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Avascular Necrosis of the Femoral Head in Sickle Cell Disease Patients

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SUMMARY

Background. Avascular necrosis of the femoral head (ANFH) has been described as a frequent outcome in patients with sickle cell disease (SCD). The objective of the current report is to present the prevalence of ANFH in patients under the age of 21 suffering from SCD as well as discuss some possible associated risk factors.

Material and methods. A cross-sectional study was carried out in a group of 100 patients. Clinical, demographic variables and risk factors were investigated. Seventy-two patients had their data completely analyzed. Eight patients were found to be affected and comprise the study group while the other 64 patients comprised the comparison group.

Results. The prevalence of ANFH was 8 out of 72 (11.1%). Age (p=0.042), weight (p=0.04) and hemoglobin levels (0.048) were associated with ANFH. Correlations with time from diagnosis (p=0.14), ulcers (p=0.013), ferritin levels (p=0.07) and a family history of thrombosis were near-significant.

Conclusion. The attention of physicians treating SCD patients must also be drawn to the possibility of ANFH in order to prevent or avoid this disastrous complication, especially in younger patients presenting with frequent hemolytic crises.

Key words: avascular necrosis, sickle cell disease, femoral head

BACKGROUND

Sickle cell disease (SCD) is the most common inherited hematologic illness worldwide, and in Brazil, its rate of prevalence amongst the population has reached 3%. Bahia State is the most affected region, accounting for 5.48% of (known) cases [1-3].

Sickle cell disease can lead to a number of thrombotic events, ranging from stroke (6-12%) to bone infarction (4-12%) [4,5]. Bone crisis, infarction, infections and avascular necrosis are some of the major problems associated with the disease [6-8].

Avascular necrosis of the femoral head (ANFH) has been described as a frequent outcome in patients with sickle cell disease compared to the general population [6,7,8,9]. ANFH is a destructive and disabling hip disease that causes severe physical limitations and loss of quality of life. Several reports suggest that thrombotic events are the main cause of ANFH in SCD. However, other risk factors associated with ANFH must certainly be implicated in its pathogenesis even in SCD patients [7-11].

Despite ANFH being an important complication of SCD, there are few reports addressing the prevalence of ANFH in SCD patients and even less research discussing associated risk factors. The objective of the current report is to present the prevalence of ANFH in patients under the age of 21 suffering from sickle cell disease as well as discuss some possible associated risk factors.

MATERIAL AND METHODS

A cross-sectional study was carried out in a group of patients selected from Centro de Hematologia e Hemoterapia do Estado da Bahia (The Bahia State Center for Hematology and Hemotherapy), in Salvador, State of Bahia, Brazil. The study was performed from December 2008 to February 2009. Patients suffering from sickle cell disease and aged six to 21 years were included in the study. Patients were invited to participate and were interviewed by the researchers by means of a standardized questionnaire containing questions about hip symptoms. Afterwards, the patients underwent a clinical and laboratory evaluation.

From the initial group of 100 patients, 92 were available for the study. The clinical and demographic variables and risk factors investigated were: presence of hip pain (ANFH), gender, age, height, weight, time from diagnosis, trauma, infection, hospitalizations, blood transfusion, hemorrhage (bleeding), jaundice, chronic venous thrombosis, history of lower limb venous ulcer, family history of thrombosis, family history of myocardial infarction, passive smoking, hemoglobin level, ferritin level, and platelet count.

The Charnley hip score was used to evaluate the hip [13]. This score is based on a scale from zero (the worst hip) to 18 points (the best one). Hips were classified according to their Charnley scores and those under 18 points were considered as potentially having ANFH. Patients scoring under 18 points were sent for a radiographic evaluation. The presence of ANFH was confirmed radiographicaly according to Catterrall's or Ficat's criteria [14,15].

Patients in whom ANFH were identified were used to calculate the overall prevalence and comprised the study group. The second group, called the comparison group, was composed of all patients without ANFH. Both groups were subsequently compared with a view to identifying associated risk factors.

Data was presented in tables according to descriptive statistics. The overall prevalence was given as a percentage. Nominal data were presented as percentages while continuous variables were presented as means and standard deviations. An odds ratio was used to compare the groups for each selected nominal risk factor and in this case the chi square test was used to verify significance. Significance of differences was evaluated by means of Student's t-test. The level of significance was established as less than p=0.05.

The study protocol had the approval of the Bahian School of Medicine and Public Health Ethics Committee. All the patients or their carers were informed about the study and gave their consent for participation in one of the groups.

RESULTS

With twenty patients lost to follow-up because of incomplete laboratory or radiographic evaluation, 72 patients had their data completely analyzed. Eight patients were found to be affected and comprised the study group, while the other 64 patients comprise the comparison group. Data from all 92 patients was used to present social, demographic and clinical characteristics of the study population. However, in order to compare both groups we only used 72 patients as described above.

