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ORIGINAL PAPER

Risk factors for osteonecrosis of the femoral head in patients with sickle cell disease

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Abstract The mechanisms involved in the pathogenesis of osteonecrosis of the femoral head in sickle cell disease are not fully known. The aim of this study was to identify risk factors for osteonecrosis of the femoral head among sickle cell disease patients. Clinical (frequency of painful crises and hospitalisation) and laboratory parameters (euglobulin clot lysis time, haematocrit, platelet count, and leucocyte count) of 25 consecutive patients with avascular necrosis of the femoral head from sickle cell disease were compared with those of 26 age- and sex-matched sickle cell disease patients without avascular necrosis. The group with avascular necrosis of the femoral head (mean age 23.7± 4.9 years) had a significantly higher rate of painful crises (p=0.03) and hospitalisations per year (p=0.002) than the group without avascular necrosis (mean age 21.6± 5.2 years). The group with avascular necrosis also had a significantly higher euglobulin clot lysis time than the group without avascular necrosis (p=0.001). In conclusion, it appears that not all patients with sickle cell disease have impaired fibrinolytic activity. The aetiology of avascular necrosis in sickle cell disease is multifactorial.

Résumé Les mécanismes de la nécrose de la tête fémorale dans la drépanocytose sont encore relativement obscures. Le but de cette étude est de mettre en évidence les facteurs de risque de la tête fémorale chez les patients présentant une drépanocytose. Matériel et méthode : l'évaluation des paramètres cliniques (fréquence des crises, nombre d'hospitalisations) et biologique (lyse du caillot, euglobuline, hématrocrite, plaquettes et numération leucocytaire) de 25 patients consécutifs présentant une nécrose avasculaire de la tête fémorale dans le cadre d'une drépanocytose ont été comparés aux données d'une série de patients âgés en moyenne de 26 ans et présentant une drépanocytose sans nécrose aseptique. Résultats : le groupe des nécroses aseptiques de tête fémorale était âgé en moyenne de 23,7± 4,9 avec un nombre de crises douloureuses significativement plus élevé (p=0,03) et un nombre d'hospitalisation également plus élevé (p=0,002) que dans le groupe des nécroses avasculaires simples, moyenne d'âge 21,6±5,2 ans. Le groupe présentant une nécrose avasculaire présentant également un taux de lyse du caillot et d'euglobuline plus élevé que dans le groupe sans nécrose (p=0,001). Conclusion : il semble que les patients porteurs d'une drépanocytose comportent sur le plan biologique une activité fribrinolytique plus importante. L'étiologie de la nécrose avasculaire dans le cadre de la drépanocytose est multifactorielle.

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Introduction

Osteonecrosis, especially of the femoral head, is a well known complication of sickle cell disease with prevalence

rates from 3.2–26.7% [2, 10, 11, 16]. The prevalence appears to be similar in patients with haemoglobin genotype SS and SC [2, 16, 17], though some studies [16] found osteonecrosis to develop later in life in haemoglobin genotype SC patients. Some aetiopathogenetic mechanisms have been suggested for osteonecrosis in sickle cell disease. Some studies have implicated thrombophilia and decreased fibrinolysis as a result of decreased levels of natural coagulation inhibitors [19]. High haematocrit, low foetal haemoglobin levels, and coexistent alpha-thalassemia trait along with increased frequency of painful crises have also been positively associated with osteonecrosis [1, 9, 16, 17]. Many studies have shown that patients with sickle cell disease have decreased levels of natural coagulation inhibitors [3, 5, 6, 8, 14, 18].

Most of these studies have compared the levels of these haematological parameters in patients with sickle cell disease and normal controls. Few studies [9, 17] have compared these parameters in sickle cell disease patients with and without avascular necrosis of the femoral head. We are not aware of any study on this topic despite the prevalence of this disorder. Why do some sickle cell disease patients develop osteonecrosis while others do not?

Identification of risk factors would help in screening and placement of appropriate measures to prevent osteonecrosis in high risk patients. This is very important because most patients with osteonecrosis present very late [2], when the only treatment option is total hip replacement with its attendant unsatisfactory results in this group of patients [16]. Furthermore, it has been shown that the natural history of asymptomatic osteonecrosis of the femoral head in adults with sickle cell disease is progression to collapse [10].

