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Ferritin level in sickle cell patients at the sickle cell referral center of Lomé in 2022

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ABSTRACT

Aim: Major sickle cell sufferers residing in tropical regions find themselves at the crossroads of several situations that can modify their iron status. Our aim was to describe ferritin levels in sickle cell patients at Centre National de Recherches et de Soins aux Drépanocytaires (CNRSD) of Lomé.

Methods: This was a cross-sectional study of sickle cell patients seen in medical consultations from May 16 to July 15, 2022. We included all sickle cell patients with anemia, who were seen in a medical monitoring during the study period and who gave their free consent. MINDRAY automatic system BC 6000, Mini-Vidas automatic system from BIOMERIEUX, and Minicap Flex Piercing from SEBIA were used to perform hemograms, ferritin levels, protidograms, and hemoglobin electrophoresis, respectively. The variables studied were patients' medical history, age, sex, hematimetric indices, ferritin levels, hemoglobin fractions, and protidograms. We used Statistical Package for the Social Sciences (SPSS) software to analyze data.

Results: 117 patients with a mean age of 15.42±11.11 years were included. The sex ratio M/F was 0.98. Ferritin levels was below 15 ng/mL in 4 (3.42% of cases) and below 30 ng/mL in an inflammatory context in 7 patients (5.98%). Median ferritin level was 178.37 ng/mL; [Q1=59.39; Q3=411.35]. SS patients were most frequent (75.21%). The mean hemoglobin level of patients was 8.10±1.21 g/dL. Non-microcytic anemia was most frequent (57.30%).

Conclusion: Elevated ferritin levels were more frequent than iron deficiency in sickle cell patients at the CNRSD of Lomé. Thus, any prescription of iron should be motivated by proof of the existence of iron deficiency.

Keywords: Ferritin level, Iron status, Sickle cell patient, Togo

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INTRODUCTION

Sickle cell disease is a qualitative, constitutional hemoglobinopathy characterized by the presence of hemoglobin (Hb) S in place of the healthy hemoglobin known as Hb A. Hemoglobin S polymerizes under conditions of hypoxia [1], resulting in sickle cells which are then considered antigenic and hemolytic targets, a source of early hemolysis [2, 3]. This massive and early hemolysis of sickle cells is at the root of the almost permanent anemia in SS and Sβ° thalassemic patients. Iron from hemolysis is recovered by the body, where it

is taken up by transferrin [4]. This molecule transports iron to the bone marrow to produce new red blood cells. Thus, some authors have shown that it is not necessary to prescribe iron to sickle cell patients, as iron from hemolysis is recovered for hemoglobin synthesis [4–6]. Based on the principle of iron recovery by the body, only folic acid supplementation for sickle cell patients is recommended [7–9]. At the sickle cell referral center of Lomé, iron is prescribed only to pregnant sickle cell patients to compensate the increased needs associated with pregnancy [10]. Sickle cell patients with anemia receive only folic acid, regardless of the type of anemia. This folic acid intake is not intended to correct the anemia in our patients, but to maintain their basic hemoglobin level, which is often below physiological thresholds. In some cases of persistent anemia, some patients self-medicate with other anti-anemic drugs, notably those containing iron. This finding prompted the following questions: is there iron deficiency in some of the anemic sickle cell patients followed at the CNRSD? Should self-medication with iron tablets be discouraged in sickle cell patients?

To answer these questions, this work was carried out with the general objective of describing the profile of ferritin levels in sickle cell patients with anemia at the CNRSD of Lomé.

MATERIALS AND METHODS

It was a cross-sectional study. Patient recruitment phase took place over two months, from May 16 to July 15, 2022. Blood samples for biological analysis were taken from major sickle cell patients medically monitored at the sickle cell disease (SCD) referral center of Lomé. The sample size was calculated using Schwartz's formula.

$N = \varepsilon^2 pq/z^2$ [11]. $q = 1 - p$, $\varepsilon = 1.96$ and precision $z = 5\%$.

