The Diagnosis of Iron Deficiency Anemia in Sickle Cell Disease

By Elliott Vichinsky, Klara Kleman, Steven Embury, and Bertram Lubin

We determined the prevalence and optimal methods for laboratory diagnosis of iron deficiency anemia in patients with sickle cell disease. Laboratory investigations on 38 nontransfused and 32 transfused patients included transferrin saturation, serum ferritin, mean corpuscular volume (MCV), and free erythrocyte protoporphyrin (FEP). Response to iron supplementation confirmed the diagnosis of iron deficiency anemia in 16% of the nontransfused patients. None of the transfused patients were iron deficient. All iron-deficient patients (mean age 2.4 yr) had a low MCV, serum ferritin <25 ng/ml, transferrin saturation <15%, and FEP >90 μg/dl RBC. Following therapy, all parameters improved and the hemoglobin concentration increased ~2 g/dl. A serum ferritin below 25 ng/ml was the most reliable screening test for iron deficiency. There were 13% false positive results with transferrin saturation, 3% with MCV, and 62% with FEP. FEP values correlated strongly with reticulocyte counts. The high FEP was in part due to protoporphyrin IX and not completely due to zinc protoporphyrin, which is elevated in iron deficiency. We conclude that iron deficiency anemia is a potential problem in young nontransfused sickle cell patients. Serum ferritin below 25 ng/ml and low MCV are the most useful screening tests.

Iron deficiency anemia is not generally recognized as a medical problem in patients who have sickle cell disease. The increased gastrointestinal absorption of iron associated with hemolysis and the iron provided by red cell transfusions are thought to provide a sufficient source of iron. Even if one considers the diagnosis, such conventional laboratory tests for iron deficiency as mean corpuscular volume (MCV), transferrin saturation, serum ferritin, and free erythrocyte protoporphyrin (FEP) may be abnormal in patients with sickle cell disease due to inflammation, hemolysis, alpha-thalassemia trait or hepatic abnormalities, and have no relationship to iron deficiency.

However, there are several reasons to believe that iron deficiency may occur in patients with sickle cell disease, especially young patients. Lanzkowsky reported a 21% incidence of nutritional iron deficiency in black children living in a low socioeconomic environment. In another study, almost 100% of black children in extremely low income groups had biochemical evidence of iron deficiency. Patients with sickle cell disease may have similar nutritional inadequacies and in addition may have excessive urinary iron loss. Even if gastrointestinal iron absorption is increased, when iron intake is limited and iron loss excessive, iron deficiency will result.

Since the effects of iron deficiency may be extensive, especially for the growing child, we have undertaken the present study to determine the incidence of iron deficiency anemia in a population of children and adults with sickle cell disease. We have also evaluated the usefulness of MCV, serum iron, iron-binding capacity, transferrin saturation, serum ferritin, and FEP for the detection of iron deficiency. The results of our study are reported herein.

MATERIALS AND METHODS

Fifty patients (age 1–27 yr) with homozygous sickle cell anemia (HbSS) and 20 patients (age 1–30 yr) doubly heterozygote for HbS and HbC (HbSC) were included in this study. None of the patients had sickle beta-thalassemia and none had received specific recommendations for either supplementation or restriction of dietary iron. Twenty-two of the 50 HbSS patients and 16 of the 20 HbSC patients had never been transfused. None of the patients had been transfused during the 3-mo interval prior to this study. All patients were stable, afebrile, and free from complications at the time blood samples were obtained.

The hemoglobinopathy diagnosis was established by electrophoretic techniques on cellulose acetate, pH 8.4, and citrate agar, pH 6.2. Quantitative HbA2 levels by column chromatography and Hbf levels by alkali denaturation confirmed the diagnosis in each case. Hematologic parameters and red cell indices were determined on venous blood using a model S Coulter Counter. Reticulocyte counts were performed by standard methods. Serum iron concentrations and iron-binding capacity were determined by the Megraw-Bouda modification of the bathophenanthroline procedure. Serum ferritin was measured by the radioimmunoassay described by Addison et al. Free erythrocyte protoporphyrin, zinc protoporphyrin, and protoporphyrin IX levels were determined on red cell extracts using an Aminco spectrophotometer. Whole blood lead levels were measured on an atomic absorption spectrometer using a modification of the method described by Delves. Reticulocyte rich and poor samples were prepared from washed red cells using a discontinuous stractan density centrifugation technique.

