Risk factors of avascular osteonecrosis of the femoral head in children at the National Reference
Center for Sickle Cell Disease in Brazzaville, Congo.

Abstract

Introduction

The avascular osteonecrosis of the femoral head (AOFH) is a common complication of sickle cell disease (SCD). It exposes to lameness and sometimes to a very debilitating handicap. It is a source of desocialization, particularly in developing countries where prosthetic surgery remains inaccessible to the majority. This survey aimed to identify the risk of occurence AOFH.

Materials and methods

It was a case-control study carried between october 2017 and september 2021 at the National Reference Center for SCD « Antoinette Sassou Nguesso » in Brazzaville. It concerned 31 children with clinical and radiographic signs of AOFH. Clinical (age at diagnosis of SCD, frequency of vasoocclusive crises and hospitalization for vasoocclusive crises, number of blood transfusion) as well as hematological examination (blood count in the intercritical period) and hydroxyurea treatment were compared with those of 62 children with no clinical and radiographic signs of AOFH. The chi2 statistical test and the odds ratio were used for the comparison ($P < 0.05$).

Results

The *sex ratio* was 1.38 *versus* 0.93 (p = 0.50). The mean age of diagnostic of SCD was 3.76 ± 2.56 years *versus* 3.94 ± 2.01 years (p = 0.81). Logistic regression showed that SCD children with AOFH had a significantly higher rate of annual frequency of VOC (4.16 ± 1.18 vs 2.91 ±

1.68 ; *P* = 0.015), annual frequency of hospitalization for VOC (3.74±1.65 vs 1.45 ± 1.28 ; *P* = 0.000) and number of blood transfusions (3.38 ± 2.69 vs 2.42 ± 2.32 ; *P* = 0.03).

Conclusion

Emphasis should be placed on the prevention and early management of acute complications of SCD. The role of hydroxyurea should be clarified by further work.

Key word : AOFH, children, femoral head, osteonecrosis, risk factors, sickle cell disease.

1. Introduction

Sickle cell disease (SCD), the most common hereditary disease in the world, is a public health problem, especially in sub-Saharan Africa where 85% of children affected by the disease are born [2,3]. It is responsible for the polymerization of hemoglobin (Hb) molecules in red blood cells, causing them to become brittle, hyperhemolysis, and loss of plasticity [1]. Osteoarticular complications are multiple, infectious or non-infectious, including aseptic osteonecrosis epiphyseal. It is a degeneration of bone tissue related to an abnormality in blood circulation. The head of the femur is the most common seat [4,5]. In Africa, the avascular osteonecrosis of the femoral head **(**AOFH) affects sometimes very young children [6]. In the Congo, nearly half of them are under the age of 11, and the diagnosis is often late, at the stage of joint destruction corresponding to the radiological stages III or IV of Arlet and Ficat [7]. Furthermore, total hip prosthesis, the only radical treatment of advanced stages, is not always available in our countries with limited resources and is often inaccessible because of its cost [8]. Moreover the current and more conservative treatment with autologous implantation of iliac crest bone marrow-derived mononuclear cells, which contains precursor cells including mesenchymal stromal cells is more inaccessible than total hip prosthesis [9]. Thus, children are often condemned to live with this debilitating pathology by the lameness, pain, and functional impotence it causes in time, until the end of their growth and even after. It is a

hindrance not only to the growth of the skeleton but also to the quality of a child's life, already disturbed by numerous episodes of vaso-occlusive crises [10-12**].** In Congo Brazzaville, AOFH is the most common chronic complication in adults [13].

The combination of these problems (early onset, late diagnosis, and limited access to joint replacement) justifies the need to identify children at risk of developing AOFH. This would allow us to put in place a strategy based on its prevention or at least its early diagnosis and management.

2. Materials and methods

This was a case-control study comparing children with SCD (under 18 years of age) with AOFH to children with SCD without AOFH. It was conducted over four years from October 1, 2017, to September 31, 2021. It was set up by the National Sickle Cell Reference Centre "Antoinette SASSOU N'GUESSO" in Brazzaville, which has been the country's largest center of management of people with SCD since 2017.

Childhood was defined as the period from birth to age 18. Children with AOFH (cases) were listed and then each was matched to two children without AOFH (controls) on an age basis. Children with a history of traumatic hip pathology, coxarthritis, or long-term corticosteroid therapy were excluded from the study. The control group consisted of children who had never had any clinical symptomatology that could evoke AOFH and had a standard, strictly normal pelvic X-ray.