In several publications, we have found that the prevalence of martial deficiency in sickle cell disease varies between 2.5% and 11% [7, 12, 13]. The mean of the two prevalences is p = 6.75%. So, the minimum sample size for this work should be 97.

All sickle cell patients with anemia who were seen in a medical consultation at CNRSD during the study period and who voluntarily agreed to take part in the study were included. Regarding minor patients, we have obtained consent from their legal guardians.

Patients in vaso-occlusive crisis, those whose last transfusion occurred within the past three months and those with normal hemoglobin levels were not included.

For each included patient, 3 mL of venous blood was taken in anticoagulant-free tube for determination of ferritin level and protidogram. A second 2 mL venous sampling was taken on an anticoagulant tube for hemogram and hemoglobin electrophoresis, which was not performed for patients who had an electrophoresis result from the capillary technique.

Blood counts were performed on MINDRAY's BC-6000. Ferritin level was determined on the BIOMERIEUX Mini-Vidas semi-automated system. Ferritin levels were interpreted as follows:

Ferritin level < 15 ng/mL: iron deficiency [14–16];
15 ng/mL ≤ ferritin level ≤ 30 ng/mL associated inflammatory context on protidogram is considered iron deficiency [17];
30 ng/mL ≤ ferritin level ≤ 150 ng/mL: normal result;
150 ng/mL < ferritin level is iron overload.

Protidogram and hemoglobin electrophoresis were performed using SEBIA's MINICAP automated system. Statistical analyses of the collected data were performed using SPSS version 21 software, with a significant difference if p value is low than 0.05. Means were compared using ANOVA, and the Chi-square test was used to compare prevalences.

RESULTS

One hundred and seventeen patients were included in our study. The mean age was 15.42±11.11 years, with extremes of 1 and 51 years. The sex ratio was 0.98. There were 88 SS patients (75.21%), 19 Sβ thalassemic patients (16.24%), and 10 SC patients (8.55%). Most patients included in this study were under 30. Patient numbers by age group are shown in Table 1.

The mean hemoglobin level was 8.10±1.21 g/dL. 67 sickle cell patients (57.62%) have non-microcytic anemia. Inflammation was noted in 66 patients. It was noted in 50 patients SS, 33 patients who had high ferritin level and in 40 cases of non-microcytic anemia (Table 2).

Overall, 66 patients (56.41%) had inflammatory context while 29 (24.79%) had normal protidograms and 22 (18.80%) had abnormalities as increased or decreased protein fractions. In addition, there was high beta-1-globulinemia in 3 patients with ferritin level below 15 ng/mL.

Ferritin levels were below 15 ng/mL in 4 (3.42% of cases) and below 30 ng/mL in an inflammatory context in 7 patients (5.98%). Median ferritin level was 178.37 ng/mL [Q1=59.39; Q3=411.35]. Table 3 shows the distribution of patients according to ferritin level.

Ferritin levels did not depend on the patient's sex (Figure 1).

Fifty patients had microcytic anemia and 7 patients (5.98%) had iron deficiency associated with microcytic anemia (Figure 2).

There were more cases of high ferritin levels in patients with non-microcytic anemia. On the other hand, there was as much normal ferritin levels as high ferritin level in SS patients (Figure 3).

Iron deficiency was present in all age groups. A peak of high ferritin level was observed in the 1 to 10 age group (Figure 4).

Table 1: Distribution of patients by age group in years

	Patients	Percentage (%)
[1–10]	46	39.32
[11–20]	36	30.77
[21–30]	22	18.80
[31–40]	8	6.84
>40	5	4.27
Total	**117**	**100**

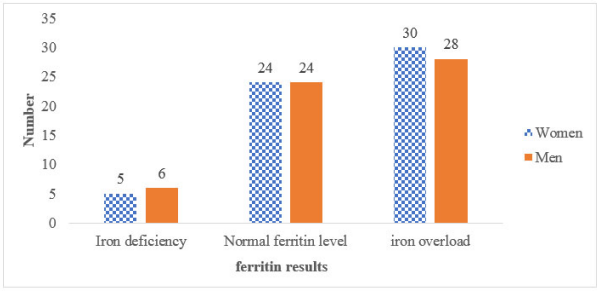
Table 2: Protidogram results according to phenotype, ferritin level, and type of anemia

