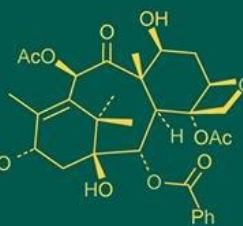
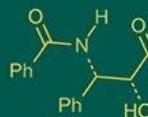


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Biochemical and hematological profiles in sickle cell patients with aseptic osteonecrosis

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Abstract

Aseptic osteonecrosis is a common complication in sickle cell patients. Its onset is insidious and constitutes a disabling condition that is very difficult and costly to treat. In Senegal, its prevalence in sickle cell patients is approximately 9.2%. The pathophysiology of osteonecrosis remains poorly understood and many risk factors have been implicated in its occurrence. Thus, the identification of biochemical and hematological disturbances associated with these risk factors could be an asset for etiological diagnosis and prevention of complications. Thus, the objective of this study was to determine the biochemical and hematological profiles of sickle cell patients with aseptic osteonecrosis. This is a prospective analytical study of sickle cell patients with osteonecrosis followed at the National Blood Transfusion Center (CNTS). Biomarker assays were performed in the Biochemistry laboratory of the Fann University Hospital Center using the Architect Plus Ci 4100 (Abbott) and Maglumi X6 (Snibe) automata for biochemical parameters, the STart Max semi-automata (Stago) and the Sysmex XN-1500 for hematological parameters. The study population consisted of 63 sickle cell patients with osteonecrosis matched with 39 controls. The mean age was 32 ± 11 years and the age range of 20 to 40 years was the most represented. SS forms predominated at 87.30% against 12.69% of SC forms. Analysis of biochemical parameters showed disturbances in the concentrations of total bilirubin > 12 mg/l and haptoglobin < 14 mg/dl respectively in 98.41% and 84.12% of patients with osteonecrosis. The study of hematological parameters showed a D-dimer level > 500 ng/ml in 92.06% of patients. The results obtained suggest that the profile of biochemical and hematological parameters is associated with several disturbances including the increase in D-Dimers, hyperbilirubinemia and the decrease in haptoglobin which could be a predictive factor for the occurrence of osteonecrosis.

Keywords: Sickle cell disease, aseptic osteonecrosis, biochemical profile, hematological profile

Introduction

Sickle cell disease is a genetic disease characterized by the presence of abnormal hemoglobin (HbS), which has the property of polymerizing in its deoxygenated form ^[1]. Epidemiologically, it is the most common hemoglobinopathy in the world and the World Health Organization has classified the fight against sickle cell disease as a priority for the African regions ^[2]. In Senegal, 8 to 10% of the population carries Hb S ^[3]. The polymerization of hemoglobin leads to a sickle-shaped deformation of red blood cells (sickle cells), which is the origin of the pathophysiology of the disease. It is a systemic disease whose osteoarticular manifestations represent the earliest and most frequent complications. Aseptic osteonecrosis (AON) or avascular necrosis corresponds to the cell death of the different components of the bone, that is to say the bone tissue but also the bone marrow ^[4]. It constitutes one of the most devastating musculoskeletal manifestations of sickle cell disease and most commonly affects the femoral head. Although the exact pathophysiology of this condition in patients with sickle cell disease is unknown, it is suggested that sickling of red blood cells and repetitive vaso-occlusion may be associated with tissue hypoxia, inflammation, and subsequent bone necrosis and collapse ^[5].

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This serious and disabling condition, with difficult and costly treatment, affects relatively young people and has significant psycho-socioeconomic consequences [4]. In Senegal, its prevalence in sickle cell patients is approximately 9.2% and studies on aseptic osteonecrosis seem to be rarely reported to our knowledge. In order to better characterize ONA, we set ourselves the objective of evaluating the biochemical and hematological profile of sickle cell patients with aseptic osteonecrosis.

Materials and Methods

Ethical approval

This study was approved by the Research Ethics Committee (CER) of Cheikh Anta Diop University (UCAD) in accordance with the rules issued by the National Health Research Ethics Committee (CNERS) of Senegal under number: 080/2021/CER/UCAD.

Setting and type of study

This is a case-control study involving sickle cell subjects with osteonecrosis covering the period from August 1, 2021 to October 30, 2024. Patient recruitment was carried out in the Clinical Hematology department of the National Blood Transfusion Center and biological parameters were analyzed in the Biochemistry laboratory of the Fann University Hospital Center.