The prevalence of ANFH was 8 out of 72 (11.1%). Age (p=0.042), weight (p=0.04) and hemoglobin levels (0.048) were associated with ANFH. Correlations with time from diagnosis (p=0.14), ulcers (p=0.013), ferritin levels (p=0.07) and a family history of thrombosis were near-significant, and these findings also need to be highlighted. (Tables 1 and 2)

Tab. 1. Overall characteristics of the population

Variables	Population (n=92) N (%) or Mean±sd *
Male	49 (53.3%)
Age	11.8 (±3.9)
Height	1.4 (±0.2)
Weight	33.6 (±109)
Time since diagnosis (years)	9.2 (±4.3)
Hospitalization/year	1.3 (±2.2)
Infection/year	1.2(±1.8)
Trauma	16 (17.4%)
Jaundice	63 (68.5%)
Splenomegaly	20 (21.7%)
Lower limb ulcer	7 (7.6%)
Blood transfusion	42 (45.6)
Transfusion/year	2.8 (±4.6%)
Passive smoking	29 (31.5%)
Platelet count	413,429.1 (±180,034.1)
Hemoglobin	8.3 (±1.6)
Hemorrhage	24 (26.1%)
Ferritin	511.4 (±658.4)
Thrombosis**	6 (6.5%)
Chronic venous disease**	23 (25.0%)
Infarction**	21 (22.8%)
Corticoid use	5 (54.4%)

*Standard deviation; **Family history.

Tab. 2. Comparison of the characteristics of the two groups

Variables	Study (n=8) N (%) or Mean±sd*	Comparison (n=64) N (%) or Mean±sd*	P
Gender (male)	5(62.5)	31(48.4)	0.710
Age	14± 2.8	11± 3.9	0.042
Height	1.6± 0.1	1.5± 1.2	0.982
Weight	40.2 ±10.8	32.2± 10.1	0.040
Time since diagnosis	10.9± 5.3	8.58± 3.9	0.140
Hospitalization/year	0.8± 1.5	1.3± 2.4	0.545
Infection/year	0.8± 1.4	1.1± 1.4	0.595
Trauma	1(12.5%)	9(14.1%)	1
Jaundice	4(50%)	48(75%)	0.206
Splenomegaly	2(25%)	14(21.9%)	1
Lower limb ulcer	2(25%)	4(6.2%)	0.130
Blood transfusion	4(50%)	24(37.5%)	0.703
Transfusion/year	1.9±3.4	2.1± 4.1	0.931
Passive smoking	3(37.5%)	19(29.7%)	0.693
Platelet count	354,833± 65.782	415, 791.8±182	0.356
Hemoglobin	7,1± 2.1	8.3±1.6	0.048
Bleeding	2(25%)	14(21.9%)	1
Ferritin	811.9± 913.9	398.5±553.8	0.070
Thrombosis*	2(25%)	2(3.1%)	0.058
Chronic venous disease**	2(25%)	14(21.9%)	1
Infarction*	2(25%)	14(21.9%)	1
Corticoid use	0	2(3.1%)	1

*Standard deviation; **Family history.

DISCUSSION

The paucity of information about the prevalence and characteristics of ANFH in sickle cell disease sufferers does not permit a complete understanding of this important clinical outcome. It is not clear whether ANFH is associated with thrombotic events caused by SCD or with associated features such as side effects of the treatment of SCD and its complications.

Our study showed an ANFH prevalence of 11.1% in SCD patients less than 21 years of age. This data is in agreement with the rare reports about the subject. Gallo et al. [16] showed an overall prevalence of 9.8% in patients of all ages. Our results also showed that age is associated with ANFH and this is in line with the study performed by Milner et al. [17]. These authors subdivided their patients according to age

and found that prevalence was as low as 3% among those less than 15 years but reached 50% in patients older than 35 years.

Despite the high prevalence we found, the current study may have underestimated the true rate because of the large amount of patient loss. We believe that most of them could have been in the study group. The fact that magnetic resonance images were not obtained may have contributed to underestimation as well. However, ethical reasons and the risks involved do not justify subjecting all patients (most of whom were children) to this kind of evaluation.

Even though the Charnley hip score was not idealized for ANFH, this scoring system was considered a suitable screening test to identify ANFH [13]. However, we had to take into account a detailed clinical story in patients with acute bone crisis or stroke in whom Charnley scores were under 18 in order to confirm the diagnosis of ANFH.

Despite the possible underestimation, the study highlighted several important features. Firstly, there is a high prevalence of ANFH in this age group. Secondly, age, weight and hemoglobin levels were significantly associated with ANFH. Lower limb ulcers, a family history of thrombosis, and ferritin levels were nearly significant, but we believe that they were not statistically significant because of an insufficient statistical power of our sample. Those findings, however, are in accordance with other papers that signaled the same group of clinical characteristics as important risk factors. [8,11,12,16]

Several authors have shown that erythrocyte-derived and platelet-derived microparticles are present in the blood of SCD patients and these particles are related to coagulation, fibrinolysis and endothelial activation [18]. Akinyoola et al. reported a poorer fibrinolytic activity in SCD patients with avascular necrosis and this finding also indicates an association between hypercoagulability states and osteonecrosis [19]. The fact that lower hemoglobin levels were associated with ANFH in our study reinforces the theory that hypercoagulability is correlated to a hemolytic state in sickle cell disease and this alteration can lead to osteonecrosis. Therefore, our results emphasize the necessity of investigating ANFH more carefully in SCD patients suffering from severe hemolytic anemia.

CONCLUSIONS

1. This study contributes to several topics discussed in the literature about ANFH in SCD patients. It represents a rare epidemiologic evaluation about the subject, focusing on younger patients (under the age of 21).
2. The prevalence of femoral head avascular necrosis was 11.1%, which was considered higher than in previous studies, and we also revealed an association of ANFH with age, weight and hemoglobin levels.
3. Our results pointed to the need for specific programs to manage this condition.
4. The attention of physicians while attending SCD patients also must be turned to ANFH in order to prevent or avoid this disastrous complication, especially in younger patients presenting with frequent hemolytic crises.

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