Scientific Research Publishing

Open Journal of Pediatrics, 2023, 13, 394-407
https://www.scirp.org/journal/ojped
ISSN Online: 2160-8776
ISSN Print: 2160-8741

Iron Metabolism Abnormalities in Children with Homozygous Sickle Cell Disease in Brazzaville

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How to cite this paper: Ollandzobo Ikobo, L.C., Ibovi Gataud, H.M., Missambou Mandilou, S.V., Galiba Atipo-Tsiba, O.F., Iwandza, R. and Mabiala Babela, J.R. (2023) Iron Metabolism Abnormalities in Children with Homozygous Sickle Cell Disease in Brazzaville. *Open Journal of Pediatrics*, **13**, 394-407.
https://doi.org/10.4236/ojped.2023.133044

Received: January 27, 2023
Accepted: May 12, 2023
Published: May 15, 2023

Abstract

Introduction: Sickle cell disease is the most common genetic disease in the world, particularly in sub-Saharan Africa. It is a protean condition with multiple complications including disturbed iron metabolism. **Objectives**: To determine the prevalence of iron metabolism abnormalities in children with homozygous sickle cell disease, to describe the epidemiological, clinical and paraclinical characteristics of children with these abnormalities and to identify associated factors. **Patients and Methods**: This was a cross-sectional analytical study conducted over 9 months in the mother-child consultation unit of the Brazzaville University Hospital, the National Reference Centre for Sickle Cell Disease and the paediatric department of the Blanche Gomes mother-child hospital. It concerned children aged between 3 months and 15 years followed up for homozygous sickle cell disease. The study was based on a haemogram, iron metabolism test, LDH, transaminases and CRP. **Results**: The overall prevalence of iron metabolism abnomalities was 40.7%. Of the 145 children included, 35.9% had iron overload and 4.8% iron deficiency. Iron overload was associated with infections, undernutrition, iron supplementation and number of blood transfusions. Iron deficiency was not significantly associated with any factor but recurrent infections were relatively more frequent. **Conclusion:** Abnormalities of iron metabolism in sickle cell patients are relatively frequent, which justifies monitoring during follow-up for early detection and better management.

Keywords

Anomalies, Metabolism, Iron, Child, Homozygous Sickle Cell Disease,

Brazzaville

1. Introduction

Sickle cell disease is a major public health problem because of its high prevalence in Africa, but also because of the high morbidity and mortality, mainly in the homozygous state [1]. It is a protean condition with multiple complications, including iron metabolism abnomalities (IMA). Indeed, the chronic hemolysis that occurs in homozygous sickle cell disease is responsible for the release of iron into the bloodstream, but also for deglobulation crises requiring blood transfusion. All this explains the tendency of iron overload in children living with homozygous sickle cell disease (CLHSCD). According to studies carried out in several African countries, the authors report varying prevalences of iron overload ranging from 22.7% to 51.6%. On the other hand, cases of iron deficiency in CLHSCD have been reported in the literature [2]-[8]. Thus, the CLHSCD in a tropical region is at the crossroads of two situations; on the one hand, he or she is exposed to the risk of iron overload (IO) linked to the state of chronic haemolysis and long-term transfusion therapy; and on the other hand, he or she is in an environment with a high risk of iron deficiency (ID) whose associated factors are among others: intestinal parasitosis and undernutrition [9] [10] [11]. In the Congo, this issue has been little addressed. In order to improve the management of CLHSCD in Congo. This work aims to determine the prevalence of IMA in CLHSCD in Brazzaville, to describe the epidemiological, clinical and paraclinical characteristics, and to identify the factors associated with the occurrence of IMA in CLHSCD in Brazzaville.

2. Patients and Methods

This is a descriptive and analytical cross-sectional study, conducted from 1er March to 30 November 2020 (*i.e.* 9 months) in the childcare centres of CLHSCD, in particular the national reference centre for sickle cell disease (NRCSCD), the mother and child consultation unit of the Brazzaville university hospital (BUH) and the paediatrics department of the Blanche Gomes specialised mother and child hospital (BGSMCH). The general population was made up of all CLHSCD received in consultation in the selected health care centers. The study population was represented by all CLHSCD seen in consultation for routine follow-up during the study period. We included children aged 3 months to 15 years with a confirmed diagnosis of homozygous sickle cell disease, seen in the inter-critical period and far from any blood transfusion. After Informed parental consent was a prerequisite for participation in the study. Children with an unconfirmed diagnosis of sickle cell disease, those without parental consent, and those whose last transfusion was less than three months old were excluded.

