were also included (6). The laboratory variables evaluated were levels of hemoglobin, ferritin, platelet counts, and leukogram (including lymphocytes) (6). Family history of thrombosis, infarction and chronic venous insufficiency of all the patients was also sought (6).

All the research subjects were re- submitted to hip examination according to the criteria of the Charnley score (9), bearing in mind that the most of the patients had been evaluated based on this criterion more than six months before. The patients who persisted with scores lower than 18 were considered as suspected of having necrosis of the femoral head. However, radiographic evaluation of all the patients was decided;this evaluation was performed by exposing the hip joint to anterior-posterior and frog-leg projections.

For the radiographic diagnosis of AVN, the Ficat and Arlet criteria (10) were used for patients with closed epiphyseal ring, and the Catterral and Lloyd-Roberts (11) criteria for patients with open epiphyseal ring. The stage of AVN was not considered, but only the presence or absence was recorded. All patients with AVN were allocated to the "AVN Group", while those without necrosis were allocated to the "Comparison Group".

Statistical Analysis

Data of both groups were presented descriptively, using the mean and standard deviation for continuous variables, and distribution by frequency of discrete variables. The AVN and Comparison Groups were evaluated in search of factors associated with osteonecrosis of the femoral head, by testing hypotheses. Comparison was made using the Student's *t*-test (or Mann-Whitney when applicable) for continuous data and the Chi-square test (or Fisher when applicable) for discrete data. All hypothesis tests were evaluated adopting 0.05 as the level of significance.

RESULTS

Based on the original number of 92 subjects at the beginning of the study, 43 individuals presented hip dysfunction, which represents 46.7 % of the total population. Only 33 of those 43 patients underwent evaluation, which implied a loss of 10 subjects (23.2 %). 13 of the re-evaluated patients were diagnosed with avascular necrosis of the femoral head (AVN), while in 20 of them, this diagnosis was not confirmed (60.6 %). This means that the overall presence of osteonecrosis of the femoral head in our study was

39.4 % among the patients with hip dysfunction. Therefore, AVN Group was composed of 13 individuals, and the Comparison Group of 20 patients.

No significant differences in demographic variables were found between the two groups, except for a discretely taller height in Group AVN (Table 1). Comparison of the clinical characteristics between the two groups showed significant differences in time of sickle cell disease diagnosis, previous history of trauma in the hip, presence of pain in the hip, and in the mean values of functional scores, both for the right and left hip (Table 2). Laboratory variables showed higher percentage rates of fetal hemoglobin, higher platelet counts and lower total hemoglobin rates in the Comparison Group (Table 3).

Table 1. Comparison of demographic characteristics of patients in the two groups

Variable	AVN Group Mean (±standard deviation) or N(%)	Comparison Group Mean (±standard deviation) or N(%)	ρ
N	13	20	
Age (months)	170.7 (±37,3)	147 (±48.4)	0.14
Sex			
Male	7 (53.8)	10 (50)	0.88
Female	6 (46.1)	10 (50)	
Weight (Kg)	41.80 (±13.4)	34.15 (±10.8)	0.08
Height (m)	1.53 (±0.1)	1.41 (±0.1)	0.03
BMI*	17.47 (±4.4)	16.60 (±2.5)	0.48

*Bone Mass Index

Table 2. Comparison of clinical characteristics of subjects in the two groups.