The diagnosis of iron deficiency anemia was established following a response to oral iron. Patients were eligible for a therapeutic trial of iron if they met one of the following laboratory criteria: (1) transferrin saturation <16%; (2) serum ferritin <25 ng/ml; (3) low MCV for age: 0.5–2 yr <70 fl, 2–5 <73 fl, 5–9 yr <75 fl, 9–14 yr <76 fl, 14–18 yr <77 fl, 18 yr or older <80 fl.

The therapeutic trial of iron consisted of 6 mg/kg/day elemental iron in the form of ferrous sulfate for a duration of 6 wk. All patients and HbC (HbSC) were included in this study. None of the patients had sickle beta-thalassemia and none had received specific recommendations for either supplementation or restriction of dietary iron. Twenty-two of the 50 HbSS patients and 16 of the 20 HbSC patients had never been transfused. None of the patients had been transfused during the 3-mo interval prior to this study. All patients were stable, afebrile, and free from complications at the time blood samples were obtained.

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The therapeutic trial of iron consisted of 6 mg/kg/day elemental iron in the form of ferrous sulfate for a duration of 6 wk. All
laboratory measurements were repeated at week seven in the treated as well as the nontreated groups. Compliance was determined by measuring the amount of medication remaining at the end of the therapeutic trial. Patients who did not take the prescribed amount of medication were excluded from the study. A diagnosis of iron deficiency was made if the hemoglobin concentration increased 1 g/dl or more at the end of the 6-wk period. Patients who continued to have microcytic red cells following iron therapy had further genetic studies to exclude alpha-thalassemia trait. Whole blood lead was determined on all patients found to have an elevated FEP.

RESULTS

Table 1 shows the initial laboratory data for the patients in this study. The results are divided according to hemoglobin type and transfusion history. Groups I and II refer to transfused and nontransfused hemoglobin SC patients, respectively. Groups III and IV refer to transfused and nontransfused HbSS patients, respectively. The hematologic parameters in patients with sickle cell anemia (HbSS) and hemoglobin SC disease were similar to those previously reported. MCV values were higher in the HbSS patients than the HbSC patients, and in both cases, were lower in the nontransfused groups than the transfused groups. The MCV(108) was markedly elevated in one HbSS patient. This patient had a normal folate level, B12 level, serum ferritin of 320 ηg/ml, and no evidence of liver disease. Ferritin levels were higher in patients with sickle cell anemia (HbSS) and hemoglobin SC disease.

The median, range, and interquartile range for each laboratory measurement are shown in Fig. 1. The interquartile range represents the range in which the middle 50% of the values fell. The outliers (clear circles) represent data points that are greater than 1.5 times the interquartile range. The median FEP value was highest in group IV. Values above the upper limit of normal (90 ηg/dl RBC) were seen in many HbSS patients but in only 1 HbSC patient. The transferrin saturation was below 16% in many patients in group IV and in several patients in group II, but was above 16% in most transfused patients. The median MCV value was similar in most transfused HbSS and HbSC patients, although the interquartile range was lower in HbSC patients. Ferritin values below 25 ηg/ml were noted only in the nontreated patients.