Out of an active group of 188 CLHSCD seen during the study period for rou-

tine follow up, 172 were selected (participation rate of 91.5%). Of these, 145 met the inclusion criteria (a response rate of 84.3%). Data were collected by the same investigator using a pre-established survey form. The sources of data were the NRCSCD follow-up shits and the children's health booklet. Prior to data collection, the study received an approval from the National Health Sciences Ethics and Research Committee (N˚321/MRSIT/IRSSA/CERSSA). For each child, socio-demographic variables (gender, age and level of education of the child, level of education of parents and socio-economic status of the family), disease related complications status, number of blood transfusions since birth, quality of follow-up, and folic acid intake were specified. On clinical examination, the following data were obtained: weight, height, body mass index, and skin tissue condition, the existence of hepatomegaly and/or splenomegaly. Biological variables included blood count and reticulocytes count, C-reactive protein (CRP), lactate dehydrogenase (LDH), liver function tests especially the Alanine transaminase (ALT) and Aspartate transaminase (AST), ferritinemia, serum iron (SI), transferrin (TSF), blood glucose, soluble transferrin receptors (STRs), total transferrin iron binding capacity (TTIB) obtained using the following formula TTIB (µmol/l) = TSF(g/l) × 25 and iron saturation coefficient (ISC); ICS = SI/ TTIB × 100 [5]. The inter-critical phase was defined as period of time during which the CLHSCD had no disease related acute complications for at least one month. Anemia was defined by a haemoglobin level < 11 g/dl, microcytosis by a MCV < 80 fl and macrocytosis when it was >100 fl, and hypochromia by a MCH < 27 pg. The normal reticulocyte count was between 100,000 - 150,000 elements/mm^3. Iron deficiency was defined when ferritinaemia < 20 µg/l, or a normal ferritinaemia simultaneously associated with microcytosis, hypochromia, a lowered iron saturation coefficient < 16% and an increased STRs > 1.76 mg/l [3] [12] [13]. Iron overload was defined by a ferritinemia > 400 µg/l. Elevation of CRP ≥ 10 mg/l reflected the extent of inflammation (normal < 10 mg/l), that of LDH > 300 IU/l the part of haemolysis (normal between 120 - 300 IU/l) and that of ALT and AST a hepatic cytolysis. Follow-up was considered regular when the patient was seen at least three times per year. Nutritional status was assessed according to the World Health Organization (WHO) child growth standards [14]. The assessment of the socioeconomic status of the family was based on the Gayral-Taminh classification [15]. Data were entered and analysed using R and Microsoft Excel 2016 softwares. Quantitative variables were expressed as mean ± standard deviation. Categorical variables were presented as numbers or proportions. Perceived statistical differences were assessed by Pearson's Chi-square test. The comparison between children with and without iron metabolism abnormalities was used to identify factors associated with iron metabolism abnormalities. For this purpose, the calculation of odds ratios (OR) and their 95% confidence intervals was required; in order to identify confounding factors, a multivariate study using the Logits method was performed. In all cases, the significance level was set at 0.05.