Study Population

The study included 63 sickle cell patients with osteonecrosis, matched with 39 sickle cell controls without osteoarticular complications according to sex and age ± 2 years. Subjects included after informed consent and an 8-hour fast, had blood samples taken and the blood was collected in dry tubes, tubes with EDTA and Citrate. The biochemical parameter assays were performed with the Architect Plus Ci 4100 (Abbott) and Maglumi X6 (Snibe) automata, the hematological and hemostatic parameters were assayed with the Sysmex XN-1500 and STart Max (Stago) automata. We used Excel for recording and XLSAT 2023.3.1 for data processing. Mann-Whitney test was used to compare means and Chi2 test to compare frequencies.

Odds ratio for association assessment. A p-value less than 0.05 was considered a statistically significant difference.

Results

Our study population consisted of 63 subjects with major sickle cell syndrome (SDS), the mean age of the patients was 33 ± 11 years with extremes of 16 and 66 years. The sex ratio was 0.61. In our population, the SDS found were the SS and SC forms respectively in 87.30% and 12.69% of patients (Table 1).

Table 1: General characteristics of the study population

	sickle cell patients ONA+	sickle cell controls ONA-
Included	63	39
Average age (years)	33 ± 11	27 ± 7
Sex Ratio	0.61	0.94
SS profile	87.30%	87.17%
SC profile	12.69%	12.82%

ONA=aseptic osteonecrosis (+=With ; -=without)

Just over half of the patients had osteonecrosis located in the left hip (50.79%) (Fig1)

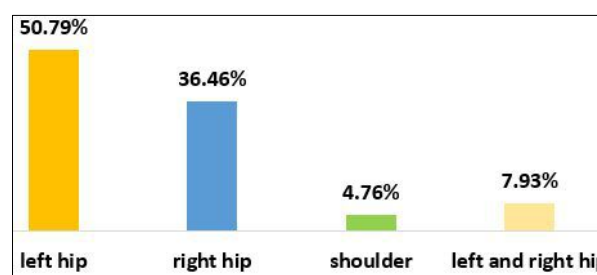


Fig 1: Locations of osteoarticular complications

Comparative analysis of variations in hematological parameters between patients with ONA and patients without osteoarticular complications showed a significant difference ($p < 0.05$) for D-Dimer, prothrombin and fibrinogen levels (Table 2).

Table 2: Comparison of means of hematological parameters

Parameters	Sick (ONA+)	Sick (ONA-)	p Value
Leukocytes ($10^3/\text{mm}^3$)	9.96 ± 2.92	9.70 ± 7.02	0.80
Neutrophil ($10^3/\text{mm}^3$)	5.44 ± 2.18	5.66 ± 2.53	0.65
Lymphocytes ($10^3/\text{mm}^3$)	3.17 ± 1.15	3.39 ± 1.33	0.410
Hemoglobin (g/dl)	9.20 ± 1.85	10.04 ± 1.87	0.084
VGM (fl)	86.05 ± 9.53	83.27 ± 12.25	0.189
CCMH (g/dl)	34.12 ± 3.23	34.62 ± 2.23	0.0771
TCMH (pg)	30.24 ± 3.2	29.14 ± 4.40	0.248
Platelets ($10^3/\text{mm}^3$)	392 ± 153	448 ± 156	0.446
Prothrombin rate (%)	84 ± 10.78	80.17 ± 10.10	0.0449*
Activated partial thromboplastin time (s)	27.69 ± 5.17	31.47 ± 5.17	0.080
Fibrinogen (g/l)	3.81 ± 1.15	2.69 ± 1.1	0.0110 *
D-Dimer (ng/ml)	1625 ± 1254	1031 ± 770	0.0231 *

*Significant difference

Comparative analysis of variations in biochemical parameters between patients with ONA and patients without osteoarticular complications showed a significant difference ($p < 0.05$) for bilirubin (total and indirect) and haptoglobin (Table 3)

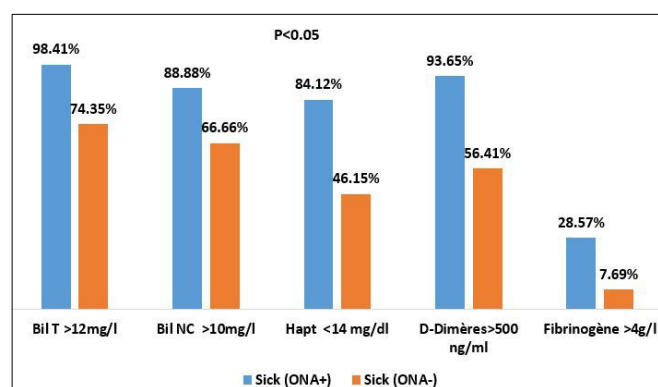
Analysis of biochemical and hematological disturbances mainly revealed a total bilirubin level higher than 12 mg/l and D-Dimers higher than 500 ng/ml in 98.41% and 93.65% of patients with osteonecrosis, respectively. Frequency comparison showed significant differences (Fig 2)