Although 19 of the 70 patients were eligible for iron therapy, only 16 patients completed a 6-wk course of iron therapy. Three patients were found to be noncompliant when residual iron was measured at the end of the therapeutic trials and were therefore excluded from the study. Six of the 16 patients responded to treatment. The laboratory data on these patients are shown in Table 2. Four of these patients had HbSS and 2 had HbSC. None of the iron-deficient patients were in the transfused group. The mean age of the patients in the iron-deficient group was 2.4 yr. All 6 patients had high FEP and low transferrin saturation, serum ferritin, and MCV. All iron-deficient patients had a low serum iron and 4 of the 6 patients had a TIBC greater than 350 ηg/dl. Following completion of iron therapy, the mean value for all parameters changed: hemoglobin concentration increased 2.1 g/dl, FEP decreased from 308 ηg/dl RBC to 220 ηg/dl RBC, transferrin saturation increased from 8% to 19%, serum iron rose from 29 to 70 ηg/dl, serum ferritin rose from 19 to 74 ηg/ml, MCV increased from 67 to 77 fl, and reticulocyte counts rose from 7% to 10%.

Ten patients eligible for iron therapy did not demonstrate a therapeutic response (Table 3). The mean age in this “nonresponder” group was 11 yr. Six of these patients had been previously transfused. FEP values were elevated in the iron-deficient as well as the non-iron-deficient group, however, the FEP values in the iron-deficient group were higher. A low transferrin saturation was found in 8 of these 10 patients. A low

Table 1. Initial Laboratory Data on Transfused and Nontransfused Patients

<table>
<thead>
<tr>
<th>No. Group</th>
<th>n</th>
<th>Age (yr)</th>
<th>Hb (g/dl)</th>
<th>MCV (fl)</th>
<th>FEP (μg/dl RBC)</th>
<th>Fe (μg/dl)</th>
<th>TIBC (μg/dl)</th>
<th>Transferrin Saturation</th>
<th>Ferritin (ng/ml)</th>
<th>Reticulocyte Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>4</td>
<td>(13-30)</td>
<td>(11-12)</td>
<td>(82-87)</td>
<td>(51-60)</td>
<td>(46-80)</td>
<td>(180-300)</td>
<td>(16-34)</td>
<td>(100-200)</td>
<td>(1-6)</td>
</tr>
<tr>
<td>II</td>
<td>4</td>
<td>(1-29)</td>
<td>(7.4-12)</td>
<td>(64-90)</td>
<td>(40-272)</td>
<td>(10-98)</td>
<td>(204-356)</td>
<td>(5-34)</td>
<td>(17-144)</td>
<td>(5-6)</td>
</tr>
<tr>
<td>III</td>
<td>19</td>
<td>(4-27)</td>
<td>(7-11)</td>
<td>(80-108)</td>
<td>(69-250)</td>
<td>(52-98)</td>
<td>(200-374)</td>
<td>(13-100)</td>
<td>(63-2,000)</td>
<td>(5-34)</td>
</tr>
</tbody>
</table>

Group I, transfused HbSC patients; group II, nontransfused HbSC patients; group III, transfused HbSS patients; and group IV, nontransfused HbSS patients. n, Refers to the number in each group; the values within parenthesis indicate the range for each measurement.
serum iron was observed in most of these patients, but only 2 patients had a TIBC greater than 350 µg/dl. All had normal serum ferritin values. In the two patients who had low MCV, genetic studies demonstrated alpha-thalassemia trait in one; chronic inflammation was suspected to be the etiology for microcytosis in the other. Two patients (nos. 1 and 3) were more anemic than most HbSC patients, however, extensive laboratory evaluation did not reveal any additional etiology. History revealed that patient no. 1 had recently recovered from a viral illness prior to the initial lab studies.

Table 4 summarizes the number of false positive screening tests for iron deficiency. The FEP was elevated in 44 of 67 patients despite normal lead levels. The FEP was elevated in all iron-deficient patients and in 38 of 61 iron-sufficient patients, resulting in a 62% false positive rate. The transferrin saturation was low in the 6 iron-deficient patients, but there were 13% (8/61) false positive values. There were no false positive or false negative results with the serum ferritin. The serum ferritin was below 22 ng/ml in all iron-deficient patients and above 36 ng/ml in all iron-sufficient patients. The MCV was low for age in all