This study is therefore aimed at finding the clinical and haematological risk factors for osteonecrosis of the femoral head in our population of sickle cell disease patients. This is to help identify patients at risk of developing this complication.

Patients and methods

Consecutive patients with avascular necrosis (AVN) of the femoral head from sickle cell disease attending the haematology and orthopaedic clinics of our hospital from May 2006 to April 2007 were compared with age- and sex-matched controls (sickle cell disease patients without avascular necrosis). The control group (non-AVN) consisted of consecutive sickle cell disease (haemoglobin genotype SS and SC) patients attending the sickle cell clinic of our hospital without clinical and radiological features of avascular necrosis. They were in their steady state and were attending the clinic for routine appointments. The proportion of patients with Hb SS to those with Hb SC was similar to that of the study group (AVN). Excluded from the study were patients in sickle cell crises at the time of the study, coexisting bacterial infections like osteomyelitis and septic arthritis, chronic liver disease, and patients with a history of blood transfusion in the past three months preceding the date of the study.

Ethical clearance was obtained from our hospital's Ethics and Research Committee and informed consent was given by each patient participating in the study.

Twenty-five patients with avascular necrosis (AVN) of femoral head who met the study criteria were compared with 26 age- and sex-matched sickle cell disease patients without AVN. Avascular necrosis was diagnosed by clinical features, plain X-rays, and computerised axial tomography scan.

Information obtained from each patient included socio-demographic data, frequency of painful crises, and hospitalisation (haematology day care centre, emergency room or wards). The euglobulin clot lysis time (ECLT) and other haematological parameters (haematocrit, platelet count, and white cell count) were measured in each patient. To determine the ECLT, 4.5 ml (plus 2.5 ml for other haematologic parameters) of venous blood was collected after a resting period of at least 30 minutes under aseptic technique and without stasis from each patient. This was added to 0.5 ml of sodium citrate (31.3 g/l). The sample was spun at 2,500 rotations per minute for ten minutes to separate the plasma. The supernatant obtained was kept at 4°C until tested for fibrinolytic activity using the Von Kaulla method [21] in duplicate on each sample. The remaining 2.5 ml was put in an ethylene diamine tetra acetic acid (EDTA) bottle for other haematological parameters (platelet count, haematocrit, white cell count) using the standard methods [4, 7]. In all cases tests were performed within six hours of collection of samples. The values obtained were analysed using Statistical Package for Social Sciences (SPSS) 10.0. The corresponding mean values were compared using independent sample *t* tests.

Results

The 25 patients with AVN included 13 females and 12 males with a mean age of 23.7 (±4.9) years (range, 18–28 years). The controls (non-AVN group) included 14 males and 12 females with a mean age of 21.6 (±5.2) years (range, 15–30 years). The mean frequency of painful (vasoocclusive) crises in the AVN group was 5.8 (±1.6) per annum and 2.1 (±1.3) in the control group ($p=0.03$). The mean hospitalisations (haematology day care, emergency room, or wards) per year was 6.2 (±2.1) in the AVN group and 1.8 (±1.4) in the control group ($p=0.002$) (Table 1).

Table 1 Sociodemographic features of patients with sickle cell disease

	AVN group	Non-AVN group	*p* value
Mean age (y)	23.7 (±4.9)	21.6 (±5.2)	0.68
Hb genotype			
SS	20 (82%)	21 (80.3%)	
SC	5 (18%)	5 (19.7%)	
Ficat and Arlet stage of AVN			
I	1		
II	7		
III	4		
IV	13		
Mean frequency of crises per year	5.8±1.6	2.1±1.3	0.03
Mean admissions per year	6.2±2.3	1.8±1.5	0.002

The radiological grades (Ficat and Arlet) of the osteonecrosis of the femoral head in the study group are also shown in Table 1.

The results of ECLT and other haematological parameters in the two groups are shown in Table 2. There was a statistically significant difference (p=0.001) in the mean ECLT values between the AVN group and the controls. There was a fairly positive correlation between the age in years and ECLT in minutes (Pearson's correlation 0.426, p=0.01, two-tailed test).

