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Iron status of sickle cell children in Libreville, Gabon: prevalences and associated factors

Abstract

Background: Iron is essential for a child's growth. In the Gabonese general pediatric population, iron deficiency is the most widespread nutrient deficiency. Quid of the sickle cell children in Libreville, Gabon?

Methods: We conducted a cross-sectional study including sickle cell children aged from 6 months to 15 years, with haemoglobin SS confirmed. Subjects included were examined in steady-state. Data collected were about the socioeconomic background of the families, medical history of the children. To determine iron status, we used: CRP, Ferritin, serum iron, Transferrin, total blood count cell and erythrocytic parameters.

Results: We included 247 children; 128 boys (51.8%) and 119 girls (48.2%). The median age of the children was 8 years [1 year - 15 years]. Following definition criteria we found: 23.9% (95% CI [18.6% - 29.2%]) of iron deficiency, 67.6% (95% CI [62.2% - 73.8%]) of normal iron status, and 8.1% (95% CI [4.7% - 11.5%]) of iron overload. Iron deficiency was associated with a child's rank >2, OR=2.1 (95%IC [1.2-6], *p<0.001*). Iron overload was associated with age >11 years OR=2.5 (95%IC [1.7-9], *p<0.001*); mothers' low educational level OR=3.6 (945% IC [1.4-9], *p=0.03*); transfusion OR=10,5 (95%IC [1,9 – 53], *p =.0.025*); a last transfusion between 4 and 6 months OR=9.1 (95%IC [3.1-21], *p<0.001*).

Conclusion: The majority of sickle cell children in our context has a normal iron status. Iron deficiency and iron overload should be monitor and treated according to associated factors, and greater studies are required to determine algorithms to assess and treat and iron imbalance.

Keywords: iron status, iron deficiency, iron overload, sickle cell disease, children, Libreville

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Introduction

Sickle cell disease (SCD) is the most common monogenetic disorder globally, affecting approximately 300,000 births annually. Its prevalence is higher in sub-Saharan Africa, India and the Mediterranean region.[1] In Gabon, the prevalence is estimated at 28% for sickle cell trait carriers and 1.8% for SS homozygotes.[2] The high infant mortality linked to this condition worldwide and in our country makes it a public health problem. Iron is a dietary trace element essential for the body's survival because of its significant role in synthesising haemoglobin, ensuring tissue oxygenation. In certain physiological or pathological situations, such as increased needs, nutritional disorders, erythropoiesis dysfunction, chronic inflammatory diseases, transfusions or drug supplements, the distribution of iron in the body may be disturbed, leading to iron deficiency or overload.[3] Iron deficiency is the most common disease worldwide, particularly in developing countries. Iron deficiency is defined as any condition in which there is insufficient iron to maintain normal physiological functions of all tissues. Martial deficiency is the leading cause of anaemia in children, affecting 61% of Libreville children aged 6 months to 5 years.[4,5]

Several studies have assessed the iron status or iron requirements of children with SCD, with varying results. While some authors found no evidence of iron deficiency or overload, others concluded that iron content was relatively higher in the reticuloendothelial system (RES) of children with SCD than in their controls.[6,7]

In this context, what is the situation of sickle cell children in Gabon? Like any child, the sickle cell child, during its growth period, has an increased need for iron on the one hand. Moreover, on the other hand, he would be exposed to the same socioeconomic risks associated with the nutritional disorders of his context, thus risk of iron deficiency.[4,5] SCD is a condition marked by frequent hemolysis related to the fragility of haemoglobin S, responsible for the release of iron into the plasma and the need for blood transfusions. These two facts justify a potential iron overload.[1,3]

We conducted a study to assess the iron status of sickle cell children aged 6 months to 15 years and determine the factors associated with each status found. We hypothesised that in the absence of a massive external transfusion, sickle cell children in Libreville are exposed to martial deficiency, as are non-sickle cell subjects.

Methodology

Type and scope of the study

We conducted a cross-sectional study for 2 years, from 1 January 2016 to 31 December 2018. It took place in Libreville and involved SS sickle cell children, aged 6 months to 15 years, seen in the inter-critical phase, i.e., more than 4 months away from any significant sickle cell crisis or transfusion. Children were recruited from public hospital registries, private clinics specialising in the management of SCD, and sickle cell associations.