3. Results

Of a total of 145 CLHSCD selected, 59 children had IMA, for an overall prevalence of 40.7%; 52 children had iron overload (35.9%) and 7 children had iron deficiency (4.8%). The socio-demographic characteristics (gender, age, level of education of the child, level of education of parents, socioeconomic status of the family) and iron metabolism variables (ferritinemia, serum iron, transferin, STRs, TTIB and ICS) of these children are shown in Table 1 and Table 2 respectively. Concerning the iron overload, the male to female ratio was 1:1, the mean age of the children was 7 years with an interquartile range of 4 to 10 years. The sickle cell disease related complications were recorded in 22 cases (42.3%), the main one being infections. The disease related complications found are recorded in Table 3. The clinical features were undernutrition (n = 21), hepatomegaly (n = 3) and splenomegaly (n = 5). Iron supplementation was noted in 22 children and blood transfusion in 43 children. The haemogram showed a mean haemoglobin level of 7.19 ± 0.8 g/dl, a mean MCV of 80 ± 8 fl, a mean MCH of 27.6 ± 3.5 pg and a mean reticulocyte count of 212,180 ± 129,354/mm^3. Mean ferritinemia was 673 ± 330 µg/l; 39 children (32%) had ferritinemia between 400 - 1000 ug/l and 5 children had ferritinemia above 1000 ug/l. the ISC was greater than 40% in 7 cases. Liver enzymes (ALT ans AST) were normal in all children (ALT = 9 ± 7 IU/l, AST = 28 ± 10 IU/l). The number of blood transfusions influenced the occurrence of iron overload. The distribution of children according to the number of blood transfusions and the level of ferritinemia is shown in Figure 1. Recurrent infections and blood transfusion between 4 and 6 were the most prevalent factors associated with iron overload as represented in Table 4. As for iron deficiency, the mean age of the children was 6 years with an interquartile

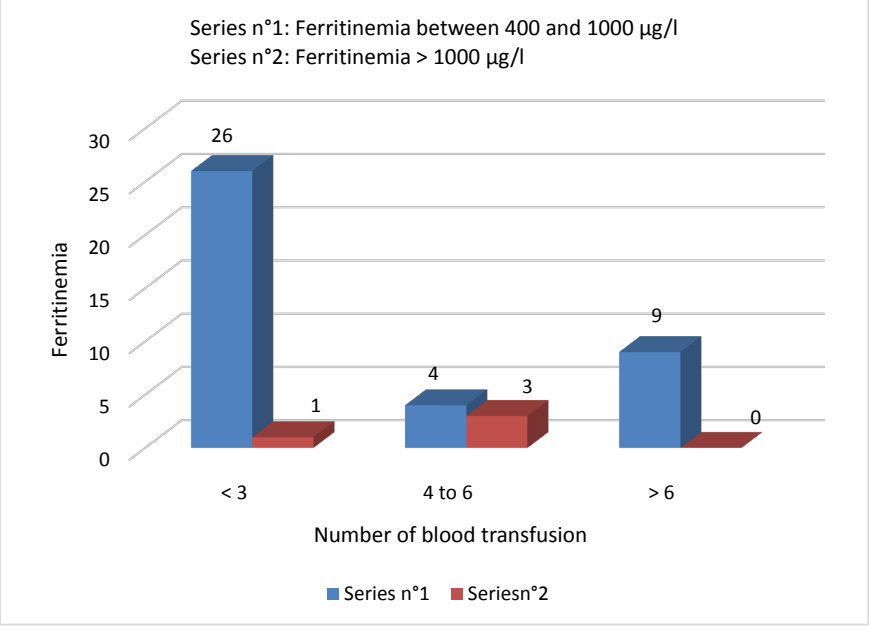

Figure 1. Distribution of children by number of blood transfusions and ferritin levels.

Table 1. Socio-demographic characteristics of children with IMA and their parents.

	Iron deficiency		Iron overload	
	n	%	n	%
Gender				
M	3	42.9	26	50
F	4	57.1	26	50
Age (years)				
<5	4	57.1	27	51.9
5 - 10	2	28.6	10	19.2
>10	1	14.3	15	28.8
Level of education of the child				
≤pre-school	2	28.6	12	23.1
Primary	4	57.1	39	75
Secondary	1	14.3	1	1.92
Level of education of parents				
≤Primary	0	0	1	1.92
Secondary	4	57.1	26	50
Superior	3	42.9	25	48.1
Socio-economic level of the family				
Bottom	1	14.3	9	17.3
Medium	5	71.4	33	63.5
High	1	14.3	10	19.2

Table 2. Distribution of children according to iron metabolism variables.

