Iron Deficiency in Sudanese Children with Sickle Cell Anaemia

M. A. Hussain, M. I. Mustafa, A. A. Y. Kordofani


Iron status was studied in 100 patients with homozygous sickle cell disease between 4 months and 16 years of age. All patients were prescribed folic acid for at least 1 month prior to the study but none was taking any other medication or had received a blood transfusion during the previous 3 months. Basic haematologic data (Hb, PCV, reticulocyte and red cell counts, MCV, MCH, MCHC and peripheral blood picture), serum iron, total iron binding capacity (TIBC) and transferrin saturation were obtained in all 100 patients. Bone marrow aspiration and staining for iron was performed in 82 patients (over 2 years of age) and these were divided into three groups according to the results of marrow iron. There were 68 (83%) patients with absent marrow iron in group 1, five (6%) with reduced iron in group 2 and nine (11%) with sufficient marrow iron in group 3. In 18 patients (under 2 years of age) bone marrow aspiration was not performed and these patients are referred to as group 4.

Patients in group 1 had the lowest mean Hb and their basic haematologic data, serum iron, TIBC and transferrin saturation were compatible with the diagnosis of iron deficiency anaemia. Patients in group 2 showed evidence of early iron deficiency as indicated by reduction in marrow iron but there was no evidence of iron deficiency in other results. Group 3 patients showed no evidence of iron deficiency. Group 4 patients had basic haematologic data, serum iron, TIBC and transferrin saturation similar to those in group 1. Although marrow iron content was not known for patients in group 4 available data were suggestive of iron deficiency anaemia in this group. Combining the results of groups 1 and 4, made the diagnosis of iron deficiency anaemia as high as 86% in this study.
It is generally assumed that patients with sickle cell anaemia have excessive iron stores because of the chronic haemolytic process which makes iron available from destroyed red cells and also because of increased iron absorption from the gut in association with haemolysis. The amount of absorbed iron clearly depends on the availability of iron in the diet. Another factor responsible for increasing iron stores is blood transfusion. This factor depends on the transfusion policy adopted in each centre. Despite the effect of these factors in increasing iron stores, iron deficiency has been reported in patients living in both developing and developed countries but there has been no report from the Sudan. The aim of the present study was to find the prevalence of iron deficiency among Sudanese children referred to hospital with sickle cell anaemia.

**Patients and Methods**

At the paediatric out-patient clinics of the Children’s Emergency Hospital and Soba University Hospital, 100 patients (51 females, 49 males), aged between 4 months and 16 years (median age 5.5 years) with the diagnosis of homozygous sickle cell disease were seen. These patients were living in Khartoum city and the surrounding villages within an area of about 30–40 miles from Khartoum. All selected patients had been free from painful crises and infections in the previous 3 weeks. They had been on regular folie acid therapy (5 mg/day) for at least 1 month but none was taking any other medication or had received blood transfusion in the previous 3 months.

A special record was kept on every patient about age, tribe, residence, history of blood transfusion or blood loss, dietary history, weight, height and the presence of pallor, jaundice and liver or splenic enlargement. After consent was obtained from the parents, 5 ml of blood was taken from each patient for basic haematologic data (Hb, PCV, red cell count, reticulocyte count, peripheral blood picture, MCV, MCH and MCHC, serum iron, total iron binding capacity (TIBC) and transferrin saturation. Bone marrow was aspirated from either the posterior or anterior iliac crest in all patients over the age of 2 years (82 patients) and marrow iron was assessed.

Basic haematologic data were obtained by standard methods. Serum iron and TIBC were estimated by the method recommended by the International Committee for Standardization in Haematology. Evaluation of iron stores in bone marrow depends on the demonstration of sideroblasts and reticuloendothelial cells containing granules of non-haem iron which stains with Prussian blue in the bone marrow aspirate. A known sample of marrow aspirate positive for iron was used as a control.

**Results**

According to the socioeconomic classification made by the Ministry of Housing for Khartoum City, 97 (97%) patients from poor residential areas fell in social classes 3 and 4. All 97 had a poor nutritional history and in particular their diets contained less than the required amount of iron per 24 hours, according to the studies by Joseph on Sudanese food composition. Three (3%) patients were resident in high social class areas; two were from high income families and their diets were satisfactory. The third patient, a daughter of a guard in one of the homes in that area had a diet similar to that of the low socioeconomic groups.