Table 3: Comparison of means of biochemical parameters

Parameters	Sick (ONA+)	Sick (ONA-)	p Value
LDH (U/l)	382±224	472±327	0.104
Bil T (mg/l)	129.9±150	33.9±23	0.00061*
NC Bil (mg/l)	85.22±128	25.98±16	0.00023*
CRP (mg/l)	17.18±40	17.93±43	0.933
Homocysteine (μmol/l)	6.85±2.31	6.98±2.78	0.797
Haptoglobin (g/l)	0.83±0.96	1.78±11.2	0.0123*
Vitamin B12 (pg/ml)	669±387	571±278	0.183
Folates (ng/ml)	28.95±50.29	22.52±35.08	0.505
Total cholesterol (g/l)	1.96±2.1	1.34±0.26	0.355
HDL-Cholesterol (g/l)	0.40±0.12	0.40±0.12	0.815
Triglycerides (g/l)	0.86±0.31	0.98±0.65	0.234
LDL-Cholesterol (g/l)	0.82±0.31	0.83±0.26	0.824

*Significant difference; LDH=lactate dehydrogenase; Bil T=total bilirubin;

Bil NC= Unconjugated bilirubin; CRP= C-reactive protein; PTH= Parathyroid hormone

**Fig 2:** Distribution of biochemical and hematological disturbances

Evaluation of the association between biological parameter disturbances and sickle cell osteonecrosis revealed a strong and significant association ($p < 0.05$) between total bilirubin, conjugated bilirubin, haptoglobin, D-Dimer and fibrinogen and sickle cell osteonecrosis (Table 4)

Table 4: Evaluation of the association between biological parameter disturbances and sickle cell osteonecrosis

	Odds Ratio	95% CI	p value
Bil T >12 mg/l	21.379	[2.6117 -175.0109]	0.0043*
NC Bil >10 mg/l	4.000	[1.4282 - 11.2030]	0.0083*
Hapt <14 mg/dl	6.183	[2.4554 -15.5714]	0.0001*
D-Dimers >500 ng/ml	3.80	[1.0620 -13.6436]	0.0401*
Fibrinogen >4 g/l	4.800	[1.3101 -17.5858]	0.0179*

*Significant difference; Bil T=total bilirubin; Hapt =Haptoglobin

Discussion

Sickle cell disease, one of the most common serious monogenic diseases in the world, has a major impact on the lives of those affected and requires regular medical monitoring to avoid the occurrence of complications, which are often unpredictable. Aseptic osteonecrosis is a common osteoarticular complication in sickle cell patients. Its onset is insidious and its treatment remains a real challenge. The study of sickle cell bone necrosis has several interests: epidemiological, diagnostic, pathophysiological and therapeutic. Thus, the objective of this study was to evaluate the biochemical, hematological and hemostatic profile of sickle cell patients with aseptic osteonecrosis. The analysis of our results shows an average age of 32 ± 11 years and the most represented age group was 20-40 years. Our results are similar to those of Coulibaly *et al*, who found in their study