Data were collected retrospectively from medical records. The variables studied were epidemiological (sex), clinical (age of diagnosis of SCD, frequency of vaso-occlusive crises and hospitalization for vaso-occlusive crises in the 3 years preceding the diagnosis of AOFH, number of blood transfusions and treatment with hydroxyurea before diagnosis of AOFH) and

paraclinical (inter-critical blood count including leukocyte count, Hb count, mean globular volume, mean corpuscular concentration in Hb, platelet count).

The inter-critialc period was defined by a period of at least 4 months characterized by the absence of acute infectious, vaso-occlusive, and/or anemic complications. Anemia was considered moderate if Hb was above 6 g/dl and severe if it was below or equal to 6 g/dl.

Data entry and exploitation were done by the Microsoft office version 2016 software. Epi info software version 7.2.1.0 was used for data analysis. The results of the qualitative variables are presented in absolute values and percentages; those of the quantitative variables are in the form of the mean (standard deviation), minimum, and maximum. The khi2 statistical tests and the Odds ratio were used for the comparison of variables, with a threshold of significance $P<0.05$ and a 95% CI confidence interval.

3. Results

The study included 31 sickle cell children with AOFH and compared them to 62 witnesses.

Among children sufferinf of AOFH, the damage was bilateral in 10/31 cases. Radiologically, stages I and II on one hand and III and IV on the other hand of Arlet and Ficat were respectively found in 45.16% and 54.84% of cases.

The average age of children was the same for the Cases and for the Controls, 11.51±2.17 years years with extremes of 8 and 17 years. The sex ratio was 1.38 *vs* 0.93.

Table 1 presents the epidemiological and clinical characteristics of the children.

Table 1: epidemiological and clinical characteristics of SCD children with AOFH and SCD children without AOFH at the National Reference Center for SCD in Brazzaville, Congo.

Parameters	Cases (N = 31)		Controls (N = 62)	
	n	%	n	%
Sexe				
Male	18	58	30	48.40
Female	13	42	32	51.60
Age at diagnostic of SCD				
Mean [min - max]	3.76 ± 2.56 years [3 month - 13 years]		3.94 ± 2.01 years [5 month – 15 years]	
0 - 5	23	74.20	44	70.97
6 - 10	6	19.35	11	17.74
≥ 11	2	6.45	7	11.29
Mean annual frequency of VOC*				
Mean [min - max]	4.16±1.18 [2 – 6]		2.91±1.68	[0 – 6]
0 – 3	10	32.26	37	59.68
4 - 6	21	67.74	25	40.32
≥ 7	0	0	0	0
Mean annual frequency of hospitalization for VOC				
Mean [min - max]	3.74±1.65 [0 – 9]		1.45±1.28 [0 – 5]	
0 – 3	14	45.16	58	93.45
4 - 6	16	51.62	4	6.55
≥ 7 e	1	3.22	0	0
Number of blood transfusion				
Mean [min - max]	3.38 ±2.69 [0-9]		2.42±2.32 [0 - 10]	
0 - 3	15	48.39	45	72.58

4 – 6	11	35.49	14	22.58
≥ 7	5	16.12	3	4.84

*Vasoocclusive crises

Biologically, Hb level was 8.1 ± 0.83 g/dl [6.8 g/dl - 10.7 g/dl] vs 7.91 ± 0.95 g/dl [6, 1g/dl - 11.2g/dl]. The other parameters of the hemogram in the interictal period are presented in Table 2.

Table 2 : characteristics of inter-critical blood count of SCD children with AOFH and SCD children without AOFH at the National Reference Center for SCD in Brazzaville, Congo.

Parameters	Cases (N = 31)		Controls (N = 62)	
	n	%	n	%
WBC* (/mm^3)				
Mean [min - max]	10.89±4.7 [4.24 – 24.21]		11.58 ± 3.6 [4.96 – 22.40]	
4000 - 12000	21	67.74	36	58.06
> 12000	10	32.26	26	41.94
MCV (FL)**				
Mean [min - max]	76.31 ± 6.82 [61.5 – 88.9]		78.88 ± 7.37[59.4 - 95]	
< 80	20	64.52	35	56.45
80 - 90	11	35.48	24	38.71
> 90	0	0	3	4.84
MCHC* (%)**				
Mean [min - max]	33.59 ± 1.90 [25.5 - 37]		33.77 ± 2.15 [26.7 – 38.2]	

< 32	1	3.23	9	14.52
32 - 36	30	96.77	53	85.48
Platelets (giga/L)				
Mean [min - max]	386 ± 187[153 - 957]		342±128 [154- 730]	
150 - 450	20	64.52	52	83.87
> 450	11	35.48	10	16.13

*****White blood cells

**Mean Corpuscular Volume

***Mean Corpuscular Hemoglobin (Hb) Concentration

Therapeutically, 16 children (51.61%) vs 19 children (30.64%) were treated with hydroxyurea.