The patients on whom bone marrow aspiration was performed were classified into three groups according to the results of marrow iron. Group 1 (68 patients) had absent marrow iron, group 2 (five patients) had reduced iron and group 3 (nine patients) had sufficient iron. In 18 patients (referred to as group 4) bone marrow aspiration was not performed because the patients were under 2 years of age. Relevant findings are shown for each of these four groups.

**Group 1**

**History and clinical findings**

The age and sex distribution of patients in this group is shown in Table 1. Fifteen (22%) had a history of blood transfusion. They had received from one to five (mean two) transfusions. A history of blood loss was obtained in 22 (32%) patients (13 of them among the transfused patients). The blood loss was in the form of epistaxis in 14 (20%) patients and from the urinary and intestinal systems in eight (12%). Sixty-five (95%) patients were below the third centile for weight and seven (10%) were below the third centile for height. All 68 patients were pale and 18 (26%) of them were jaundiced. Hepatosplenomegaly was present in 23 (33%) patients (all below 6 years of age). Hepatomegaly alone was present in 37 (54%) patients (4–15 years old) and splenomegaly alone in two patients (age 3.5 and 4 years).

**Table 1**

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Male</th>
<th>Female</th>
<th>Total no. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td>16</td>
<td>25</td>
<td>41</td>
<td>60.3</td>
</tr>
<tr>
<td>5-7</td>
<td>5</td>
<td>4</td>
<td>9</td>
<td>13.2</td>
</tr>
<tr>
<td>8-10</td>
<td>5</td>
<td>3</td>
<td>8</td>
<td>11.8</td>
</tr>
<tr>
<td>11-13</td>
<td>6</td>
<td>2</td>
<td>8</td>
<td>11.8</td>
</tr>
<tr>
<td>14-16</td>
<td>–</td>
<td>2</td>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>32</td>
<td>36</td>
<td>68</td>
<td>100</td>
</tr>
</tbody>
</table>

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### Table 2
Basic haematologic findings in all groups of patients with sickle cell anaemia

<table>
<thead>
<tr>
<th>Value</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range (± SD)</td>
<td>Range (± SD)</td>
<td>Range (± SD)</td>
<td>Range (± SD)</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>2.7–8.6</td>
<td>6.2±1.2</td>
<td>6.6–9.2</td>
<td>7.7±1.1</td>
</tr>
<tr>
<td>PCV (1/l)</td>
<td>0.10–0.31</td>
<td>0.23±0.04</td>
<td>0.21–0.30</td>
<td>0.27±0.03</td>
</tr>
<tr>
<td>RBC (x 10^12/l)</td>
<td>1.6–3.6</td>
<td>2.2±0.6</td>
<td>2.5–3.2</td>
<td>2.7±0.2</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>20–65</td>
<td>53.8±14.2</td>
<td>66–91.4</td>
<td>78.2±10.6</td>
</tr>
<tr>
<td>MCH (pg/cell)</td>
<td>16–23.9</td>
<td>16.9±2.4</td>
<td>26–28.6</td>
<td>28±1.5</td>
</tr>
<tr>
<td>MCHC (g/dl)</td>
<td>16.5–23.9</td>
<td>21.2±2.5</td>
<td>25.5–31.4</td>
<td>28.9±2.5</td>
</tr>
<tr>
<td>RBC</td>
<td>2–23</td>
<td>10.2±3.6</td>
<td>7.2–13.5</td>
<td>10.3±2.2</td>
</tr>
<tr>
<td>Reticulocytes (%)</td>
<td>2–23</td>
<td>10.2±3.6</td>
<td>7.2–13.5</td>
<td>10.3±2.2</td>
</tr>
</tbody>
</table>

### Laboratory findings
Basic haematologic data for patients in this group are presented in Table 2. Mean Hb, PCV, MCV, MCH and MCHC values were remarkably lower than those obtained for a group of normal Sudanese children of the same age and sex studied in the same laboratory. The peripheral blood picture showed mainly sickle and target cells, microcytosis, hypochromia and polychromasia. Serum iron, TIBC and transferrin saturation are shown in Table 3. The mean values for serum iron and transferrin saturation were lower and TIBC was higher than the values obtained in normal children. All findings in this group were compatible with the diagnosis of iron deficiency anaemia.