Variable	AVN Group Mean (±standard deviation) or N (%)	Comparison Group Mean (±standard deviation) or N (%)	ρ
N	13	20	
Time of Diagnosis (months)	96.61 (±77.3)	8.55 (±4.6)	<0.01
Hospitalization rate (per year)	1.53 (±2.8)	1 (±1.5)	0.49
Infection rate (per year)	1.46 (±1.6)	1.55(±2.5)	0.91
Previous hip trauma	12 (92.3)	3 (15)	<0.01
Jaundice	7 (53.8)	17 (85)	0.11
Splenomegaly	3 (20.1)	4 (20)	1.00
Late Puberty	2 (15.4)	7 (35)	0.25
Anemia	10 (76.9)	17 (85)	0.65
Lower limb ulcer	2 (15.4)	2 (10)	0.60
Bleeding signs	2 (15.4)	6 (30)	0.67
Medication usage	13 (100)	20 (100)	0.62
Transfusion (total)	7 (53.8)	8 (40)	0.67
Transfusion rate (per year)	2,69 (±4.0)	3.15 (±5.2)	0.79
Passive smoke	6 (46.15)	7 (35)	0.70
Family history of CVI*	2 (15.3)	4 (30.7)	0.90
Family history of embolism	-	-	
Family history of thrombosis	2 (15.4)	1 (5)	0.69
Family history of infarction	3 (23.9)	6 (30)	0.97
Hip pain	8 (61.5)	4 (20)	0.04
Side			
Right	5	-	
Left	2	1	
Bilateral	1	3	
Hip score (right)	14.76 (±3.8)	17.40 (±1.4)	0.01
Hip score (left)	15.61 (±3.4)	17.55 (±0.9)	0.02

*Chronic Venous Insufficiency

Table 3. Comparison of laboratory characteristics of subjects in the two groups

Variable	AVN Group Mean (±standard deviation) or N (%)	Comparison Group Mean (±standard deviation) or N (%)	ρ
N	13	20	
HbF	7.24 (±4.3)	11.84 (±2.8)	<0.01
Ferritin	636.23 (±815.4)	522.40 (±673.9)	0.66
Hemoglobin	10.8 (±3.1)	8.11 (±1.3)	<0.01
Hematocrit	26.08 (±7.8)	25 (±4.2)	0.60
Platelet	327000 (±95021.1)	411275 (±21256.2)	<0.01
Leucogram	11566.66 (±5008.7)	12051 (±4445.6)	0.77
Lymphocyte	3745.87 (±2114.9)	3918 (±1589.4)	0.79

DISCUSSION

Results demonstrate that the prevalence of avascular necrosis of the femoral head in pediatric patients with clinical hip dysfunction is 39.4%. Evidence also showed that osteonecrosis was significantly associated with taller height in patients, a longer diagnosis time, previous trauma and presence of pain in the hip, as well as lower Charnley score mean value, lower fetal hemoglobin rate, and higher hemoglobin value.

A taller height is justified by the slightly older patients included in the group with osteonecrosis of the femoral head. Avascular necrosis is a complication associated with age, thus a higher incidence is expected in older patients. Milner (12) divided patients with sickle cell disease into age groups, and this study also confirmed that the prevalence of osteonecrosis of the femoral head increases with age, and is approximately of 3 % in patients under 15 years of age and around 50 % in over 35. In a previous study, conducted in a population involving children, Matos (6) also found a higher mean age in the group with osteonecrosis of the femoral head in comparison with those who did not have this condition.

Previous trauma, presence of pain in the hip and lower Charnley Score are three intrinsically associated variables. In a final analysis, the Charnley score is just a functional evaluation for detecting pain and loss of amplitude in the movements of the hip joint (9). Osteonecrosis of the femoral head is an incapacitating disease, which causes dysfunction of the hip and may severely affect the quality of life of patients. Malheiros (13) associated pain and previous trauma with hip dysfunction in patients with sickle cell anemia; in this study, the three variables are shown as independent predictors of a worse quality of life for the patients.

The presence of high levels of fetal hemoglobin (HbF) in specific groups of patients with sickle cell anemia has not been completely elucidated yet; all we know is that these levels appear to be genetically determined (14). On the other hand, there is a broad consensus that HbF is the most important modulator of the clinical and hematological characteristics of patients with sickle cell anemia. High levels of HbF have been reported to be a protective factor against painful falcemic crises, leg ulcers, osteonecrosis in general, and acute thoracic syndrome; these high levels are also associated with less general severity of the disease (14). Powars (15) studied the relationship between the fetal hemoglobin rate and the incidence of morbid events in patients with sickle cell anemia, and found a significantly lower incidence of avascular necrosis (considering any location) when the HbF levels were above 10 %.