Table 2. Response to Iron Therapy in Sickle Cell Disease: Responders

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dx</th>
<th>Age (yr)</th>
<th>Hb (g/dl)</th>
<th>FEP (µ/dl RBC)</th>
<th>Transferrin Saturation</th>
<th>Ferritin (mg/ml)</th>
<th>MCV (fl)</th>
<th>Reticulocyte (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre Post</td>
<td>Pre Post</td>
<td>Pre Post</td>
<td>Pre Post</td>
</tr>
<tr>
<td>1</td>
<td>SC</td>
<td>1.5</td>
<td>8.3</td>
<td>12</td>
<td>255 177</td>
<td>18/356 (5%) 53/360 (15%)</td>
<td>17 30</td>
<td>68 73 1 3</td>
</tr>
<tr>
<td>2</td>
<td>SS</td>
<td>2</td>
<td>7.6</td>
<td>8.8</td>
<td>300 230</td>
<td>48/475 (10%) 95/400 (24%)</td>
<td>20 90</td>
<td>72 80 11 16</td>
</tr>
<tr>
<td>3</td>
<td>SS</td>
<td>6</td>
<td>7.8</td>
<td>9.0</td>
<td>285 218</td>
<td>35/370 (9%) 70/284 (26%)</td>
<td>19 152</td>
<td>70 80 12 13</td>
</tr>
<tr>
<td>4</td>
<td>SS</td>
<td>2</td>
<td>6.9</td>
<td>8.1</td>
<td>235 180</td>
<td>30/280 (11%) 51/355 (14%)</td>
<td>18 29</td>
<td>70 80 8 10</td>
</tr>
<tr>
<td>5</td>
<td>SC</td>
<td>2</td>
<td>9.6</td>
<td>11.3</td>
<td>272 114</td>
<td>20/330 (6%) 94/488 (19%)</td>
<td>20 115</td>
<td>66 76 2 2</td>
</tr>
<tr>
<td>6</td>
<td>SS</td>
<td>1</td>
<td>5.0</td>
<td>8.3</td>
<td>500 291</td>
<td>27/424 (6%) 66/324 (19%)</td>
<td>22 28</td>
<td>61 76 8 17</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>2.4</td>
<td>7.5</td>
<td>9.6</td>
<td>308 220</td>
<td>29/372 (8%) 70/368 (19%)</td>
<td>19 74</td>
<td>67 77 7 10</td>
</tr>
</tbody>
</table>
iron-deficient patients. Although there was a 3% false positive rate (2/61), this included the one patient with alpha-thalassemia trait. Since FEP was elevated in the majority of HbSS patients, and since FEP is frequently used to screen for iron deficiency, we investigated the etiology of this abnormality. In order to determine if elevated FEP was related to red cell age, reticulocyte counts were compared to FEP values (Fig. 2). The HbSS patients had higher FEP values and reticulocyte counts than the HbSC patients, and there was a good correlation between reticulocyte count and FEP value ($p < 0.001$, $r$ value $= 0.62$). In two experiments in which FEP values in reticulocyte-rich and reticulocyte-poor samples obtained from the same patient were compared, the FEP value was 40% higher in the reticulocyte-rich fractions than in the reticulocyte-poor fractions. Spectrofluorometric analysis of the acetone-acetic acid extract revealed that the ratio of protoporphyrin IX to zinc protoporphyrin was fourfold higher in the reticulocyte-rich fractions than in the reticulocyte-poor fractions (Fig. 3) and that the elevated FEP in reticulocytes was in part due to the increase of protoporphyrin IX.

**DISCUSSION**

We detected iron deficiency anemia in 9% of our study group. Transfusion history and patient age were predictive variables. None of the 32 patients who had a history of red cell transfusions were iron deficient. In contrast, among the 38 patients who were not transfused, 6 iron-deficient patients were identified. All of the iron-deficient patients were 6 yr of age or less.