Conduct of the study

Calculation of the number of subjects needed

We calculated the sample size using Statcalc from Epi info7.2 software. We estimated the size of the target population: sickle cell patients aged 6 months to 15 years. We used the prevalence of the disease in the general population at 1.8% and the estimated population of children in this age group in Gabon (https://www.populationpyramid.net/fr/gabon/2017), 736,000 children.[2] The target population was 13248 sickle cell children aged 6 months to 15 years. The acceptable margin of error was 5%. We took as reference the prevalence of martial deficiency among sickle cell patients in Yemen 13.3%. The attenuation factor of our survey model was 1.3, the confidence interval 95%, the number of clusters was 4. The result was a total number of subjects needed of 228, i.e. 57 per cluster.

Sampling

The study population consisted of children aged 6 months to 15 years, identified from lists of sickle cell patients from two hospitals, two private clinics and two sickle cell associations. We randomly selected subjects, and parents were contacted by telephone. Inclusion was based on the voluntary participation of both parents and the child. The biological work-up was part of their usual check-up, to which the team added ferritin, CRP, transferrin and serum iron measurements.

We included any child aged 6 months to 15 years with a confirmatory haemoglobin SS (HbSS) electrophoresis test seen more than 4 months after a transfusion or a significant clinical event. Parents were asked to sign the informed consent. We did not include parental refusals, children outside the age range, children without a test confirming their HbSS status, infants less than 1-year-old born prematurely, children who received a transfusion within 4 months.

The data for the study were collected during a semi-structured interview on a data collection form. These data concerned:

i. Age, gender and sibling rank ;

ii. the age, education and occupation of each parent;

iii. The child's medical history included the number of transfusions, dates of transfusions, number of packed red blood cells.

iv. Assessment of iron status and inflammatory state. Haemoglobin level and erythrocyte parameters were assayed on Sysmex XT-2000i ©. Serum ferritin in micrograms per litre (µg/L) was determined on Mini Vidas©. Serum iron in micromoles per litre (µmol/L) and Transferrin (g/L) on ABX Pentra©, the saturation coefficient of Transferrin was calculated from these two assays. C-reactive protein (CRP) in milligrams per litre (mg/L) was determined on Cobas C111©.

Case definition

We have considered as :

i. iron deficient, all children with at least 2 of the following criteria: Mean corpuscular volume (MCV) less than 75%, mean corpuscular haemoglobin content (MCH) less than 24 pg per Red cell (RC), ferritinemia less than 24µg/L, transferrin saturation coefficient less than 16%, without any inflammatory state: CRP less than 6 mg/L.

ii. iron overloaded are all subjects with at least one of the following criteria: a serum ferritin level greater than 300ng/L, a Transferrin saturation coefficient greater than 45%, if the CRP is less than 6 mg/L

iii. normal status a subject with the following criteria: a CMV between 85-95 fL, MCH between 24-33 pg/RC, a serum ferritin level between 25-500 ng/L, a total transferrin binding capacity between 50-95 micromol per litre.

Ethical considerations

Gabonese General Directorate of Health, the university hospitals and health centres participating in the study approved before the field deployment. Following the instructions of these directors, we did not collect information on the religion or ethnicity of the children's parents, and we obtained parents agreement by signing an informed consent form.

Statistical analysis

We collected data on Epi Info 7.2.2. We performed a descriptive analysis to determine the sample's characteristics and estimate the prevalence of the different iron statuses with a 95% confidence interval. Quantitative data were expressed as median and quartiles, including 1st quartile (Q1) and 3rd quartile (Q3) for children age, and parental age was expressed as the mean. The categorical data were expressed as frequencies; to compare them, we used the Chi-square test of independence, and when the number of children did not allow it, we used Fisher's correction. The Wilcoxon-Mann-Whitney test was used to compare the medians of the different groups.

We created logistic regression analyses (adjusted odd ratio - aOR) to measure the relationship between parent and child parameters and immunisation schedule completeness or timeliness. The dependent variables in the univariate model were: age and sex of the child, sibling rank, age of both parents, income-earning activity of both parents, transfusion procedure, number of bags. The variables were selected based on statistical significance in univariate models and relevance based on the literature. The threshold of statistical significance was set at $p < 0.05$ for a two-tailed test. The analysis was performed using Epi Info 7.2.2 from the CDC, the verification of our results on MS Excel software, the multivariate analysis was performed using the online statistical analysis software Pvalue (https://www.pvalue.io/fr/).

Results

Characteristics of the children included

We included 247 children; 128 boys or 51.8% and 119 girls or 48.2%. The median age of the children was 8 years[1 year - 15 years], the median age of the girls was 9 years, the median age of the boys was 8 years (p =NS). The distribution of the sample by age groups showed: [6 months - 5 years] 31.2% (n=77), [6 to 10 years] 34.4% (n=85),[11 to 15 years] 34.4% (n=85).