### Group 2

#### History and clinical findings
There were five patients (three females, two males) aged between 6.5 and 16 years. Three patients with a history of blood transfusion (one, two and five transfusions) also gave a history of blood loss mainly in the form of epistaxis. Four patients were below the third centile for weight and two of them were also below the third centile for height. Three patients were pale and one of them was jaundiced. In four patients the liver was enlarged.

### Laboratory findings
Basic haematologic data for patients in this group are shown in Table 2. The mean Hb was lower than the mean Hb level of normal children but mean MCV, MCH and MCHC values were within the normal range. The peripheral blood picture showed mainly sickle and target cells, hypochromia and normocytosis. Serum iron, TIBC and transferrin saturation are shown in Table 3. They were within the range obtained for normal children.

### Table 3
Serum iron, TIBC and transferrin saturation in all groups of patients with sickle cell anaemia

<table>
<thead>
<tr>
<th>Value</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range (± SD)</td>
<td>Range (± SD)</td>
<td>Range (± SD)</td>
<td>Range (± SD)</td>
</tr>
<tr>
<td>Serum iron (μmol/l)</td>
<td>4.2–10.7</td>
<td>9±1.5</td>
<td>13.7–14.4</td>
<td>14±0.3</td>
</tr>
<tr>
<td>TIBC (μmol/l)</td>
<td>64.2–86</td>
<td>71.9±5.6</td>
<td>55–57.1</td>
<td>56.7±0.9</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>6.6–12.4</td>
<td>9.5±0.4</td>
<td>24–25.9</td>
<td>24.9±0.7</td>
</tr>
<tr>
<td></td>
<td>14.1–17.5</td>
<td>15±1.2</td>
<td>51.9–57.8</td>
<td>54.4±2.3</td>
</tr>
<tr>
<td></td>
<td>56.6–76.7</td>
<td>67.8±5.6</td>
<td>27.1–30.2</td>
<td>27.7±2.6</td>
</tr>
<tr>
<td></td>
<td>14.1–15.5</td>
<td>14.9±1.9</td>
<td>8–11.9</td>
<td>10.1±0.9</td>
</tr>
</tbody>
</table>
of patients in group 1. The peripheral blood picture showed mainly target cells and sickle cells, hypochromia and microcytosis. Serum iron, TIBC and percentage transferrin saturation for patients in this group are shown in Table 3. The results were also similar to those of patients in group 1.

Discussion
The results of this study show that the majority of patients on whom bone marrow aspiration was performed had iron deficiency anaemia. This probably resulted in the lower Hb levels seen in these patients compared with those in group 2 and 3. Features of iron deficiency started to show in five patients (group 2) as evidenced by reduction in marrow iron but that was not severe enough to affect other parameters. The number of patients with iron deficiency anaemia is probably more than can be seen from the results of marrow iron since 18 patients (group 4) in whom bone marrow was not performed showed basic haematologic data and serum iron and transferrin saturation results similar to patients in group 1. The diagnosis of iron deficiency anaemia in patients with sickle cell disease is, however, not reliable when based on evidence from red cell morphology, and indices, or on results of serum iron and transferrin saturation. The coinheritance of α-thalassaemia with SS disease which is found in the US Black — and many West African populations results in the appearance of microcytic hypochromic red cells and has a marked effect on red cell indices. Although the incidence of coinheritance of α- and β-thalassaemia with sickle cell disease is not known in the Sudan, the results of the red cell counts in the present study are not suggestive of the presence of thalassaemia. Serum iron and transferrin saturation can be low in malnutrition, liver disease and chronic infections, conditions likely to be present in sickle cell disease.

The iron status in patients with sickle cell anaemia is a reflection of the balance between factors responsible for increasing iron stores and others for reducing the stores. The results of this study stress the dominance of the latter factors and two obvious causes were the poor dietary history and blood loss. Other possible causes which were not investigated in these patients were parasitic infestations, other infections and malabsorption. Whatever the cause may be, the result is generally related to the high incidence of iron deficiency anaemia in Sudanese children (Hussain et al., unpublished work).