a mean age of 31 years and the most represented age group was that of 21 to 30 years [6]. This relatively young population could be explained by the fact that young people are particularly active, which makes them more prone to developing necrosis at the level of the head of the femur due to wear [6]. The evolution of ONA from the pre-radiographic stage (stage I) to the higher stages is also more rapid and necrosis is detected earlier. In our study, we found a sex ratio of 0.94. In a study carried out in Senegal on sickle cell patients with ONA, Sene *et al*. reported a similar sex ratio [7]. This rediscovered female predominance could be explained by the appearance of physiological changes linked to hormones. Indeed, adipose tissue, which is more developed in women, constitutes a true endocrine organ, secreting numerous substances and hormones involved in lipid metabolism [8]. An unfavorable metabolic background, such as hyperlipidemia (Type I and V) or diabetes [9], promotes intramedullary lipidosis, and is responsible for medullary hyperpressure, and extravascular obstruction. In our population, the major sickle cell syndromes found were the SS and SC forms in 87.30% and 12.69% of patients respectively. The homozygous SS form is by far the most frequent and the most serious, it evolves rapidly towards acute and chronic complications. However, ONA is a particularly frequent complication in SC sickle cell patients, more than in SS patients [10]. This is corroborated by the work of Ngo Sack *et al*. and Colella *et al* [11,12]. The prevalence of this complication in SC sickle cell patients could be explained by the hypercoagulability which is more marked in these patients [12]. Our population consisted of sickle cell patients with osteonecrosis, 50.79% of whom had a location at the left hip and 36.50% at the right hip. In the study by Coulibaly *et al*, the location at the right hip was the most frequent, i.e. 37.5% versus 28.1% for the left hip. A bilateral involvement of 34.4% was found in the study of Sene *et al*. The frequency of localizations at the level of the femoral head is explained by the reduced caliber of its vessels and the lack of collateral circulation of replacement [6]. Furthermore, since the hip supports the weight of the body, any increase in intra-articular pressure secondary to thrombosis of synovial vessels aggravates ischemia at the level of the femoral head [13]. Bilateral necrosis is secondary to the progression of unilateral necrosis [14]. Analysis of the means of hematological and hemostatic parameters showed a higher fibrinogen concentration in patients with osteonecrosis with a mean of 3.81 g/l versus 2.69 g/l for controls with a significant difference ($p=0.0110$); In a similar study, Pósán *et al*. reported a mean concentration of 3.96 g/l [15]. Increased fibrinogen levels during sickle cell disease have been reported by several studies due to chronic inflammation [16]. We found a fibrinogen level greater than 4g/l in 28.57% of ONA+ patients and a significant association ($p=0.0179$) was found between hyperfibrinogenemia and osteonecrosis. Increased fibrinogen levels undoubtedly enhance in vitro measures of platelet amenability and estimation of plasma fibrinogen levels in patients with sickle cell disease could be a useful indicator of hypercoagulability [16]. In our population we found a mean concentration of D-Dimers of 1625 ng/ml in patients against 1031 ng/ml in controls, the comparison of means showed a significant difference ($p=0.0231$). A D-dimer level > 500 ng/ml was found in 93.65% of patients with osteonecrosis. In a study conducted in 96 sickle cell patients, Devine *et al*. showed a statistically significant association between D-dimer level and complications of sickle cell disease [17]. Shitrit *et al*. demonstrated significantly higher D-dimer levels in Gaucher disease patients with osteonecrosis compared to those without

osteonecrosis [18]. Sickle cell disease is accompanied by a state of hypercoagulability linked to several factors including an increase in circulating thrombin, a lack of regulation by a decrease in anticoagulant proteins (proteins C and S), and an abnormal activation of the fibrinolytic system generating more d-dimers [19, 20, 21]. The hypothesis that increased intravascular coagulation could be the pathogenetic mechanism leading to osteonecrosis has been consistently supported [22]. Analysis of the means of biochemical parameters showed higher concentrations of total and unconjugated bilirubin in patients with osteonecrosis with respective means of 129.9 mg/l and 85.25 mg/l compared to 33.9 mg/l and 25.98 mg/l for controls with a significant difference ($p < 0.05$). A significantly lower mean haptoglobin concentration was found in ONA+ patients. We found in the literature few studies evaluating the association between hemolysis and osteonecrosis. Dubert *et al*, showed in a study carried out in African sickle cell patients that the association between chronic hyperhemolysis and sickle cell vascular complications is statistically significant but of low amplitude, particularly in children [23]. The existence of hypercoagulability has long been described in hemoglobinopathies (mainly sickle cell disease and thalassemia), appearing to be at least partly responsible for their vascular complications [24]. There are many prothrombotic factors during hemoglobinopathies, some of which appear to be more specific. In addition to multifactorial platelet activation induced by extracellular hemoglobin and the exposure of negatively charged phospholipids on the surface of red blood cells that promote thrombin formation [25], structural alteration of erythrocytes has been shown with the formation and precipitation of hemichromes resulting from the oxidation of globin subunits, a source of free radicals and oxidative stress [26]. The 2010 recommendations of the High Health Authority (HAS) on sickle cell disease, updated in 2015, recommend systematic preventive anticoagulation in the event of permanent bed rest during a vaso-occlusive crisis, or in the event of acute thoracic syndrome [27].

Conclusion

The results obtained suggest that the profile of biochemical and hematological parameters is associated with several disorders including increased D-Dimer, hyperfibrinogenemia, increased bilirubin (total and conjugated) and decreased haptoglobin. The characterization of these disturbances could be an asset for the etiological diagnosis and prevention of sickle cell osteonecrosis.

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Authors' Declaration

The authors declare having no conflict of interest in related to this article.

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