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ORIGINAL ARTICLE

Serum Ferritin Levels In 41 Multiple-Transfused Sickle Cell Patients at the Yaoundé Central Hospital, Cameroon, Africa: A Pilot Study

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ABSTRACT

AIM: Serum ferritin is widely used to assess iron load. Transfusion is usually indispensable in management of sickle cell disease. Iron overload is a major factor associated with morbidity in these patients when they benefit from repeated blood transfusions. We assessed serum ferritin levels of multiple transfused sickle cell patients using an Enzyme-Linked Immuno-Sorbent Assay in order to determine the frequency of hypo and hyperferritinemia. C-reactive protein was determining to find an acute inflammatory process.

RESULTS: A total of 41 patients received a minimum of two blood transfusions. Their ages ranged from 15 to 59 years with a mean of 27.2±9.8 years. Females represented 64.3% of patients. Each patient received about 2 to 18 red blood cell transfusions. All patients received transfusion for anaemia management; serum ferritin levels ranged from 31 à 1,255 µg/L, with high levels (>150 µg/L for female and >200 µg/L for male) found in 46.3% of patients. In our study population 34.1% had normal C-reactive protein. There were 17% of patients with elevated serum ferritin levels without an associated inflammatory process. Our study showed weak correlation between ferritin levels and number of blood transfusions in patients with normal CRP (r =0.02), as well as in the whole studied population (r = 0.14).

CONCLUSION: Hyperferritinemia is frequent in sickle cell disease patients having history of transfusion. However, it does not seem to be associated to frequency of blood transfusions in Cameroon.

Key words: Ferritin; Transfusion; Sickle cell disease; Iron overload

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INTRODUCTION

Homozygous sickle cell disease (SCD) is an autosomal recessive genetic disease that results from the substitution of valine for glutamic acid at position 6 of the β-globin gene, leading to production of a defective form of hemoglobin, hemoglobin S (HbS). It is the most frequent genetic disorder in the world. In Cameroon the prevalence of sickle cell trait is about 25% and the disease affects about 2% of the population[1]. This disorder is still an incurable disease and improving the quality of life of those affected remains a major challenge. Blood transfusion is an important element in the management of sickle cell disease. It remains an essential component of care for SCD, but associated complications include iron overload, transfusion reactions, infections, acute lung injury, pain crisis, stroke, immunomodulation, anaphylaxis, and alloimmunization. Transfused red cells will significantly increase oxygen-carrying capacity, blood viscosity, potentially reducing blood flow. However, it increases the risk of iron overload. Then, iron overload is a major factor associated with morbidity in these patients when they benefit from repeated blood transfusions, because the body has no regulatory process

for eliminating excess iron[2]. Serum ferritin is the most accessible marker to explore of iron stores. This study was conducted to assess ferritin levels of multiple-transfused sickle cell in order to determine the frequency of hypo and hyperferritinemia. The relation of serum ferritin to iron load estimated from transfusion history was examined.

METHODS

It was a descriptive and cross-sectional study. Sickle cell patients were targeted for this study. Selection criteria were all patients who ever received more than two blood transfusions. Patients were recruited from Monday to Saturday during two months (January-February 2013) in the hematology and oncology department of the Yaoundé Central Hospital, Cameroon. It was a consecutive sampling. All patients who fulfilled selection criteria were included in the study. The minium sample size of this study was determined based on the prevalence of hypoferritinemia reported by Hafsia & al[2]. The exclusion criteria were: non-consent, the lack of medical records, patients whose last transfusion was less than three months, vaso-occlusive crisis that occurred during or within eight days of blood collection, a fever during sampling (temperature>38°C), undocumented transfusions, bleeding disorders, pregnant women, and documented liver disease. Medical records and a questionnaire were used to investigate transfusion history. To calculate the amount of iron received, 1 mL of red blood cells was estimated to contain 1 mg of iron[3]. Patient weights were recorded. To calculate transfusion iron load, cumulative iron load received was divided by the weight.