	Iron deficiency		Iron overload	
	N	**%**	**n**	**%**
Ferritinemia (µg/l)				
20 - 400	7	100.00	0	0.00
400 - 1000	0	0.00	47	90.4
>1000	0	0.00	5	9.6
Serum iron (mg/l)				
<11	6	85.7	16	30.8
10 - 23	1	14.3	31	59.6
>23	0	0.00	5	9.62
Transferrin (g/l)				
<2	0	0.00	15	28.8
2 - 4	6	85.7	37	71.2
>4	1	14.3	0	0.00

Continued

Soluble receptors (mg/l)				
0.76 - 1.76	0	0.00	0	0.00
>1.76	7	100	52	100
Total iron binding capacity (µmol/l)				
<55	1	14.3	27	51.9
55 - 100	5	71.4	25	48.1
>100	1	14.3	0	0.00
Saturation coefficient (%)				
<20	7	100	16	30.8
20 - 40	0	0.00	29	55.8
>40	0	0.00	7	13.5

Table 3. Complications of sickle cell disease in children with iron overload.

	N	%
Stroke	1	1.92
Acute chest syndrome	1	1.92
Recurrent infection	19	36.5
Heart disease	2	3.85
Chronic osteomyelitis	3	3.85
Vesicular lithiasis	1	1.92

Table 4. Factors associated with iron overload.

	n (%)	GOLD	IC	p-value
Recurrent infections	19 (36.5%)	3.23	1.43 - 7.32	0.005
Undernutrition	21 (40.4%)	2.39	1.13 - 5.07	0.025
Iron supplementation	22(4.23%)	2.59	1.22 - 5.47	0.014
Number of blood transfusions between 4 - 6	7 (85%)	19.5	7.61 - 2.37	0.022

range of 4 to 8 years. Four (04) were girls and three (03) were boys. The parents had a secondary level of education in 4 cases, in 5 cases the socio-economic status of the family was mean. Disease related complications such as recurrent infections were found in 3 children. The mean haemoglobin level was 7.6 g/dl ± 0.77, MCV 66 ± 6 fl, MCH 21.8 ± 2.5 pg and reticulocyte count 185,657 ± 90,340/mm^3. Serum iron was low < 11 mg/l or hyposideremia in 6 cases, ISC was low < 16% and ferritin was normal in all cases, no child was found to have elevated transferrin > 4, STRs was elevated > 1.76 mg/l in all children (100%). For all study variables, none was found to have a significant link with iron deficiency, as in all cases the p-value was >0.05.

4. Discussion

The overall prevalence of IMA was 40.9%. This result could have been higher; indeed, we recognise some limitations to this work including small sample size, failure to assess intrahepatic iron stores and the absence of liver magnetic resonance imaging. The prevalence of iron overload was 35.9%. This result is similar to that observed in Kinshasa (35%) [2]. Higher prevalences than ours have been reported by other authors in Congo (51.6%) [16], and in Tunisia (41.5%) [4]. In contrast, the prevalence reported by Malian authors was lower than ours (22.7%) [17]. The prevalence of iron deficiency was 4.8%, higher than that of Hafsia *et al.* in Tunisia (3.19%) [4] and Traoré *et al.* in Mali, 2.5% [5]. However, Tshilolo *et al.* in Kinshasa and Akinbami *et al.* in Nigeria reported higher prevalences of around 7.7% and 20% respectively [2] [8]. Differences in methodology could be the explanation of these results, particularly the definition of these anomalies which differs from one author to another. On the other hand, CLHSCD are known to develop chronic inflammatory syndrome and recurrent infections which could lead to a non-specific increase in ferritin levels [4]. The diagnosis of iron overload is based on the determination of hepatic iron concentration [18]; whereas the diagnosis of iron deficiency in sickle cell disease is challenging because of the lack of specific laboratory tests.