Possibly, high levels of HbF act as protection, especially against co-morbidities related to vaso-occlusion and increased viscosity (15,16). The pathophysiology of sickle cell anemia depends on the falcization of the erythrocytes as a consequence of the polymerization of hemoglobin S. The cells containing a high level of HbF (around 20 %), known as F cells, have a longer survival than the so-called non-F cells, which contain only HbS (15,16). Experimental studies have also revealed that high levels of HbF in the erythrocytes may delay hemoglobin polymerization, bearing in mind that the mixture of HbF-HbS produces an antipolymerizing effect with the potential to inhibit up to 50 % of the polymerization of HbS (16).

There is great variation in the mean levels of HbF in ethnically different populations, and there is also a variation in the results that point towards HbF as a protective factor for morbidities associated with sickle cell disease (16). Silva (17), in a study with Brazilian patients, reported that high levels of HbF are associated with a lower frequency of vaso-occlusive crises and leg ulcers, although he did not find any significant relationship with femoral necrosis. These authors confirmed, in a population similar to the one evaluated in this study, that HbF is a possible protective factor for complications dependent on vaso-occlusive crises, as in the case of avascular necrosis of the femoral head (17). Nevertheless, the reduced number of cases with osteonecrosis of the femoral head (7 in total) affect the statistical power of the cited study for defining the role of HbF in this complication.

Akinyoola (18) demonstrated that patients with osteonecrosis of the femoral head presented higher hospitalization frequency and painful falcemic cri-

ses than patients with sickle cell disease without osteonecrosis of the femoral head. These authors also identified diminished fibrinolytic activity in the patients with osteonecrosis of the femoral head group, suggesting an important role of hypofibronolysis generated by the decrease of natural inhibitors of clotting in these patients (18). The findings of this study point towards the implications of vaso-occlusive and/or thrombolytic phenomena associated with osteonecrosis, and although pain in the hip is clearly related to falcemic crises, supporting the increase in frequency of hospitalizations was not possible.

Moreover, finding slightly higher rates of hemoglobin in the group with osteonecrosis of the femoral head, without significant difference in hematocryt, does not seem to make clinical sense in this study. In spite of this, various similar studies found an association between high hematocryt and/or hemoglobin levels with osteonecrosis of the femoral head (12,19,20). Milner (12) found that vaso-occlusive crisis, high hematocryt values, lower medical corpuscle volume and low level of aspartate aminotransferase are risk factors for avascular necrosis in patients with sickle cell anemia. Our findings, however, do not coincide and cannot be evaluated with such level of certainty.

Of the total number of patients evaluated (92 individuals), initially, 43 were considered dysfunctional, for a total of 46.7 % of hip dysfunction in the pediatric age group with sickle cell disease. Among hip dysfunction cases, the prevalence of osteonecrosis of the femoral head reached 39.4 %, which emphasizes the relevance of early evaluation of the hip of children with sickle cell disease, and also the search of risk factors associated with osteonecrosis of the femoral head in these individuals. This search may result in greater prevention, early treatment and possible reduction of the sequelae that increase physical and social suffering of these children (future incapacitated adults), or of consequences that directly diminish the quality of life of persons with sickle cell anemia.

This study presents a relevant association between clinical dysfunction of the hip and osteonecrosis of the femoral head for the first time in scientific literature. In conclusion, pediatric patients with sickle cell anemia and hip dysfunction have a prevalence of 39.4 % of osteonecrosis of the femoral head, which is associated with a longer time of diagnosis of the disease (97 months), previous trauma in 92 % of the cases, and a mean Charnley score of 15 points. There is also an association between osteonecrosis of the femoral head and a lower rate of fetal hemoglobin (7.2 versus

11.8), supporting the hypothesis that fetal hemoglobin may function as a protective factor against avascular necrosis.

Conflict of interest: None.

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