There have been several studies of iron deficiency and its possible causes in patients with sickle cell anaemia but the present study has the highest incidence. Oluboyede et al. reported absence of bone marrow iron in 58 (68.1%) of 85 Nigerian patients aged 3–30 years and they related that to the high incidence of iron deficiency anaemia in Nigeria. In another study from Nigeria, Okeahialam & Obi found that marrow iron was depleted in 21 (40.7%) of 45 children with sickle cell anaemia and serum iron was below the normal mean for age in 14 (31%) of these patients. They suggested that the possible causes of iron deficiency in these patients include dietary deficiency, malabsorption, loss through hookworm infestations and increased requirements during growth spurt. In a more recent study Jeyakumar et al. found that 15 (63%) of 24 Nigerian children with sickle cell disease were iron deficient. Their patients were under 10 years old and their findings were based on results of serum iron, TIBC, transferrin saturation and free erythrocyte protoporphyrin (FEP)/haem ratio. Nkrumah et al. studied bone marrow aspirates from 33 Ghanaian children with sickle cell anaemia and reported absence of marrow iron in 14 (42.4%) of them. They also attributed iron deficiency in their patients to the high prevalence of nutritional deficiency in the community.

Other reasons for iron deficiency in patients with sickle cell anaemia have been reported in places where nutritional inadequacies are not common.
Davies et al.\textsuperscript{5} investigated iron status in 37 patients with sickle cell disease living in Britain. Five of their patients were found to be iron deficient and five additional patients had lower than normal serum ferritin. Analysis of case histories disclosed that peptic ulceration, recurrent epistaxis and multiple pregnancies could account for iron loss in seven patients. Rao et al.\textsuperscript{6} in Chicago studied iron status in 60 patients with sickle cell anaemia. Seventeen (28\%) were found to have absent bone marrow iron and there was a significant positive correlation between marrow iron, serum ferritin and transferrin saturation. None of their patients had demonstrable blood loss on investigation but 24-h urinary iron excretion secondary to chronic intra-vascular haemolysis was increased in most patients and that was thought to explain the high prevalence of iron deficiency.

Similarly Natta et al.\textsuperscript{7} reported one case of sickle cell anaemia and iron deficiency in New York with no evidence of blood loss but 24-h urinary iron excretion was excessive. Haddy & Castro\textsuperscript{8} from Washington reported three cases with HbSS and one case with HbSC disease, with iron deficiency which was proved by high TIBC and low serum ferritin. The iron deficiency in these patients was found to be due to uterine and intestinal bleeding. In another study which was conducted in Oakland, Vichinsky et al.\textsuperscript{9} studied 38 non-transfused and 32 transfused patients with HbSS and HbSC disease. Six patients in the non-transfused group had iron deficiency, all of them were 6 years of age or less. None of the transfused group had evidence of iron deficiency and they concluded that iron deficiency is a potential risk in young non-transfused patients.

The incorporation of iron into the treatment of iron deficiency anaemia is still debatable. Two of 11 patients with sickle cell anaemia and proven iron deficiency showed a significant rise in Hb level in response to oral iron therapy.\textsuperscript{16} Also six of 16 patients with sickle cell anaemia and iron deficiency who were given a 6-week course of iron therapy, showed significant rise in Hb, transferrin saturation and serum ferritin levels.\textsuperscript{9}

One of the authors of the present study (Hussain) has observed that when iron is given to Sudanese children with sickle cell anaemia and associated iron deficiency, it results in an increase in Hb levels, reduction in transfusion requirement and general improvement in the quality of life of these patients. However, some people advocate that iron therapy in such patients may result in complications because an increase in Hb concentration may lead to an increase in the sickling process and hence worsening of the clinical course of the disease.\textsuperscript{17}

Iron therapy increased the number of painful crises in two patients with both sickle cell anaemia and iron deficiency, and one patient had a painful crisis for the first time after treatment of his iron deficiency anaemia.\textsuperscript{18} In addition to increasing the degree of anaemia, iron deficiency is also associated with multisystemic disturbances including growth retardation, impairment of intellectual function, changes in behaviour, alteration of skin and mucosa and gastrointestinal disturbances.\textsuperscript{18} These effects are considerably harmful especially for growing children whether they are sicklers or not. Treatment with iron is followed by disappearance of all these complications in iron-deficient children not suffering from sickle cell anaemia without causing adverse effects.

A controlled study is needed to examine such effects in sickle cell anaemia patients and to determine the relationship between the Hb concentration in the red cells and the sickling phenomenon.

References
\textsuperscript{4}Nkrumah FK, Neeyequaye JE, Anka-Badu G. Bone marrow in sickle cell anaemia at time of anaemic crisis. \textit{Arch Dis Childh} 1984; 59: 561–565.
\textsuperscript{8}Hady T, Castro O. Overt iron deficiency in sickle cell disease. \textit{Arch Intern Med} 1982; 142: 1621–1624.