Iron overload (IO) was the most frequently encountered IMA in our study, the mean age of children was 9.7 years. The majority of children (86.5%) were regularly followed up. Clinical features, mainly splenomegaly and hepatomegaly were observed in 9.6% and 5.8% of cases respectively. Hafsia *et al.* in Tunisia found splenomegaly and hepatomegaly in 6.5% and 29% of cases [4]. These differences could be explained by the sample size and the fact that biological abnormalities in IO are usually early onset. Chronic liver damage in sickle cell disease is not uncommon. The most encoutered complication was undernutrition (42.9% of cases), with a significant association ($p = 0.025$). This link can be explained by the fact that in its severe presentation, sickle cell disease exposes patients to recurrent infections (36.5%; $p = 0.005$). Cardiac complications (3.8%), although not statistically significant ($p = 0.486$), have been already reported in the same city with a lower proportion by Mpemba Loufoua *et al.* (1.85%) [19] and a very high proportion by Ellenga Mbola *et al. (*48.4%) [20]. These results can be explained by the fact that cardiac morphological investigations (electrocardiogram and/or cardiac echography) were not performed in this study. In term of treatment, iron supplementation was observed in 42.3% and blood transfusion in 86.9% of cases, which is not new in our context [21]. Regarding the biological characteristics, the mean haemoglobin level in these children was 7.1 g/dl. This result is lower than that reported by Hafsia *et al.* and Traoré who found a value of 9 g/dl [4] [5]. Thirty-two percent had a ferritin level between 400 - 1000 µg/l and 3.8% above 1000 µg/l. Lower results (between 15.3% and 18.09%) for ferritinemia between 400 - 1000 µg/l have been reported in Tunisia, Mali and India; whereas for ferritinemia above 1000 µg/l, the same authors report signifi-

cantly higher results than ours (ranging from 7% to 23%) [4] [5] [22]. This variability can be explained by methodological differences, but also by the high frequency of primary haemochromatosis in Tunisia in particular. The saturation coefficient above 40% was noted in 13.5% of CLHSCD. This is much higher than that observed by Mohanty *et al.* in India (10.8%). Liver enzymes were normal in all cases, as in the work of Mohanty *et al. [22]*. Iron supplementation was associated ($p = 0.0013$) with iron overload, as noted by Brissot *et al. [23]*. It is the consequence of parental self-medication or prolonged medical prescription without biological monitoring. The increase in ferritinemia was positively correlated with the number of blood transfusions (OR = 19.5 and $p = 0.022$), as already described in the literature [2] [22] [24].

Iron deficiency (ID) was found in low proportions in CLHSCD in our series (4.8%). This observation had already been confirmed by Mohanty *et al.*, 10.8% [22]. The mean age was 7.3 years, higher than that of Akodu *et al.* in Nigeria (2.6 years) [13]. Indeed, ID is the most common nutritional deficiency in the world and young age is a determining factor. More than half of the parents (57.1%) had a secondary education level and 71.4% of them had a middle socio-economic status. These factors did not influence the occurrence of ID ($p = 0.738$). On clinical examination, undernutrition was observed in 42% of cases and was related to the severity of sickle cell disease, as already reported by Mabiala Babela *et al.* in Congolese children with sickle cell disease [25]. Anorexia was the only symptom less reported. Recurrent infections were the only complication recorded in these children. This observation has already been made by other authors [22] [26]. Clinical and laboratory findings often differ in ID. The most classic diagnostic presentation is when investigating a child for hypochromic microcytic anaemia is [27]. The mean haemoglobin level was 7.6 g/dl. In our study, anaemia was associated with microcytosis, hypochromia and bone marrow regeneration as reported by Traoré [5]. Hyposideraemia was observed in 85.7% of cases, which is higher than that reported by Lopez-Sall *et al.* (17.5%) [3]. The iron saturation coefficient was low in all children as also noted by Lopez-Sall *et al. [3]*. Ferritin levels were normal in all children, in contrast to the hyposideremia often reported in ID. STRs were high in all children, as observed by Lopez-Sall *et al.* (97.5%) [3]. Sickle cell disease, like all chronic haemolytic anaemias, is associated with a 3 to 6 fold increase in STRs as compared to normal values [3] [28]. These different disturbances are thought to be related to the pro-inflammatory state caused by sickle cell disease [3] [29]. Consequently, all these elements illustrate the limits of the usual laboratory investigations, especially ferritinemia, transferrin and serum iron, for the diagnosis of ID in sickle cell disease patients. Therefore, the diagnosis of ID requires the integration of several parameters.