4 mL of venous blood was collected in a dry tube. This was to determine serum ferritin by enzyme immunoassay (ELISA Biorex United kingdom ISO 13485), and C-reactive protein (CRP) by latex particle agglutination. These laboratory tests were performed in the hematology laboratory of the University Teaching Hospital of Yaoundé, Cameroon. We considered normal range of serum ferritin between 15-200 µg/L for male and 15-150 µg/L for female.

Each participant signed a consent form at the recruitment. The national Ethical committee provides a clearance for this study as well as the Central Hospital of Yaoundé. Statistical analyzes were performed using Epi Info 6 software, SPSS 12 (Statistical Package for the Social Sciences) and Microsoft Excel 2007. The correlation between ferritin levels and the volume of transfusions received was tested using the Pearson correlation coefficient "r". The statistical significance was set at 5%.

RESULTS

A total of 41 patients were recruited. The age ranged between 15 and 59 years, with an average age of 27.2±9.8 years. Female gender was the most represented (64.3%). Each patient received between 2 and 18 transfusions since their births. The date of the last transfusion was between March 2005 and September 2012. All patients received whole blood transfusion mainly to deal with severe anemia. Hemoglobin levels during the last transfusion ranged between 2.9 and 5.8 g/dL with a mean of 4.4±0.8 g/dL. Sixteen patients had received 1 to 3 sessions of exchange transfusions during pregnancy, stroke, cardiomyopathy and priapism. Only one patient had exchange transfusion twice to prevent stroke. The evaluation of iron administered in transfusions varies between 500 and 4,500 mg/per patient, with an average of 1,774±960 mg, knowing that blood bag contains approximately 250 mg of iron (250 mL red blood cells). The estimating cumulative iron load received was divided by the weight. It appears that patients received doses ranging from 7.2 mg/kg to 76.0 mg/kg, with an average of 31.4±17.6 mg/kg. Serum ferritin levels ranged from 31 to 1,255 µg/L. High serum ferritin levels (>150 µg/L for female and >200 µg/L for male) were found in 19 patients (46.3%). CRP was negative (<6 mg/L) in 14 patients (34.1%). It was found that 7 patients (17%) had high ferritin levels without an associated acute inflammatory process, with values ranged from 242 to 1,240 µg/L. This study shows weak correlation between serum ferritin levels and number of transfusions received in patients with a negative CRP (r =0.02) (Figure 1, table 1).

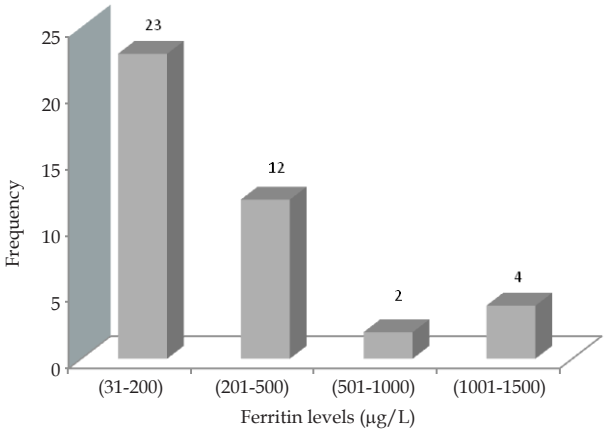

Figure 1 Serum Ferritin levels in 41 sickle cell patients.

Table 1 Number of patients according to number of blood transfusion received.

Number of blood transfusion received	Estimate volume of Red blood cell received (mL)	Number of patients
2	500	4
3	750	2
4	1,000	4
5	1,250	7
6	1,500	5
7	1,750	3
8	2,000	5
9	2,250	1
10	2,500	4
12	3,000	1
13	3,250	1
14	3,500	2
15	3,750	1
18	4,500	1
Total	31,500	41

DISCUSSIONS

Sickle cell disease causes a chronic hemolytic anemia generally well tolerated; blood transfusions are used mainly in case of severe anemia[4]. If the goal is an acute reduction in the proportion of sickled red cells in addition to an increase in oxygen-carrying capacity, exchange transfusion is the therapy of choice. The indications for exchange transfusion include acute stroke, acute chest syndrome with severe hypoxia, acute multi-organ failure, and possibly acute severe priapism. Partial exchange transfusion is indicated for hemoglobin SC patients undergoing major surgery. Transfusion requirements in sickle cell patients have not been established precisely in resources-limited context, although in practice, blood transfusion seems to be frequent. This is due to a lack of traceability and hémovigilance data related to poor documentation and archiving.