Tables 3 analyze the link between certain epidemiological, clinical and paraclinical aspects as well as the occurrence of necrosis of the head of the femur.

Table 3: comparison of epidemiological, clinical et biological characteristics between SCD children with AOFH and SCD children without AOFH at the National Reference Center for SCD in Brazzaville, Congo.

History of SCD	Odds - Ratio	95% CI	*P*
Age at the diagnosis of SCD (years)			
0 – 5	1.17	0.41 – 3.62	0.81
≥ 6	0.85	0.27 – 2.45	
Sex			
Male	1.47	0.61 – 3.52	0.50
Female	0.6	0.28 – 1.61	
Mean annual frequency of VOC			
0 – 3	0.32	0.11 – 0.86	**0.015**
≥ 4	3.10	1.15 – 8.64	
Mean annual frequency of hospitalization for			
VOC	0.05	0.01– 0.21	**0.000**
0 – 3	17.60	4.59 – 80.01	
≥ 4			
Number of blood transfusion			
0 – 3	0.35	0.13 – 0.95	**0.03**
≥ 4	2.82	1.04 – 7.62	
MCV (fl)			
< 80	1.40	0.53 – 3.81	0.50
≥ 80	0.71	0.26 – 1.88	
MCHC (g/dl)			
< 32	0.19	0.004 -1.55	0.15
32 - 36	5.09	0.64 – 230.60	

WBC (/mm ^{3})			
4000 – 12000	1.51	0.56 – 4.23	0.49
≥ 12000	0.65	0.23 – 1.77	
Hydroxyurea treatment	3.53	1.32 – 9.77	0.006

4. Discussion

The male predominance in Cases contrasted with the female predominance of Controls, but the difference was not significant. Mahadeo reported that male gender was a risk factor identified by univariate analysis (P = 0.02) and multivariate logistic regression analysis showed an independent association with it (OR 3.1, 95% CI: 1.05, 9.02, P = 0.04) [14].

Concerning the relationship between AOFH and clinical status, children with AOFH had a significantly higher mean number of VOC and hospitalizations for VOC. Those who had been transfused more than three times since birth also had a higher risk of developing AOFH. Frequent VOC remains the most consistent comorbidity of AOFH [14, 15, 16-18]. 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 levels are associated with increased intravascular sickling and high viscosity, predisposing to AOFH [19]. In a systematic review, Leandro showed that among multiple clinical factors which have been studied as possible markers associated with AOFH, the severity of the disease appears to be the most important risk factor to be considered including manifestations such as the number of acute chest syndrome, pain crisis, hospitalizations or even limb ulcers [15]. A longitudinal prospective study of AOFH incidence and progression conducted in a cohort of

30 pediatric subjects with sickle cell anemia from Kuwait showed that participants with progressive AOFH had frequent VOCs [20].

Moreover, Worral reported that elevated systolic blood pressure above 115 mmHg is another parameter which can be used as a marker of AOFH risk [21]. Elevated blood pressure may contribute to AOFH by causing endothelial dysfunction and by worsening hypercoagulability, contributing to bone ischemia [21, 16, 22].

Among laboratory markers, the most studied in the literature were full blood count variables. Unlike other several studies, we did not find any association between AOFH and MCV, MCHC and white blood cell count [21, 23]. In Mukizi's study, only elevated haemoglobin levels were associated with the occurrence of AOFH, which suggests that increased blood viscosity contributes to the condition [24]. Worral showed that an elevated Hb/HCT ratio above 0.33, which is equivalent to a MCHC above 33, was an excellent predictor of AOFH ($p=2.06\times10^{-6}$, OR=5.17) [21]. It may relate to the HbS concentration within the red blood cell with certain rheological features of the blood and circulatory vessels known to affect polymerization and RBC sickling rates [25, 26]. In Adekile's study, the number of reticulocytes and platelets are the only parameters of the full blood count that have a significant influence on the occurrence of AOFH in Kuwaiti children and adolescents with SCD [23]. The association between AOFH and reticulocytosis suggests that hemolysis may play a role in AOFH development [27]. Other markers have been implicated in the occurrence of AOFH in patients with SCD such as a higher haematocrit level [14], a longer euglobulin clot lysis time [16] and a lower count of fetal hemoglobin, supporting the hypothesis that fetal hemoglobin may function as a protective factor against avascular necrosis [17].