	Inflammatory context	No inflammation	Total (%)
Phenotype			
SC	7	3	10 (8.55)
SS	50	38	88 (75.21)
Sβ-thalassemic	9	10	19 (16.24)
Ferritin level (ng/mL)			
<15	1	3	4 (3.42)
15–30	7	1	8 (6.84)
30–150	25	22	47 (40.17)
>150	33	25	58 (49,57)
Type of anemia			
Microcytic anemia	26	24	50 (42.74)
Non-microcytic anemia	40	27	67 (57.26)

Table 3: Distribution of patients according to ferritin level

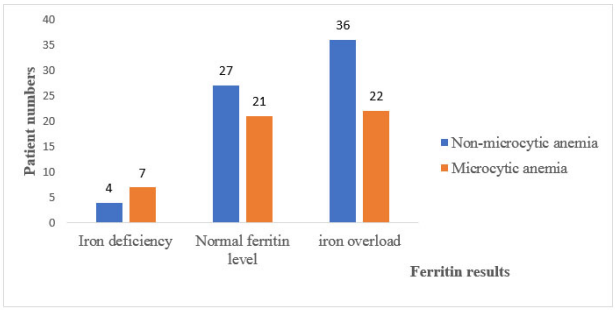
Ferritin (ng/mL)	Patients	Percentage (%)
<15	4	3.42
15–30[a]	7	5.98
15–30	1	0.86
30–50	47	40.17
>150	58	49.57
Total	**117**	**100**

[a]Inflammatory context.



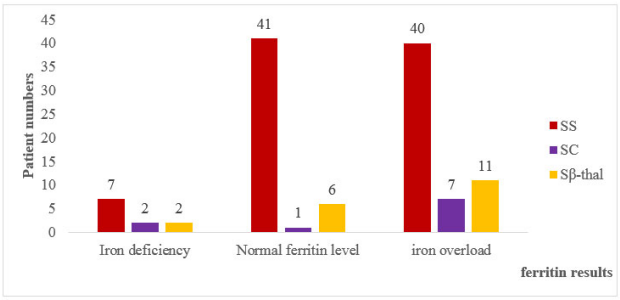
p = 0,675

Figure 1: Ferritin results according to the patient's sex.



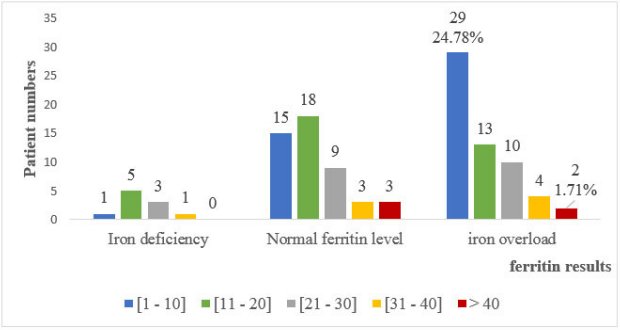
p = 0,0001

Figure 2: Ferritin results according to type of anemia.



p = 0,0001

Figure 3: Ferritin results according to hemoglobin phenotypes.



p = 0,000

Figure 4: Ferritin results by age group.

DISCUSSION

The aim of this study was to describe the profile of ferritin level in sickle cell patients with anemia at the CNRSD in Lomé. Our study population consisted mainly of SS patients (75.21%), confirming that anemia is predominant in these forms of sickle cell disease. The mean Hb level of our patients was 8.10 g/dL, which is within the range of the hemoglobin level of SS patients who are in the majority.