The female gender was predominant in our study. This female predominance also found in the study of Hafsia *et al*[2] emphasizes the hypothesis that female sickle cell patients could be more transfused, since in addition to chronic hemolytic anemia, menstrual blood loss and pregnancy increase iron needs. However, these observations were not evident in the current study. Hemoglobin levels were all very low when patients were transfused. Indeed, severe anemia has been reported to be one of the most frequent condition related to blood transfusion during sickle cell anemia crisis[5]. Only sixteen patients had received 1 to 3 sessions of exchange transfusions. This is probably due to the lack of equipment and the fact that exchange transfusion requires large amounts of blood products.

Iron stores are normally saturated after 20 transfusions or 5,000 mL of red blood cells[6], which corresponds to an intake of 5,000 mg of iron. Here, the maximum volume was 4,500 mL of packed RBC, or 4,500 mg of iron brought to the body. It means that in theory, none of the patients had an iron overload, although high ferritin levels were found. The estimate of the iron intake based on the weight gives the maximum value of 76.0 mg/kg. Complications of iron overload appear at doses of 400 to 500 mg/kg[7].

Iron stores in the body are mainly in the form of ferritin. The references values are 15-200 µg/L for men, and 15-150 µg/L in women[8]. Normally ferritin presents a close correlation with iron stores. According to World Health Organization recommendations on the interpretation of serum ferritin during inflammatory processes[8], none of patients had an iron deficiency.

The mechanism is different in inflammation and infection, where the iron is transferred directly from hemoglobin to reticulo-histiocytic reserves, serum ferritin may be normal or even increased[9]. It is also an acute phase protein and increases in inflammatory process. It complicates the analysis of normal or elevated serum ferritin values in areas where infectious or inflammatory diseases are widespread. In the absence of inflammation or liver disease, high serum ferritin level indicates iron overload[10]. The lack of exploration of liver function does not suggest those results are only due to transfusions. Ferritin increases significantly with CRP (r =0.57).

When we excluded individuals with acute inflammation (CRP>6 mg/L), it remains seven patients with high ferritin levels. However sickle cell anemia is a disorder with common inflammatory processes. Such an exclusion mechanism could artificially weaken high ferritin levels. It emerged naturally weak correlation between serum ferritin and blood volume received (r =0.14) in the whole population. It is the same result in patients with a negative CRP (r =0.02). This goes against the results indicated by Hafsia *et al* in which a significant strong correlation (r =0.74) was found. Nevertheless our results are similar to the study of Hamartz *et al*[10] in who assessed 20 sickle cell patients with chronic transfusions.

In fact, this study found weak correlation between serum ferritin and the number of transfusions (r =0.30, p=0.200), although the results of liver biopsy iron stores increase with the duration of transfusion. Similarly, in the study of Brown *et al* concerning 27 children subjected to chronic transfusions without chelating therapy[11], there was no correlation between serum ferritin and volume of transfusions, although the correlation between the volume of transfusions and liver iron concentration was established. However, a study done by Fung *et al*[12] on 199 sickle cell transfused patients and 64 non-transfused SCD has noted a significant difference in serum ferritin (3459 mg/L) in the first group versus 90 mg/L. Multiple transfusions lead undeniably increased iron stores. But this lack of correlation highlights the limitations of serum ferritin as a faithful marker of iron stores, especially in sickle cell disease in which hemolysis influences iron metabolism. We have not assessed serum ferritin level according to period of transfusion in this pilot study since patients were transfused in a very irregular intervals.

Hyperferritinemia is frequent in sickle cell disease patients having history of transfusion. However, it does not seem to be associated to frequency of blood transfusions in Cameroon. Hyperferritinemia should be assessed in all patients with past history of multiple transfusions regardless of number of transfusions received.

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CONFLICT OF INTERESTS

The author has no conflicts of interest to declare.

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