5. Conclusion

IMAs in CLHSCD are common, especially IO compared to ID. Factors associated with the occurrence of IO were recurrent infections, undernutrition, iron sup-

plementation and number of blood transfusions. In contrast, ID was non-significantly associated with recurrent infections. Systematic screening for IMA and investigation of the underlying associated factors during the follow-up of these children is necessary to ensure the quality management and thus to reduce the morbidity and mortality associated with this condition.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix

Survey form

Tittle: Iron metabolism abnormalities in children with homozygous sickle cell disease in Brazzaville

Date: …… Place ……

Form n° ….

1) Patient identity

- Name …….
- First name ……
- Date of birth: ……. /……./…… age: …….. (months/years)
- Level of education: none: …… primary: …… Secondary: …… college: ……
- Mailing address ……
- Phone number ……..

2) Past medical history

- Disease history
- Age at diagnosis
- Electrophoretic profile: Hb S: …… HbA2: ……. HbA
- Basal hemoglobin:
- Acute complications:
  - Number of vasoocclusive crises per year
  - Number of severe anemias requiring blood transfusion since birth
  - Blood transfusion: yes: …… No: ……

If yes, how many: …….

Date of the last blood transfusion: …….

  - Has he/she experienced stroke: yes….. no…..

If yes, how many times since birth ……

  - Acute chest syndrome: yes…… no……..

If yes, how many times since birth

  - Priapism: yes ……. No ……..

If yes, how many times since birth

- Chronic complications:
  - Heart failure
  - Chronic osteomyelitis
  - Chronic osteonecrosis of femoral head
  - Leg ulcer
  - Vesicular lithiasis
- Recurrent infections
- Menarche (if girl): yes …… no ……..

If yes, at what age

- Admissions
  - How many times since birth
  - Date of the last
  - Cause

- Quality of the follow up: regular …….. irregular ……..
- Medication:
  - Folic Acid: yes … no ……
  - Penicillin: yes …… no ……..
  - Hydroxyurea: yes …… no ……..
- Indications …….
- Starting date …….
- Immunization:
  - EPI calender up to date: yes …….. no …….
  - Specific vaccinations received: yes …… no ……..
- Did he/she already recieve iron supplementation since birth: yes …… no ……
- If yes, at what age:……, reason ……, treatment duration ……..

- Other:

- Parents:
  - Father:
    - Age
    - Level of education: none: …primary ……. Secondary ….. college: ……
    - Profession
    - Socioeconomic status: low ….. middle ……. High …..
    - Number of children in the family ……..
  - Mother:
    - Age
    - Level of education: none: …primary ……. Secondary ….. college: ……
    - Profession
    - Socioeconomic status: low ….. middle ……. High …..
    - Number of children in the family ……..
  - Guardian/tutor:
    - Age
    - Level of education: none: …primary ……. Secondary ….. college: ……
    - Profession
    - Socioeconomic status: low ….. middle ……. High …..
    - Number of children in the family ……..
  - Family structure: monoparental: …… biparental: ……..

3) Clinical axamination:

- Anthropometrics:
  - Weight
  - Height
  - Weight for height (for children < 5 years old): ……
  - BMI (for children ≥ 5 years old)
- Jaundice: yes ……. No ……..

If yes: mild …… moderate …… severe

- Splenomegaly: yes …… no ……
- Symptoms of iron deficiency:

- Dry ski: ……..
- Anorexia: …….
- Dry, brittle hair: yes ……. No …….
- Brittle nails: yes …….. no ……
- Chapped skin: yes ……. No …….
- Stomatitis: yes …… no …….

- Symptoms of iron overload:

- Hepatomegaly: yes …… no …….
- Melanodermia: yes …… no …….

4) Laboratory investigations

- Hemogram
  - WBC: …….
    - Neut: ….
    - Lymph …….
    - Eo ……..
    - Baso ……
    - Mono …….
  - HGB ……
    - MCV ……..
    - MCH ……
  - PLT ……..
- Reticulocytes count ……..
- CRP ……
- Ferritinemia …….
- Serum iron ……
- Transferrin ……..
- Total Iron Binding Capacity of Transferrin ……
- soluble transferrin receptors ……..
- Iron saturation coefficient
- LDH …….