Discussion

Avascular necrosis of the femoral head is an important cause of morbidity in sickle cell disease. The mechanisms involved in the pathogenesis of osteonecrosis in sickle cell disease have not been fully explained. The significant activation of intravascular coagulation during the crisis period and steady state as a result of decreased levels of natural coagulation inhibitors has been noted. The euglobulin clot lysis time (ECLT) was significantly higher in sickle cell disease patients with AVN than in those without AVN in this study (p=0.001). The ECLT is a measure of fibrinolytic activity. Urano et al. [20] found both tissue plasminogen activator (tPA) and its inhibitor (PAI-1) to show significant correlation with ECLT. Though not as specific as standard tests like D-Dimers (cross-linked fibrin derivatives) and assay of protein C and protein S activities, ECLT is a sensitive measure of fibrinolytic activity. Previous studies [3, 5, 8] have shown it to be higher in patients with sickle cell disease than in normal controls. The higher ECLT in the AVN group in this study indicates poorer fibrinolytic activity as a result of decreased functional releasable tissue plasminogen activator (tPA). The implication of this finding may be that not all patients with sickle cell disease have impaired coagulation and thus predisposition to avascular necrosis. The role of thrombotic and fibrinolytic disorders in nontraumatic osteonecrosis of the femoral head is still a subject of debate. While some workers found a high incidence of thrombophilic and hypofibrinolytic coagulation abnormalities in patients with osteonecrosis [12], others could not confirm an aetiological role [13, 15].

Another factor that has been associated with increased predisposition to osteonecrosis of the femoral head in sickle cell disease is a high haematocrit or haemoglobin level [9, 16, 17]. This is not supported by the results of this study as there was no significant difference in the haematocrit values in the two groups (p=0.95).

The group with avascular necrosis of the femoral head had a significantly higher mean number of hospitalisations (p=0.002) and frequency of painful crises (p=0.03). It is well known that the pain rate is a measure of clinical severity in sickle cell disease. High rates of pain episodes have been found to be associated with high haematocrit and low foetal haemoglobin levels. Low foetal haemoglobin levels and high haematocrit are associated with increased intravascular sickling and high viscosity, predisposing to avascular necrosis of femoral head [9, 16, 17].

The coexistence of other variants of abnormal haemoglobin like alpha-thalassemia with haemoglobin SS genotype is also associated with increased risk of osteonecrosis [1, 16]. This is believed to be an important risk factor for osteonecrosis in some patients in the Mediterranean region.

This study has shown that decreased fibrinolytic activity appears to be an important factor in the pathogenesis of

Table 2 Haematological parameters of patients with sickle cell disease

Parameters	AVN group	Non-AVN group	*p* value
ECLT (minutes)	242.3±35.2	130.6±28.6	0.001
PCV (%)	24.4±6.8	24.7±5.4	0.95
Platelets (x1000/cmm)	295.4±150.9	256.4±100.6	0.43
White cell count (total x 1000)	8.8±4.1	9.5±4.1	0.65
Neutrophils (%)	56.8±10.7	58.7±15.9	0.75
Lymphocytes (%)	41.4±10.0	38.89±15.1	0.58
Eosinophils (%)	1.8±1.5	2.6±2.1	0.3

osteonecrosis of the femoral head in our population of sickle cell disease. Furthermore it is possible that not all patients with sickle cell disease have significantly impaired coagulation. Further studies are needed to explain differences in the prevalence of osteonecrosis among different populations of sickle cell disease. Each sickle cell disease patient must be screened for predisposing factors for osteonecrosis as early as possible to prevent this crippling complication.