The role of hydroxyurea in the occurrence of AOFH is controversial [28]. It is a molecule with various effects, among which: increase in HbF levels, reduction in red blood cells count and leukocytes' adhesion to the endothelium or even reduction of vasoconstriction by braking

of the expression of endothelin-1 regulatory genes [3, 28]. Its positive effects in reducing the frequency of VOC could have led to the belief that it would be indubitably "protective" in the occurrence of AOFH. However, some authors found independent associations between AOFH and hydroxyurea exposure [14], others found no association [29, 30]. Most recently, Adekile surmised that hydroxyurea may protect against AOFH onset and delay its progression in children and adolescents with SCD [23].

5. Conclusion

A relationship was found between the AOFH and the frequency of VOC, hospitalization for VOC as well as blood transfusion frequency in SCD children. Emphasis should be placed on prevention and early management of acute complications of SCD. The role of hydroxyurea should be clarified through larger-scale studies and in multivariate analysis taking into account the indications for treatment.

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Authors' contributions

Galiba Atipo-Tsiba Firmine Olivia designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Bilongo-Bouyou Arnauld managed the analyses of the study. Elira JA, Gatsongui BM, Malanda F, Ngolet LO and Elira Dokekias A managed the literature searches. All authors read and approved the final manuscript.

References

1. Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Dewi M, et al. Global epidemiology of Sickle haemoglobin in neonates: A contemporary geostatistical model based map and population estimates. The Lancet. 2013;381(9861):142-151.
2. Piel FB, Patil AP, Howes RE. Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. Nat Commun. 2010;1:104.
3. Odièvre MH, Quinet B. Drépanocytose chez l'enfant. J Pediatr Pueric. 2022;35(2):73-92.
4. Milner PF, Kraus AP, Sebes JI, Sleeper LA, Dukes KA, Embury SH, et al. Sickle cell disease as a cause of osteonecrosis of the femoral head. N Engl J Med. 1991;325:1476-81.
5. Naseer ZA, Bachabi M, Jones LC, Sterling RS, Khanuja HS. Osteonecrosis in sickle cell disease. South Med J. 2016;109(9):525-30.
6. Mouba JF, Mimbila M, Lentombo LE, Thardin JF, Ondo A. Nécrose aseptique de la tête fémorale chez l'enfant drépanocytaire : expérience de Libreville (Gabon). Santé 2011;21(2):89-92.
7. Galiba Atipo-Tsiba FO, Bilongo-Bouyou ASW, Gatsongui BM, Ngolet LO, Osseke N, Malanda F, et al. Aseptic osteonecrosis of the femoral head in children living with sickle cell disease at the National Reference Center for sickle cell disease of

Brazzaville, Congo. J Blood Disord Med 2023;5(1): dx.doi. org/10.16966/2471-5026.131.

8. Coulibaly Y, Coulibaly T, Maiga AK, Konate M, Keita S, Traore SY. Osteonécrose aseptique de la tête fémorale chez les drépanocytaires : aspects épidémiocliniques et thérapeutiques dans le service de chirurgie orthopédique et traumatologique. Mali Médical 2009 ; 4 :43-46.
9. Daltro G, Do Socorro Salim Ramos N, SarmentoTrindade SM, Cortez de Araujo PI, Borges SM. Pediatric sickle cell disease osteonecrosis of the femoral head : a treatment proposal. Clin Pediatri. 2020;3:1022.
10. Malheiros CD, Lisle L, Castelar M, Sá KN, Matos MA. Hip dysfunction and quality of life in patients with sickle cell disease. Clin Pediatri (Phila) 2015;54(14), 1354-58.
11. Matos MA, Silva LLS, Alves GB, Alcântara Júnior WS, Veiga D. Necrosis of the Femoral Head and Health-Related Quality of Life of Children and Adolescents. Acta Ortop Bras 2018;26:227-30.
12. Tezol O, Karahan F, Unal S. Sickle cell disease and psychosocial well-being : comparison of patients with preclinical and clinical avascular necrosis of the femoral head. Turk Arch Pediatr. 2021;56(4): 308-15.
13. Ngolet LO, Okouango Nguelongo Ova JD, Ntsiba H, Elira DA. Complications chroniques du sujet drépanocytaire adulte à Brazzaville. Heal Sci Dis 2017;18: 56-59.
14. Mahadeo KM, Oyeku S, Taragin B, Rajpathak SN, Moody K, Santizo R et al. Increased prevalence of osteonecrosis of the femoral head in children and adolescents with sickle cell disease. Am J Hematol. 2011; 86(9): 806-8.
15. Leandro MP, De Sá CKC, Filho DPS, De Souza LAA, Salles C, Tenório MCC, et al. Association and risk factors of osteonecrosis of femoral head in sickle cell disease : a systemati creview. Indian J Orthop. 2021;56(2):216-25.