The median number of children in the home was 3, with extremes[1 – 13], Q1= 2, Q3=5. The median sibling rank was 2, with extremes[1 – 13], Q1 =1 and Q3=3. Children had received at least one transfusion in 74.5% (n=184) of cases (95% CI [69%-80%]). The median number of transfusions performed in each child was 3, with a median time to last transfusion of 11 months (Table 1). According to the date of last transfusion, 18.5% (n=34) had been transfused between "4 to 6 months" before inclusion, 40.2% (n=74) "7 to 12 months" before inclusion, and 41.3% (n=76) "more than 12 months" before inclusion.

According to their socioeconomic characteristics, the distribution of mothers showed that 47% of them had a secondary school education, and 55.9% were gainfully employed (Table 2).

Martial status of sickle cell children in the sample

According to the selected criteria we found :

Citation: Minto'o S, Kuissi Kamgaing E, Mimbila-Mayi M et al. Iron status of sickle cell children in Libreville, Gabon: prevalences and associated factors. *HematolTransfus Int J.* 2022;10(1):18–22. DOI: 10.15406/htij.2022.10.00275

23.9% iron deficient (59/247) 95% CI [18.6% - 29.2%]

67.6% normal iron status (168/247) 95% CI [62.2% - 73.8%]

8.1% iron overload (20/247) 95% CI [4.7% - 11.5%].

Calculating the frequencies of the different iron statuses according to gender showed:

Among iron deficient people: 45.8% of girls (n=27/59) and 54.2% of boys (n=32/59)

In normal status subjects: 50.6% girls (n=85/168) and 49.4% (n=83/168) boys.

Among the iron overloaded subjects: 35% (n=7/20) girls and 65% (n=13/20) boys. (*p=NS*).

Table 1 Transfusion characteristics of children in the sample

	Min	Q1	Median	Q3	Max
Blood transfusions	1	2	3	5	12
Red cell packs received	1	2	3	5	15
Last transfusion (months)	4	6	11	36	144

Table 2 Characteristics of parents in the sample

	n	Frequency
Mother's level of education		
No	23	9,3%
Primary	19	7,7%
Secondary	116	47%
University	89	36%
Mother's income-generating activity		
Working mother	138	55,9%
Non-working mother	109	44 ,1%
Economic category of the head of household		
Independent	36	14,6%
Frame	69	27,9%
Non-executive public sector	57	23,1%
Non-executive private sector	33	13,4%
Unemployed	52	21,1%

The prevalence of each martial status according to age groups showed a martial deficiency present in each group but more critical in the 0 to 5 years old (28.6%). Iron overload was present in all age groups but was most prevalent in the oldest age group with 15.3% (Figure 1).

The median age of overweight children was statistically higher than that of normal children or deficient children (Table 3). According to the transfusion, overweight children were transfused in 100% of cases (n=20), normal children in 83.2% (n=153), and deficient children in 19.3% of cases (n=11).

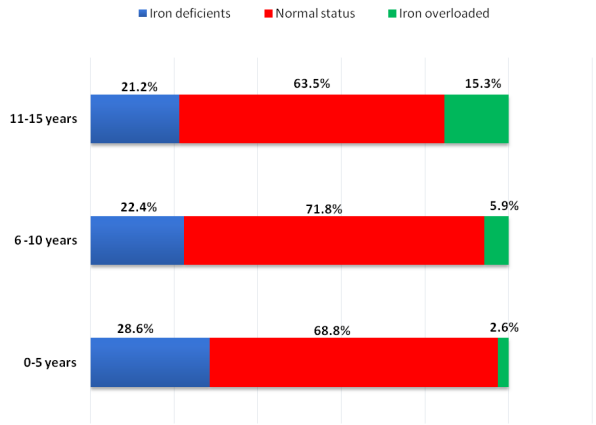

Figure 1 Prevalence of iron status in each age group.

Table 3 Characteristics of children by iron status of children

	Normals	Deficient	Overloaded	*p*
Median (years)	8	7	9	0,001
Median rank	4	3	5	0,036
Median children in the home	2	2	3	ns

Calculation of the odds ratio between the factors analysed and each iron status of the children in our sample showed that the act of transfusion was statistically associated with overload (OR=10.1) and normal status (OR=15.8). Iron deficiency was associated with a child with a higher than median sibling rank (OR=2.1) (Table 4).

Discussion

The iron status of the sickle cell child is not a primary concern in the daily management of SCD. This condition is dominated by acute attacks and chronic complications that are the hallmark of the condition. The recommendations concerning the management of iron overload related to multiple transfusions have recently appeared.[8] This study determined the prevalence of different iron statuses in sickle cell children and identified the factors associated with these different statuses.