Each of the four tests for iron deficiency anemia differed in their sensitivity and specificity. Transferrin saturation below 16% was very sensitive but not specific. A low transferrin saturation is found in chronic inflammatory disease, and it is likely that chronic inflammation contributes to the depression in transferrin saturation in sickle cell anemia.6'22 The TIBC appears to be a more discriminatory screening tool than the transferrin saturation. However, two of the six iron-deficient patients had normal TIBC, and therefore TIBC has limited usefulness as a screening test for iron deficiency.

Age-dependent MCV values were a useful screening test for iron deficiency. Even though reticulocytes may elevate the MCV in HbSS patients, the use of normal MCV values for age did not result in false negative MCV measurements. Furthermore, HbSS patients who developed iron deficiency had red cell MCV values below the normal for age.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dx</th>
<th>Age (yr)</th>
<th>Hb (g/dl)</th>
<th>FEP (μg/dl RBC)</th>
<th>Transferrin Saturation</th>
<th>Ferritin (ng/ml)</th>
<th>MCV (fl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SC</td>
<td>6</td>
<td>8.3</td>
<td>8.7</td>
<td>108/91</td>
<td>10/204 (5%)</td>
<td>60/250 (24%)</td>
</tr>
<tr>
<td>2</td>
<td>SS</td>
<td>20</td>
<td>11.3</td>
<td>11.3</td>
<td>73/82</td>
<td>52/392 (13%)</td>
<td>44/380 (11%)</td>
</tr>
<tr>
<td>3</td>
<td>SC</td>
<td>6</td>
<td>8.7</td>
<td>9.1</td>
<td>71/80</td>
<td>46/300 (15%)</td>
<td>35/305 (11%)</td>
</tr>
<tr>
<td>4</td>
<td>SS</td>
<td>12</td>
<td>7.8</td>
<td>7.5</td>
<td>220/200</td>
<td>48/378 (12.5%)</td>
<td>41/300 (14%)</td>
</tr>
<tr>
<td>5</td>
<td>SS</td>
<td>6</td>
<td>9.8</td>
<td>9.3</td>
<td>193/176</td>
<td>20/224 (9%)</td>
<td>91/460 (20%)</td>
</tr>
<tr>
<td>6</td>
<td>SS</td>
<td>1</td>
<td>8</td>
<td>7.8</td>
<td>202/185</td>
<td>36/276 (13%)</td>
<td>322/278 (11%)</td>
</tr>
<tr>
<td>7</td>
<td>SS</td>
<td>20</td>
<td>8</td>
<td>8</td>
<td>237/243</td>
<td>42/330 (13%)</td>
<td>34/329 (10%)</td>
</tr>
<tr>
<td>8</td>
<td>SS</td>
<td>7</td>
<td>8.2</td>
<td>7.8</td>
<td>234/234</td>
<td>15/312 (6%)</td>
<td>38/370 (10%)</td>
</tr>
<tr>
<td>9</td>
<td>SC-α-thal</td>
<td>13</td>
<td>10.6</td>
<td>10.3</td>
<td>79/89</td>
<td>90/276 (32%)</td>
<td>75/260 (29%)</td>
</tr>
<tr>
<td>10</td>
<td>SS</td>
<td>18</td>
<td>8.5</td>
<td>8.8</td>
<td>118/106</td>
<td>88/288 (30%)</td>
<td>80/236 (34%)</td>
</tr>
</tbody>
</table>

| Mean | 11   | 8.8     | 8.9       | 153/149         |

**Table 4. False Positive Screening Tests for Iron Deficiency in Patients With Sickle Cell Disease**

<table>
<thead>
<tr>
<th>FEP &gt;90 μg/dl RBC</th>
<th>Transferrin Saturation &lt;16%</th>
<th>Ferritin &lt;25 mg/ml</th>
<th>MCV (fl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive results</td>
<td>44/67</td>
<td>15/67</td>
<td>6/67</td>
</tr>
<tr>
<td>False positive</td>
<td>38/61</td>
<td>8/61</td>
<td>0/61</td>
</tr>
</tbody>
</table>