16. Akinyoola AL, Adediran IA, Asaleye CM, Bolarinwa AR. Risk factors for osteonecrosis of the femoral head in patients with sickle cell disease. Int Orthop 2009;33:923-6.
17. Almeida-Matos M, Carrasco J, Lisle L, Castelar M. Avascular necrosis of the femoral head in sickle cell disease in pediatric patients suffering from hip dysfunction. Rev Salud Publica (Bogota). 2016 ;18(6):986-95.
18. Adesina O, Brunson A, Keegan THM, Wun T. Osteonecrosis of the femoral head in sickle cell disease : prevalence, comorbidities, and surgical outcomes in California. Blood Adv 2017 ; 1(16), 1287-95.
19. Adekile A. The genetic and clinical significance of fetal hemoglobin expression in sickle cell disease. Med Princ Pract. 2021;30(3):201-211.
20. Gupta R, Adekile AD. MRI follow-up and natural history of avascular necrosis of the femoral head in Kuwaiti children with sickle cell disease. J Pediatr Hematol Oncol. 2004;26(6):351-353.
21. Worrall D, Smith-Whitley K, Wells L. Hemoglobin to hematocrit ratio : the strongest predictor of femoral head osteonecrosis in children with sickle cell disease. J Pediatr Orthop 2016 ; 36(2) : 139-44.
22. Naik RP, Streiff MB, Lanzkron S. Sickle cell disease and venous thromboembolism : what the anticoagulation expert needs to know. J ThrombThrombolysis2013; 35:352-358.
23. Adekile AD, Gupta R, Al-Khayat A, Mohammed A, Atyani S, Thomas D. Risk of avascular necrosis of the femoral head in children with sickle cell disease on hydroxyurea : MRI evaluation. Pediatr Blood Cancer. 2019;66(2):e27503.

24. Mukisi-Mukasa M, Samuel-Leborgne Y, Kéclard L, Le Turdu-Chicot C, Christophe-Duchange E. Prevalence, clinical features and risk factors of osteonecrosis of femoral head among adult patients with sickle cell disease. Orthopedics 2000;23: 357-63.

25. Galkin O, Pan W, Filobelo L, Hirsch RE, Nagel RL, Vekilov PG. Two-step mechanism of homogeneous nucleation of sickle cell hemoglobin polymers. Biophys J 2007;93:902-13.

26. Uzunova VV, Weichun P, Galkin O, Vekilov PG. Free heme and the polymerization of sickle cell hemoglobin. Biophys J. 2010; 99:1976-85.

27. Kato GJ, Gladwin MT, Steinberg MH. Deconstructing sickle cell disease : reappraisal of the role of hemolysis in the development of clinical subphenotypes. Blood Rev. 2007;21(1):37-47.

28. Adesina OO, Neumayr LD. Osteonecrosis in sickle cell disease : an update on risk factors, diagnosis, and management. Hematology Am Soc Hematol Educ Program. 2019 ; 2019(1): 351-58.

29. Voskaridou E, Christoulas D, Bilalis A, Plata E, Varvagiannis K, Stamatopoulos G, et al. The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients withsicklecell syndromes : results of a 17-year, single-center trial (LaSHS). Blood. 2010;115(12):2354-63.

30. Adekile A, Menzel S, Gupta R, Al-Sharida S, Farag A, Haider M, et al. Response to hydroxyurea among Kuwaiti patients with sickle cell disease and elevated baseline HbF levels. Am J Hematol. 2015;90(7) :138-39.