References

1. Adekile AD, Gupta R, Yacoub F, Sinan T, Al-Bloushi M, Haider MZ (2001) Avascular necrosis of the hip in children with sickle cell disease and the high Hb F: magnetic resonance imaging findings and influence of alpha-thalassemia trait. Acta Haematol 105(1):27–31
2. Akinyoola AL, Adediran IA, Asaleye CM (2007) Avascular necrosis of the femoral head in sickle cell disease in Nigeria: a retrospective study. Niger Postgrad Med J 14(3):217–220
3. Aluoch JR (1998) Fibrinolytic activity in adult Kenyan patients with sickle cell disease. East Afr Med J 75(6):351–352
4. Bain BJ (1995) Basic haematological techniques. In: Dacie JV, Lewis SM (eds) Practical haematology, 8th edn. Churchill Livingstone, London, pp 37–66
5. Bayazit AK, Kilinc Y (2001) Natural coagulation inhibitors (protein C, Protein S, antithrombin) in patients with sickle cell anemia in a steady state. Pediatr Int 43(6):592–596
6. Busari FI, Shokunbi WA, Jeremiah ZA (2007) Plasma fibrinogen levels in Nigerian homozygous (Hb SS) sickle cell patients. Hemoglobin 31(1):89–92
7. Dacie JV, Lewis SM (1995) Preparation and staining methods for blood and bone marrow film. In: Dacie JV, Lewis SM (eds) Practical haematology, 8th edn. Churchill Livingstone, London, pp 75–85
8. Famodu AA (1988) Plasma fibrinolytic activity in sickle cell disease. Trop Geogr Med 40(4):331–333
9. Hawker H, Neilson H, Hayes RJ, Serjeant GR (1982) Haematological factors associated with avascular necrosis of the femoral head in homozygous sickle cell disease. Br J Haematol 50(1):29–34
10. Hernigou P, Habibi A, Bachir D, Galacteros F (2006) The natural history of asymptomatic osteonecrosis of the femoral head in adults with sickle cell disease. Bone Joint Surg Am 88(12):2565–2572
11. Iwegbu CG, Fleming AF (1985) Avascular necrosis of the femoral head in sickle cell disease. A series from the Guinea savannah of Nigeria. J Bone Joint Surg (Br) 67(1):29–3
12. Jones LC, Mont MA, Le TB, Petri M, Hungerford DS, Wang P, Glueck CJ (2003) Procoagulants and osteonecrosis. J Rheumatol 30(4):783–791
13. Koo KH, Song HR, Ha YC, Kim JR, Kim SJ, Kim KI, Chang KC, Ahn IO, Cho SH (2002) Role of thrombotic and fibrinolytic disorders in the etiology of Perthes' disease. Clin Orthop Relat Res 399:162–167
14. Kurantsin-Mills J, Ofosu FA, Safa TK, Siegel RS, Lessin LS (1992) Plasma factor VII and thrombin-antithrombin III levels indicate increased tissue factor activity in sickle cell patients. Br J Haematol 81(4):539–544
15. Lee JS, Koo KH, Ha YC, Koh KK, Kim SJ, Kim JR, Song HR, Cho SH (2003) Role of thrombotic and fibrinolytic disorders in osteonecrosis of the femoral head. Clin Orthop Relat Res 417:270–276
16. Milner PF, Kraus AP, Sebes JI, Sleeper LA, Dukes KA, Embury SH et al (1991) Sickle cell disease as a cause of osteonecrosis of the femoral head. N Engl J Med 325(21):1476–1481
17. Mukisi-Mukaza M, Elbaz A, Samuel-Leborgne Y, Keclad L, Le Turdu-Chicot C, Christophe-Duchange E, Merault G (2000) Prevalence, clinical features, and risk factors of osteonecrosis of the femoral head among adults with sickle cell disease. Orthopedics 23(4):357–363
18. Nsiri B, Gritli N, Bayoudh F, Messaoud T, Fattoum S, Machghoul S (1996) Abnormalities of coagulation and fibrinolysis in homozygous sickle cell disease. Hematol Cell Ther 38(3):279–284
19. Posan E, Szepesi K, Gaspar L, Csernatony Z, Harsfalvi J, Ajzner E, Toth A, Udvardy M (2003) Thrombotic and fibrinolytic alterations in the aseptic necrosis of femoral head. Blood Coagul Fibrinolysis 14(3):243–248
20. Urano T, Sakakibara K, Rydzewski A, Urano S, Takada Y, Takada A (1990) Relationship between euglobulin clot lysis time and the plasma levels of tissue plasminogen activator and plasminogen activator inhibitor 1. Thromb Haemost 63(1):82–86
21. Von Kaulla KN (1963) Chemistry of thrombosis. Human fibrinolytic system. Charles C Thomas, Illinois, pp 49–60