Citation: Minto'o S, Kuissi Kamgaing E, Mimbila-Mayi M et al. Iron status of sickle cell children in Libreville, Gabon: prevalences and associated factors. *HematolTransfus Int J.* 2022;10(1):18–22. DOI: 10.15406/htij.2022.10.00275

We conducted a cross-sectional study to meet our objectives. This design reduced the time and resources that would have been required for a cohort study. We did not have funding, as team members' own money funded our study. The cross-sectional study design is adopted in most investigations exploring the iron status of children with SCD.[3,7–9] Although robust and functional, the cohort studies had a small sample of subjects.[10]

The relevance of markers of iron status is paramount in the assessment of iron homeostasis. The choice of markers in this study: haemoglobin level, ferritin, serum iron, Transferrin (and saturation coefficient), CMV and MCH, is based on the literature data in the same context.[4,7,9] The non-use of hepcidin and soluble transferrin receptors (sTfR) in this study is due to its absence of routine determination in our context, to the financial and logistical difficulty of obtaining reagents outside Gabon. This absence does not alter the relevance of the markers and definition criteria used here, as Gomez et al. had already demonstrated a correlation between hepcidin or sTfR levels with CMV or MCH in sickle cell subjects compared to non-sickle cell subjects. The authors state that erythrocyte markers are as reliable as the two protein markers in assessing iron status in sickle cell patients, without the drawback of the influence of chronic inflammation of the sickle cell patient in the production of protein markers.[9] The study by Mandese et al.[10] assessed iron status from conventional erythrocyte count and ferritin.[10]

The martial status of the subjects in our study was dependent on transfusion. All iron-deficient subjects had never received a transfusion, and all iron overloaded subjects had received at least one transfusion. Iron deficiency is not uncommon in our context; it concerned 23.9% of the children participating in the survey; the youngest age group (0 to 5 years) was the most affected, with 28.6%. Other teams have found the existence of iron deficiency in sickle cell patients. Kassim et al. in Yemen found 13% of deficient subjects, with ages varying from 5 to 30 years, and only 1 subject out of 10 had received a transfusion during his life.[11] The authors conclude that iron deficiency should be sought in all non-transfused sickle cell subjects. In Brazil, Rodrigues et al., in a study of sickle cell patients under 2 years of age, found 17.8% (95% CI [11.3% - 24.3%]) to be iron deficient, with a majority of Hb SS subjects compared to Hb SC subjects.[12] A Nigerian study found no iron deficiency in evaluated sickle cell patients. However, this result has a drawback: the authors did not specify the existence or not of transfusion in the medical history of the subjects included.[13] Iron deficiency was significantly associated with a child rank > 2; this factor is also found in the non-sickle cell population of Gabon, where iron deficiency in the 0 to 5 years old population was 61%.[5] Our finding is that iron deficiency is present in SCD but less frequent than in the general population, as described in the study by Akodu et al. with 3 times more risk of iron deficiency in the non-sickle cell population.[14]

Iron overload is present from early childhood with increasing prevalence across age groups. The factors associated with this condition were socioeconomic and medical. Among the socioeconomic factors, the child's rank above the median and the mother's low level of education were also found. We can assume that a low level of education of the mother could lead to difficulties in understanding the child's disease, and thus to insufficient prevention leading to repeated attacks, more frequent transfusions, and thus to iron overload in the end. A previous study on the iron status of children without SCD, in which the low educational level of the mothers was associated with a poor health status of the children, support this hypothesis.[5] We also recall that the lower the schooling level, the lower the mother's income, and therefore less frequent access to health care for her child.[4,5]

Iron overload is related to transfusion, with the main sub-factor being the short time of transfusion: the more recent the transfusion, the greater the risk of overload. The exogenous supply of iron by transfusion and iron from hemolysis may be progressively integrated by the different functions requiring iron in the body. Our survey reports a history of transfusion of more than 10 years. In iron saturation, cerebral, renal and hepatic deposits are observed, provoking damage to these three organs.[15,16] Thus, one could have deposits and thus old lesions if the overload is not managed.

Conclusion

Our study found that most sickle cell subjects had a normal status; iron deficiency is visible at any age in our context; we found iron overload from early childhood, and its prevalence increases with age. Non-transfused sickle cell patients could benefit from iron supplementation. As there is no argument that their dietary iron intake is different from that of other children with whom they live, they are at the same risk of iron deficiency. Transfused subjects should be monitored for iron overload. The results and limitations of this study prompt further investigation into the routine detection of iron status in children with SCD, and the management of iron deficiency or overload in these young patients.

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Conflicts of interest

The author declares no conflicts of interest.

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