Fig. 2. Correlation between reticulocyte count (percent) and FEP (μg/dl RBC) in iron-sufficient sickle cell disease patients ($p < 0.001$, $r$ value $= 0.62$). The results from two experiments on reticulocyte-rich and poor samples are included in this figure.
IRON DEFICIENCY IN SICKLE CELL DISEASE

Fig. 3. Fluorescence emission spectra made from acetone–acetic acid extracts of reticulocyte-rich (fraction 1) and reticulocyte-poor (fraction 2) sickle cell blood. The scanning spectrofluorometer (excitation 408 nm) shows the clear separation of zinc protoporphyrin (590 nm peak) and protoporphyrin IX (640 nm peak). Prior to fractionation on a discontinuing stration density gradient, the sickle cell blood contained 10% reticulocytes; after fractionation, sample 1 contained 40% reticulocytes and sample 2 contained 2.5% reticulocytes.

The elevated FEP values in HbSS patients who are iron sufficient appear to be secondary to an increased amount of protoporphyrin in reticulocytes. This increase is due to an accumulation of both protoporphyrin IX and zinc protoporphyrin. In contrast, in both iron deficiency and lead poisoning, the quantity of only zinc protoporphyrin is elevated. The cause of the elevated FEP and in particular the protoporphyrin IX appears to be related to red cell age and not a peculiarity of sickle cell disease. Similar elevations in protoporphyrin have been noted in reticulocytes from patients with other forms of hemolytic anemia. Our results are also consistent with previous reports of increased protoporphyrin IX in sickle cell disease and in reticulocytes obtained from newborns. Since FEP screening tests usually measure the total protoporphyrin levels and do not discriminate between protoporphyrin IX and zinc protoporphyrin, unless a specific screening technique is developed to identify only zinc protoporphyrin, the diagnostic limitations of elevated FEP values in sickle cell anemia must be recognized.

The serum ferritin measurement was the most specific test for iron deficiency. There were no false positive values. In normal children, a serum ferritin value below 12 ng/ml is usually diagnostic of iron deficiency. However, in patients with chronic inflammatory disease or hemolytic anemia, conditions recognized to elevate serum ferritin, a serum ferritin value below 25 ng/ml has been used to predict absent bone marrow iron stores and response to iron therapy.

Although rare, there have been a few reports of iron deficiency in sickle cell disease. Peterson et al., in a clinical study that required bone marrow aspiration, reported that 11 of 43 adult patients had no evidence of marrow iron stores. Two of these 11 patients received iron supplementation and both demonstrated a significant rise in hemoglobin concentration. In children with sickle cell disease, Rao and Sur and Ajayi and Luboyede reported absent bone marrow iron stores, but neither group reported the response of these children to iron supplementation. Powars, in a review of 422 sickle cell disease patients, described 8 children with severe iron deficiency who demonstrated a response to iron therapy.

While there is theoretical evidence that iron deficiency may prevent red cells from sickling on the basis of a decrease in the mean corpuscular hemoglobin concentration, this hypothesis lacks clinical verification. Since iron-deficient red cells are less deformable than iron-sufficient red cells, iron deficiency could potentially contribute to hemolytic and vaso-occlusive complications. From a nutritional standpoint, the nonhematologic implications of iron deficiency in children such as impaired intellectual performance, abnormal behavior, anorexia, and poor weight gain are considerable and should be prevented.

We recommend that infants with sickle cell disease, if not breast fed, be given iron-fortified formula or iron supplementation similar to that given to normal children for at least the first year of life. Furthermore, we recommend that all nontransfused sickle cell patients be screened for iron deficiency anemia. Patients who have a low MCV for age should have appropriate studies to distinguish iron deficiency from thalassemia trait; the FEP may have limited value in...
this regard. If a patient with a low MCV has either a low serum ferritin or low percent transferrin saturation, our results indicate that a therapeutic trial of iron is warranted.

ACKNOWLEDGMENT
The authors wish to thank Drs. J. R. Davis, J. E. Addiego, and J. H. Feusner for helping to obtain blood specimens, and also thank Michelle Glenn for the superior help in typing the manuscript.

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