Anemia is the most frequent sign of iron deficiency. However, many pathological situations are accompanied by iron deficiency, sometimes without anemia [18]. For example, iron deficiency has been reported in many forms of cancer (43%), chronic inflammatory bowel disease (45%), chronic kidney disease (24–85%), chronic heart failure (43–100%), and many other chronic inflammatory

conditions [18, 19]. None of these pathologies were present in the patients included in our study.

The interpretation of ferritin level depends on whether the patient has inflammation or not [15, 17, 19]. For this reason, we have associated the protidogram with our work. We found biological signs of inflammation in 66 patients (56.41%), whereas Tshilolo et al. reported a prevalence of 49% (22 out of 45 SS sickle cell patients) in Congo [13]. Biologically, iron deficiency is characterized by a decrease in ferritin level, mean corpuscular volume, mean corpuscular hemoglobin concentration, and an increase in transferrin [13]. Ferritin level is sufficient for diagnose iron deficiency [15], hence our choice to use it only, to study iron metabolism in our patients.

Four patients had ferritin levels below 15 ng/mL. In 7 patients, it was below 30 ng/mL, associated with an inflammatory context. The prevalence of iron deficiency was 9.40%. It falls within the prevalence range described for the general population, which ranges from 5% to 18% [20]. The 4 patients with ferritin levels below 15 ng/mL were placed on oral iron supplements with monthly monitoring of ferritin levels. The prevalence of iron deficiency found in our patients is higher than the 2.5% prevalence obtained in 2013 by Traoré et al. who, as in our work, relied solely on ferritin level to diagnose iron deficiency but at a threshold of 20 ng/mL [12]. In contrast, Tshilolo et al. in 2016 found a prevalence of 11% [13]. The difference with Tshilolo's work is the criterion for defining iron deficiency; they equated microcytic hypochromic anemia in sickle cell disease with iron deficiency.

There were more cases of high ferritin levels (49.57%) than iron deficiency (9.40%) in sickle-cell patients monitored at the CNRSD in Lomé. So sickle cell patients should be advised to avoid self-medication with iron-containing tablets. High ferritin level may be of metabolic origin, due to a decrease in hepcidin levels responsible for intestinal hyperabsorption of iron. It may be of non-metabolic origin, due to iterative transfusions in sickle cell patients or excess iron intake. In the case of our sickle-cell patients, who continuously suffer from hemolysis and tend to self-medicate, the cause is more likely to be non-metabolic overload.

In our work, ferritin level is related to age, type of anemia, and patient phenotype, contrary to the findings of Raouf et al. in Tunisia [21].

About sickle cell patients, ferritin level status can be influenced by iterative red blood cells (RBC) transfusions, intestinal parasitosis and dietary habits. Of the 58 patients whose ferritin's level was greater than 150 ng/mL, 4 adults had received more 3 adult red blood cell unit (ARBC) transfusions. This could explain their result, given that iterative RBC transfusions are a source of iron overload. In fact, each gram of hemoglobin contains around 3.4 mg of iron, and an ARBC unit must contain a minimum of 40 g of hemoglobin. In other situations, high ferritin levels may be due either to self-medication with iron-containing drugs or to dyserythropoiesis characterized by a defect in iron utilization.

CONCLUSION

Iron deficiency is the most common nutritional problem worldwide, particularly in low-resource countries. In the general population, it is more common than high ferritin level. In sickle cell patients monitored at the CNRSD in Lomé, it is the opposite. Cases of high ferritin level were most frequent. Iron deficiency is relatively rare in sickle-cell disease but should be considered in the event of a progressive drop in the patient's hemoglobin level despite regular folic acid intake. Ideally, all sickle-cell patients should be screened for martial deficiency as part of the initial paraclinical work-up and periodic medical check-up. Sickle-cell patients should be made aware of the urgent need to stop self-medicating with iron-containing drugs or food supplements.

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Author Contributions

Magnang Hèzouwè – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Mawussi Koffi – Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Womey Kodzovi Mawulé Corcellar – Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Kuéviakoé Messanh Délagnon Irénée – Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Fétéké Lochina – Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

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Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.